ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES (ACCORD) TRIAL

MANUAL OF PROCEDURES

1. Organization, Management and Policy Issues

1.1 Overview

The ACCORD organizational structures and responsibilities are similar to those of other, large multicenter clinical trials sponsored by government or industry. Seven Clinical Center Networks (CCNs) and a Coordinating Center are contracted by the National Heart, Lung and Blood Institute to work together through the Steering Committee to successfully design and conduct the trial (see Figure 1.1). Each CCN is responsible for several clinical sites within its network. In addition, there is a Central Chemistry Laboratory, an ECG Reading Center, and a Drug Distribution Center. Scientific leadership is provided by the Steering Committee (see Figure 1.2).

1.2 Participating Centers

Names, addresses, telephone numbers, fax numbers, and email addresses can be found using a searchable directory on the ACCORD web site at www.accordtrial.org/. Directions for accessing the ACCORD web site are contained in Appendix A.1.

1.2.1 Clinical Center Networks and Clinical Sites

ACCORD participants are recruited, randomized, treated, and followed through seven Clinical Center Networks (CCNs) located in the United States and Canada. A list of the seven CCNs and associated Principal Investigators is included on pages 10 - 12 in this chapter. Each CCN consists of a network of collaborating clinical sites, which contain medical facilities and/or individual practices that are involved in the evaluation, enrollment and treatment of patients in the trial. The CCN hub is responsible for the activities of their clinical sites. CCN investigators oversee their clinical sites during the trial on issues related to recruitment, compliance with the ACCORD Protocol, and quality control. While these Clinical Sites interact principally through their CCNs, they will transmit their data directly to the Coordinating Center and the other central units, if necessary. Similarly, data queries are sent directly to the Clinical Sites, with copies to the appropriate CCN.

1.2.2 The Coordinating Center

The Coordinating Center (CC), with input from the ACCORD Steering Committee, is responsible for coordinating the writing and updating of the protocol; coordinating development and distribution of the Manual of Procedures; training trial personnel in the standardized protocol implementation and data collection; providing rapid feedback to the CCNs and Core Laboratories on the quality of data submitted and proposing corrections; maintaining the trial data base and web site; and analyzing all data. The CC will conduct yearly visits to each CCN to monitor and assure high performance throughout the trial. CC investigators and staff are also active members of each of the Steering Committee subcommittees. Contact information for the Principal Investigator of the CC is listed on pages 10 and 11 in this chapter.

During the recruitment phases of the trial, the CC is responsible for monitoring patient recruitment and provides weekly reports to the CCNs, the Executive Committee, the Steering Committee, the NHLBI Project Office, Core Laboratories, and the Drug Distribution Center. Included in the reports are measures of progress in recruiting women and minorities. These weekly reports assist the Recruitment and Retention Subcommittee with evaluating and correcting recruitment problems. The CC also develops (with the assistance from the Steering Committee) criteria for the certification of new clinical sites.

1.2.3 ECG Center, Central Laboratory, and the Drug Distribution Center

The ECG Center and the Central Laboratory provide central interpretation of resting ECGs, HbA1c and other blood measurements on trial participants. Each core unit is responsible for development and distribution of specific measurement procedures, timely data gathering, and analysis. The Drug Distribution Center (DDC) is responsible for the development and implementation of plans for drug acquisition, packaging, labeling, and dispensing according to the study protocol. The DDC also assists with monitoring compliance and provides data to the Coordinating Center for further analyses. Contact information for these Centers is listed on page 12 of this chapter.

1.2.4 NHLBI Project Office and Other Government Representatives

ACCORD is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). The NHLBI Project Office is responsible for the administration and monitoring of the trial. Representatives from the NHLBI Project Office participate in the scientific, general organizational and fiscal management of the trial. NHLBI statisticians provide statistical consulting. The National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) and the Centers for Disease Control and Prevention (CDC) are co-sponsors of ACCORD. In addition to NHLBI personnel, representatives from these agencies participate as scientists in the Steering Committee. Contact information for the NHLBI Project Officer is listed on page 12 in this chapter.

1.3 Administration and Governance

1.3.1 The ACCORD Steering Committee

The ACCORD Steering Committee provides the leadership for the study and establishes scientific and administrative policy. It is composed of the Principal Investigators from the seven Clinical Center Networks, the Principal Investigator from the Coordinating Center, the NHLBI Project Officer, the Chairs of the three major intervention working groups (glycemia, lipid, and blood pressure), the Steering Committee Chair, and the Steering Committee Vice-Chair. The Steering Committee oversees the overall conduct of the trial throughout all phases. During Phase I (the planning phase), this committee develops the trial design, prepares the final protocol, and approves the study forms and Manual of Procedures (MOP). During the data collection phases of the trial, this committee oversees data collection practices and procedures to

identify and correct deficiencies. The committee also considers and adopts changes in study procedures as necessary during the course of the trial.

The Steering Committee is lead by the Steering Committee Chair, who serves as the senior executive officer of the investigative group. The Steering Committee also has a Vice-Chair. Contact information for the Steering Committee Chair and Vice-Chair is listed on page 10 in this chapter.

Voting Steering Committee members include the Principal Investigators from the seven Clinical Center Networks, the Principal Investigator from the Coordinating Center, and the NHLBI Project Officer. The Steering Committee Chair, or Vice-Chair in his absence, votes only to break a tie.

There are eight standing subcommittees of the Steering Committee (Figure 1.2). Subcommittee membership and contact information can be found on the ACCORD web site at www.accordtrial.org/. During the protocol development phase of ACCORD, the Subcommittees of the Steering Committee were responsible for developing specific portions of the protocol and for making recommendations to the ACCORD Steering Committee for approval. During the data collection phases of the trial, the Subcommittees are responsible for monitoring specific portions of the conduct of the trial and providing periodic status reports to the Steering Committee.

1.3.2 Medical Interventions Subcommittee

This subcommittee developed the medical intervention plans for the trial, including the glycemic, lipid, and blood pressure components of ACCORD. This work was accomplished through three intervention-specific working groups within the subcommittee. A fourth working group, the Lifestyle/Background Therapy Working Group, developed the plans for smoking cessation, weight control, exercise improvement, dietary modifications, and background treatments. During the data collection phases of the trial, the Medical Interventions Subcommittee monitors the progress of protocol-specified medical management strategies, as well as adherence to the study medications and lifestyle regimens. The subcommittee develops strategies to maximize adherence to medications and lifestyle modifications. An additional charge to this subcommittee is to monitor the safety of the interventions and to make recommendations regarding possible changes to the protocol/MOP for patient safety or other reasons.

1.3.3 Recruitment and Retention Subcommittee

This subcommittee developed the trial eligibility criteria, as well as the screening and recruitment strategies for patient accrual. During the recruitment phases of the trial, this subcommittee monitors recruitment and screening, and identifies/assists the Clinical Center Networks (and their component clinics) experiencing recruitment difficulties. Adjustments to eligibility criteria, if necessary to improve overall participant accrual, are considered by this group. During the follow-up phases of the trial, this subcommittee monitors all aspects of participant retention, including visit and procedure adherence.

1.3.4 Measurement Procedures and Quality Control Subcommittee

This subcommittee developed the general data collection forms for use in the trial (in conjunction with other ACCORD subcommittee recommendations) and identified (with input from other subcommittees) clinical laboratory data to be collected. This subcommittee also established criteria under which the clinics, the Coordinating Center, and Core Units are expected to perform. This subcommittee reviews all aspects of data quality control monitoring and acts on these reports. Deviations from performance levels are brought to the attention of this subcommittee by the Coordinating Center. The monitoring activities include, but are not limited to, monitoring data quality, timeliness, completeness; monitoring alert levels; monitoring data entry, and, with respect to the core labs, reviewing the processing of samples. Reports from the site visitors to the CCNs and to the Central Laboratory are reviewed by this Subcommittee to determine whether action should be taken.

1.3.5 Design and Analysis Subcommittee

This subcommittee reviewed alternative designs for the trial, including the impact of various designs on sample size, statistical power, and patient recruitment. This subcommittee works closely with the Medical Interventions Subcommittee and the Recruitment and Retention Subcommittee on the development of analysis plans for recruitment and adherence monitoring. This subcommittee develops the analysis plans for the Vanguard phase, considers implications of Vanguard results on study design, and develops the analyses for the full-scale trial.

1.3.6 Health-related Quality of Life/Cost-Effectiveness Subcommittee

This subcommittee established which measures of health-related quality of life and cost-effectiveness are best studied in this trial, and developed plans for analyses of these data. During follow-up, this subcommittee monitors and assesses the progress of this portion of the trial and prepares reports for the Steering Committee.

1.3.7 Operations Subcommittee

The charge of this group is to assure communication among the clinical sites with respect to overall study coordination and implementation of procedures. The Operations Subcommittee is comprised of selected CCN staff as well as representatives from the Coordinating Center and the Project Office. The Committee coordinates training of the Project Coordinators on trial procedures. The CCN Project Coordinators, who are most aware of the day-to-day issues at the sites, are an invaluable resource to the trial and are invited to make recommendations regarding the conduct of the trial to the Steering Committee for review and consideration

1.3.8 Morbidity and Mortality Subcommittee

This subcommittee developed the definitions to be used for the classification of study events including the primary and secondary ACCORD outcome measures. This

Subcommittee develops procedures for collecting the relevant information from the clinical centers, for classifying each applicable event, and for quality control for ascertainment and classification of these clinical events. During the data collection phases of the trial, this subcommittee oversees the work of the Event Classification Working Group (made up of ACCORD investigators, who may or may not be on the Morbidity and Mortality Subcommittee), who will meet on a regular basis, and who use the procedures and criteria adopted by the trial to classify the occurrence of clinical events in a masked fashion and to monitor event ascertainment/classification quality control.

1.3.9 Publications and Presentations Subcommittee

This subcommittee developed the policies and procedures by which ACCORD investigators will conduct analyses, write papers, and make presentations. Included in the responsibilities of this subcommittee are approval of analyses/papers/presentations, solicitation of writing group members, and monitoring progress of all proposed papers to ensure their prompt completion and publication. This subcommittee is responsible for reviewing proposed ancillary studies and for making recommendations to the Steering Committee regarding the proposals.

1.3.10 Executive Committee

The ACCORD Executive Committee is the operational arm of the Steering Committee and makes decisions on behalf of the Steering Committee on day-to-day operational issues requiring immediate action. It makes recommendations to the Steering Committee for consideration. It meets at least biweekly by conference call to review trial progress and any study issues that may arise. This committee also develops Steering Committee Meeting agendas and time lines for the accomplishment of tasks.

The members of the Executive Committee include the Steering Committee Chair, Steering Committee Vice-Chair, Coordinating Center personnel, Project Office personnel, one CCN PI and the Chair of the Operations Subcommittee. The CCN Representative PI is appointed annually by the Executive Committee so that each PI has the opportunity to serve.

1.3.11 The Protocol Review Committee

An independent Protocol Review Committee (PRC) reviewed and commented upon the protocol. Members of the Committee, appointed by the Director of NHLBI, are senior experts in the areas of cardiovascular medicine, diabetes, biostatistics, and bioethics. The Study Chair, the Vice-Chair, the senior staff of the Coordinating Center, the CCN PI's, and representatives from the NHLBI and other sponsoring Federal agencies and Institutes participated in PRC meetings as non-voting members. The Protocol Review Committee met at the end of the protocol development phase of the trial and reported to the NHLBI regarding the scientific merit and feasibility of the trial. Recommendations were made to NHLBI regarding approval of the Protocol.

1.3.12 The Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) monitors data and oversees patient safety. Members of the DSMB, appointed by the Director of NHLBI, are senior experts in the areas of cardiovascular medicine, diabetes, biostatistics, and bioethics. The Study Chair, the Vice-Chair, the Principal Investigator and senior staff of the Coordinating Center, and representatives from the NHLBI and other sponsoring federal agencies and institutes participate in DSMB meetings as non-voting members. The DSMB meets at least once a year to monitor safety, to advise the NHLBI about study progress, including contractor performance, and to make recommendations to the NHLBI regarding study continuation. In addition, the Coordinating Center provides data to the DSMB Chair at his/her request at regular intervals to ensure early identification of any major adverse outcomes of therapy.

1.3.13 The Hypoglycemia Monitoring Committee

A Hypoglycemia Monitoring Committee (HMC) will provide external oversight and monitoring for cases of serious hypoglycemia events in ACCORD and provide feedback to enhance participant safety. All members of the HMC are endocrinologists with experience in the care of diabetes. The HMC is considered a subcommittee of the ACCORD Data and Safety Monitoring Board (DSMB) and, as such, is appointed by the NHLBI and reports to the DSMB and to the NHLBI. The committee complements DSMB monitoring by providing more frequent monitoring than provided by the DSMB and focusing on individual cases. The committee can recommend collection of additional information to ensure that data collected are appropriate for the monitoring needs and can recommend establishment of additional processes within the study to ensure that procedures are in place to enhance participant safety. The committee can recommend to NHLBI that the ACCORD DSMB review specific issues, or convene by conference call or in person, at times other than regularly scheduled DSMB meetings if the need arises.

FIGURE 1.1 ACCORD Organizational Chart
FIGURE 1.2 ACCORD Committees
ACCORD Principal Investigators and Central Units

Figure 1.1: ACCORD Organizational Chart

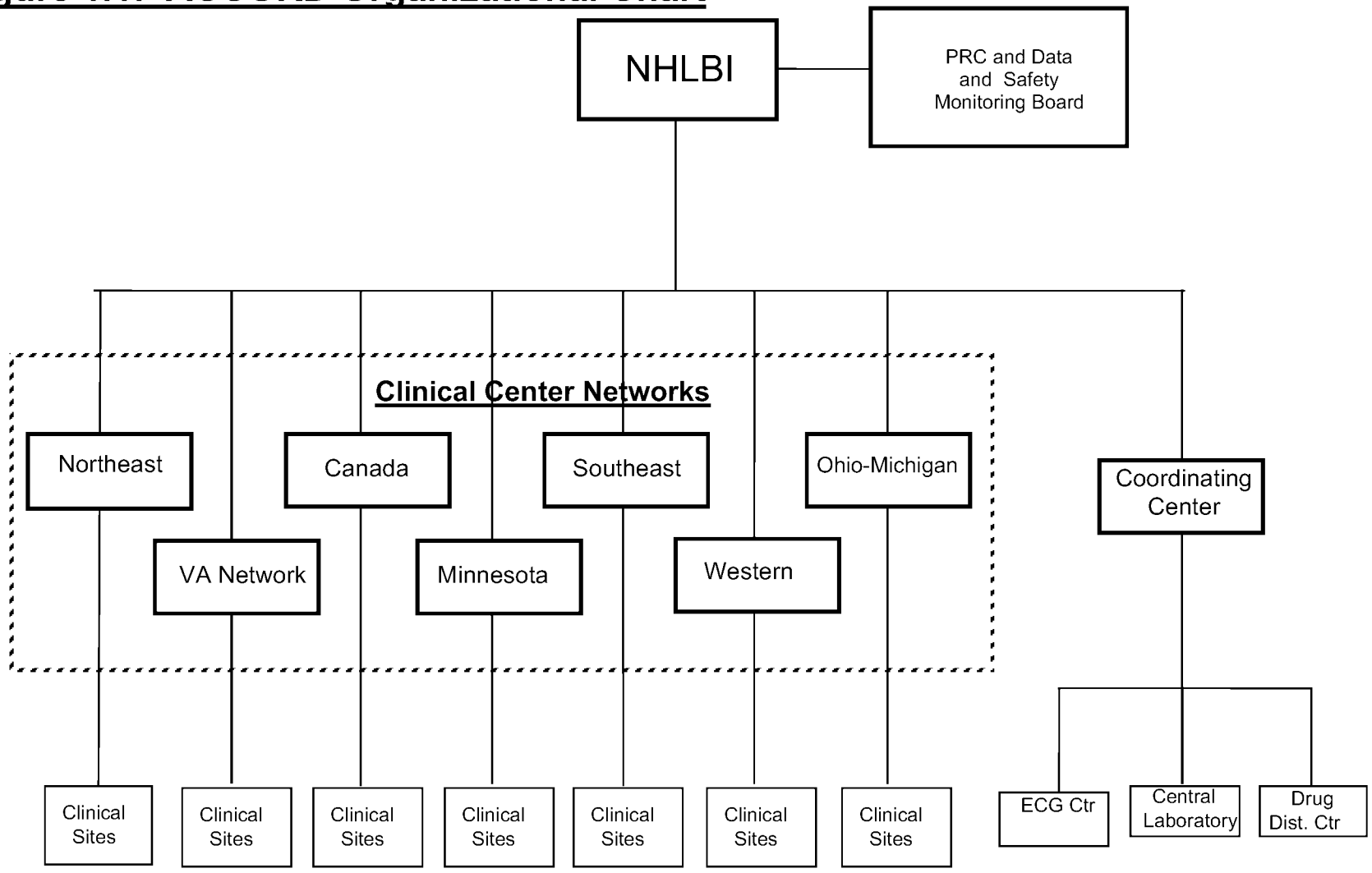
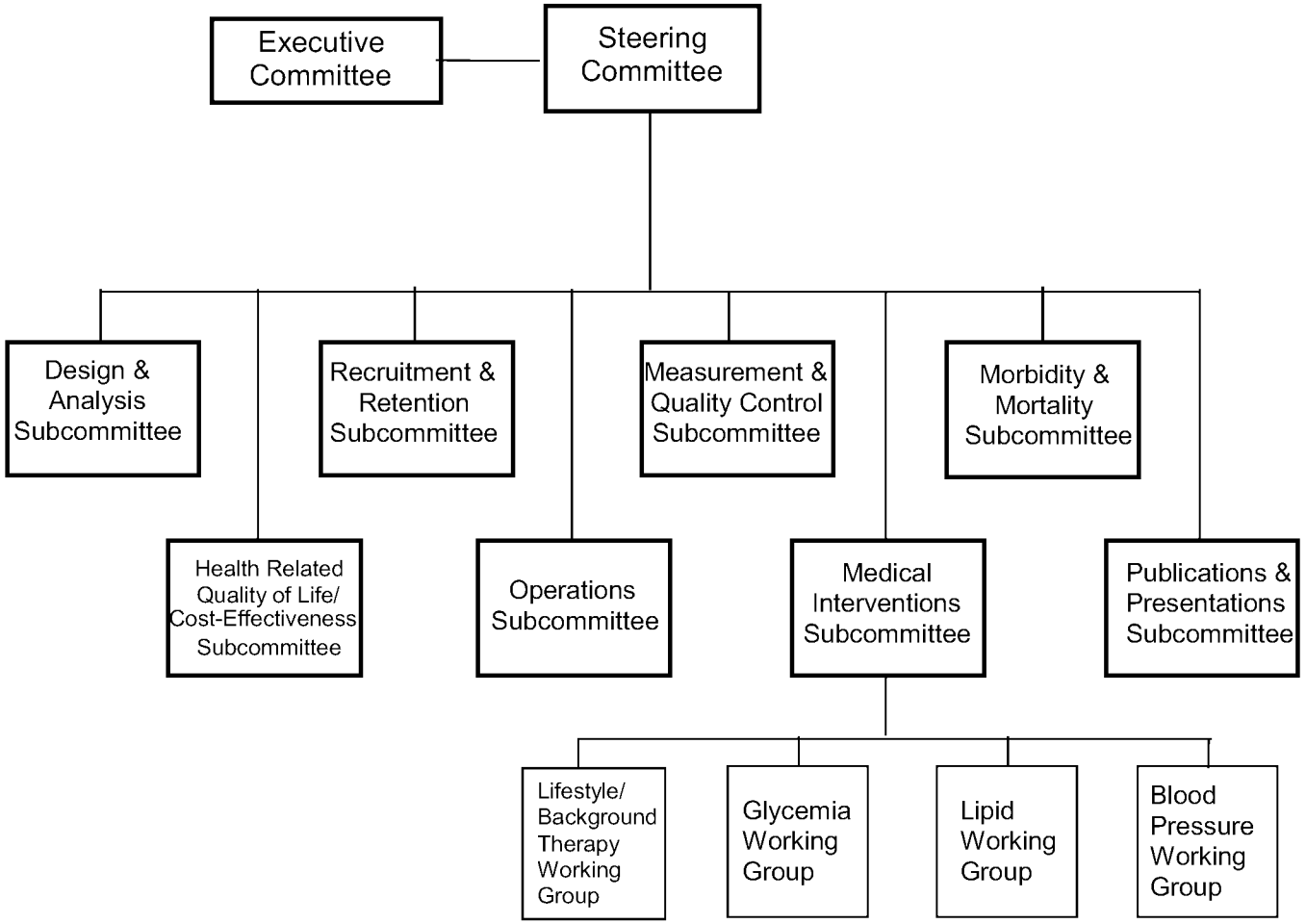


Figure 1.2: ACCORD Committees



ACCORD Principal Investigators and Central Units

Steering Committee Chair

Columbia University
College of Physicians and Surgeons & School of Public Health
Division of Epidemiology
600 West 168th Street PH
New York, NY 10032

Steering Committee Vice-Chair

UNC Diabetes Care Center
Highgate Specialty Center
5316 Highgate Drive.
Durham, NC 27713

Clinical Center Network Principal Investigators

College of Physicians & Surgeons of Columbia University
630 West 168th Street, Room PH
New York, NY 10032

VAMC Memphis
1030 Jefferson Avenue
Memphis, TN 38104-2193

Case Western Reserve University
Division of Clinical and Molecular Endocrinology
10900 Euclid Avenue,
Cleveland, OH 44106-4951

Department of Medicine
1200 Main Street West
Hamilton, ON

Wake Forest University School of Medicine
Department of Public Health Sciences
Section of Epidemiology
Medical Center Boulevard
Winston Salem, NC 27157

HCMC Department of Medicine
701 Park Avenue
Minneapolis, MN 55415

SWOG Statistical Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue, North,
Seattle, WA 98109

Coordinating Center Principal Investigator

Wake Forest University School of Medicine
Department of Public Health Sciences
Section of Epidemiology
Medical Center Boulevard
Winston Salem, NC 27157

NHLBI Project Officer

Division of Epidemiology and Clinical Applications
National Heart Lung, and Blood Institute

Two Rockledge Centre, Room
6701 Rockledge Centre Drive
Bethesda, MD 20892-7936

ACCORD Central Laboratory

Northwest Lipid Research Laboratories
University of Washington
2121 North 35th Street
Seattle, Washington 98103

ACCORD Drug Distribution Center

Clinical Research Pharmacy Coordinating Center
2401 Centre Avenue, SE
Albuquerque, NM 87106-4180

ACCORD ECG Center

Wake Forest University School of Medicine
Department of Public Health Sciences – Epicare
Medical Center Boulevard
Winston-Salem, NC 27157

1.4 Publications and Presentations

The ACCORD study encourages study investigators to propose publications and presentations using ACCORD data. Proposals for publications and presentations must follow the general policies governing all use of ACCORD data. Policies specific to the use of data in publications and presentations have been approved by the Steering Committee and can be found in the Publications and Presentations Manual contained in Appendix A.2.

1.5 Ancillary Studies

An ancillary study is an investigation that is not part of the ACCORD protocol but uses ACCORD participants, samples, or data collected by ACCORD. In most cases, an ancillary study will involve acquisition of additional data that are not compiled as part of the standard ACCORD data set and will require outside (non-ACCORD) funding.

Investigators are encouraged to propose and conduct ancillary studies. Such studies enhance the value of ACCORD and ensure the continued interest of the diverse group of investigators who are critical to the success of the study as a whole. They provide an exceptional opportunity for investigators, either within or outside of ACCORD, to conduct additional projects at minimal cost. Policies specific to the conduct of ancillary studies in ACCORD have been approved by the ACCORD Steering Committee. These policies can be found in Appendix A.2.

1.6 ACCORD Conflict of Interest Policy

This section describes the ACCORD Conflict of Interest (COI) Policy and form to be used. The policy was accepted by the ACCORD Steering Committee on January 10, 2000. The paper version of the COI disclosure form follows the policy (Figure 1.3). Those with access to the password-protected area of the ACCORD web site can retrieve the form at www.accordtrial.org/. The policy itself is available on the public access portion of the web site.

Conflict of Interest Policy: General Principles

1. This full policy should be made public in publications when possible. It is also contained on the ACCORD web site at www.accordtrial.org/. This full policy is to be made public on our Web site and in publications when possible.
2. Our primary concerns are twofold. First, that the ACCORD Investigators maintain the internal integrity of our study by which we mean the confidence among ourselves (investigators and staff), as we develop and modify the detailed protocol, that advice is being given and decisions are being made in as unbiased and fully informed manner as possible. Second, that we maintain the external integrity of the study by which we mean the acceptance of our process and results as having met public standards of conduct.
3. To meet these goals we will obtain full disclosure by all of the key members of the study (defined below) of their, and their immediate family's, financial relationships with all pharmaceutical and biomedical companies judged to have an active or potential interest in the conduct and outcome of the study. These are to be reported on a standard form, each of which will be reviewed on at least an annual basis, or more frequently if there is a significant change from the last report, by a small subset of the Executive Committee (termed the Oversight Committee). The Oversight Committee will be comprised of the Chair of the Steering Committee, the PI of the Coordinating Center, and the NHLBI Project Officer. The information to be reported will be detailed, but will not include specific dollar amounts, although the definitions below require that certain relationships be segregated by those above and below certain dollar thresholds.
4. All of the study PIs, co-PIs, and the Steering Committee and its various subcommittees' members are covered by this policy.
5. A conflict of interest will not necessarily exclude any member of the study from participating in study discussions, unless required in individual cases by the Oversight Committee. However, full disclosure of all potential conflicts of interest, will be made at each meeting to all attendees in an effective, but non-cumbersome manner. This includes the full Steering Committee as well as each of its subcommittees.
6. A significant financial conflict of interest, defined below, will cause a person to excuse himself or herself from voting on all issues related to the conflict. All such actions will be recorded and kept as part of the study record in the Coordinating

Center. This policy applies most especially to the subcommittees making recommendations to the full Steering Committee during the protocol design phase, as well as to the Steering Committee itself.

7. All financially relevant relationships are to be reported. Only those relationships that are between the individual and the specific company (rather than between the individual's parent institution and the specific company, for example) present the potential for a significant financial conflict of interest defined under paragraphs 9a and 9b below. Specifically, research funding for contracts or grants to the parent institution which provide support to the individual, his/her laboratory or his/her close scientific collaborators is not ordinarily judged to present the potential for a financial conflict of interest, although such awards are to be fully disclosed as a part of this policy.
8. Those financially relevant relationships that are to be reported include employment, consultancies, board membership, honoraria, stock ownership or options, grants, contracts, patents received or pending, and royalties. The Oversight Committee will decide, with #9 below as a guideline, whether any of these relationships in each individual case are significant enough to warrant refusal from voting or discussions.
9. A significant financial relationship is defined to exist:
   a) when the dollar amount awarded on an annual basis, or expected-to-be awarded on an annual basis, with regard to each related corporate relationship exceeds $25,000. The Oversight Committee may also judge lower dollar amounts as significant in specific/individual circumstances.
   b) or when there is any equity holding in a related company (excluding mutual funds and blind trusts). Again the Oversight Committee may decide in individual circumstances that the equity holdings are relatively minor enough to not present a real conflict of interest.
10. Significant financial relationships in existence since October 1, 1999 between ACCORD investigators and all pharmaceutical and biomedical companies judged to have an active or potential interest in the conduct and outcome of the study will be described in all study reports and publications. Similar relationships, but which are not significant, as well as actions taken early in the design phase of ACCORD that end significant financial relationships (e.g., stock divestment) will all be described on the ACCORD web site, but will not ordinarily be listed in study reports or publications. In addition we will obviously meet or exceed the reporting standards of the journals publishing our manuscripts.

Figure 1.3

ACCORD Conflict of Interest Disclosure Form version 121202 for Period January 01, 2002 to December 31, 2002

	Stock Ownership	Member of Board of Directors	Major Consultant (# of days)	Amount of Personal Compensations Received (see Note for compensation)	Unrestricted Grant/Contract to Individual	Other Grant/Contract Support*
Abbott Laboratories	Yes / No	Yes / No		$	Yes / No	Yes / No
Aimsco	Yes / No	Yes / No		$	Yes / No	Yes / No
AstraZeneca	Yes / No	Yes / No		$	Yes / No	Yes / No
Aventis	Yes / No	Yes / No		$	Yes / No	Yes / No
Bayer Corporation	Yes / No	Yes / No		$	Yes / No	Yes / No
Becton Dickinson	Yes / No	Yes / No		$	Yes / No	Yes / No
Bio-Rad	Yes / No	Yes / No		$	Yes / No	Yes / No
Biovail	Yes / No	Yes / No		$	Yes / No	Yes / No
Boehringer Ingelheim	Yes / No	Yes / No		$	Yes / No	Yes / No
Bristol-Myers Squibb	Yes / No	Yes / No		$	Yes / No	Yes / No
Can-Am Care	Yes / No	Yes / No		$	Yes / No	Yes / No
Chronimed	Yes / No	Yes / No		$	Yes / No	Yes / No
Criticon	Yes / No	Yes / No		$	Yes / No	Yes / No
Eli Lilly	Yes / No	Yes / No		$	Yes / No	Yes / No
Eon Labs	Yes / No	Yes / No		$	Yes / No	Yes / No
Forest Laboratories	Yes / No	Yes / No		$	Yes / No	Yes / No
Fortec	Yes / No	Yes / No		$	Yes / No	Yes / No
GlaxoSmithKline	Yes / No	Yes / No		$	Yes / No	Yes / No
Healthcheck	Yes / No	Yes / No		$	Yes / No	Yes / No
IVAC	Yes / No	Yes / No		$	Yes / No	Yes / No
King Pharmaceutical	Yes / No	Yes / No		$	Yes / No	Yes / No
Knoll Pharmaceutical	Yes / No	Yes / No		$	Yes / No	Yes / No
Kos Pharmaceutical	Yes / No	Yes / No		$	Yes / No	Yes / No
LifeScan, Inc.	Yes / No	Yes / No		$	Yes / No	Yes / No
MediSense	Yes / No	Yes / No		$	Yes / No	Yes / No
Medtronic (incl. MiniMed)	Yes / No	Yes / No		$	Yes / No	Yes / No
Merck	Yes / No	Yes / No		$	Yes / No	Yes / No
Merck-Lipha	Yes / No	Yes / No		$	Yes / No	Yes / No
Metrika	Yes / No	Yes / No		$	Yes / No	Yes / No
Monarch Pharmaceutical	Yes / No	Yes / No		$	Yes / No	Yes / No
Mylan Pharmaceutical	Yes / No	Yes / No		$	Yes / No	Yes / No
Nissei Shokai	Yes / No	Yes / No		$	Yes / No	Yes / No
Novartis	Yes / No	Yes / No		$	Yes / No	Yes / No
Novo Nordisk	Yes / No	Yes / No		$	Yes / No	Yes / No
Omron	Yes / No	Yes / No		$	Yes / No	Yes / No
Pfizer (incl. Parke-Davis)	Yes / No	Yes / No		$	Yes / No	Yes / No
Pharmacia (incl. Searle)	Yes / No	Yes / No		$	Yes / No	Yes / No
Phillips Pharmaceutical	Yes / No	Yes / No		$	Yes / No	Yes / No
Provalis	Yes / No	Yes / No		$	Yes / No	Yes / No
Roche Diagnostics	Yes / No	Yes / No		$	Yes / No	Yes / No
Sankyo Pharmaceutical	Yes / No	Yes / No		$	Yes / No	Yes / No
Sanofi	Yes / No	Yes / No		$	Yes / No	Yes / No
Schering Plough	Yes / No	Yes / No		$	Yes / No	Yes / No
Servier	Yes / No	Yes / No		$	Yes / No	Yes / No
Sidmark Laboratories	Yes / No	Yes / No		$	Yes / No	Yes / No
Systema	Yes / No	Yes / No		$	Yes / No	Yes / No
Takeda	Yes / No	Yes / No		$	Yes / No	Yes / No
TheraSense	Yes / No	Yes / No		$	Yes / No	Yes / No
Unimed Pharmaceutical	Yes / No	Yes / No		$	Yes / No	Yes / No
Visomat	Yes / No	Yes / No		$	Yes / No	Yes / No
Wyeth-Ayerst	Yes / No	Yes / No		$	Yes / No	Yes / No
Other 1	Yes / No	Yes / No		$	Yes / No	Yes / No
Other 2	Yes / No	Yes / No		$	Yes / No	Yes / No
Other 3	Yes / No	Yes / No		$	Yes / No	Yes / No

Note: Personal compensation includes all money received for board membership, consulting activities, honoraria for talks, and any other compensation that can not be classified as unrestricted grant or contract compensation.

*Includes any restricted grant/contract to individual or institution and any unrestricted grant/contract to institution.

Do you and/or spouse and/or your dependents have financial holdings or other interests or activities (e.g. travel, gifts, etc.), other than any mentioned above that you consider to be a potential conflict of interest?	Yes / No *(If Yes, please specify below)*
Specify:	

Miscellaneous Comments:

I have reviewed the information above and confirm that it is correct and complete.

Signature: _____ Print Name: _____ Date: _____

PLEASE FAX TO: ACCORD Coordinating Center

1.7 IRB Approval, Reporting and Re-Approval and other Regulatory Issues

Every **ACCORD** clinic must obtain approval from an Institutional Review Board (IRB) before conducting screening visits and enrolling participants in the study. An IRB is charged with the review of all research, development, and related activities in which human subjects will participate in that institution. All study protocols are reviewed for purposes of:

- approving the appropriateness of methods used to secure informed consent
- protecting the rights and welfare of study participants
- evaluating the risks to subjects in relation to the potential medical benefits of the investigation.

1.7.1 What needs IRB Approval?

An IRB is constituted to review and approve studies to be carried out on human subjects in that institution. The review focuses on the ethics of the proposed research and on the adequacy of the proposed patient informed consent process. Local IRBs are also initiating certification for programs on Good Clinical Practice (GCP) Guidelines that each investigator may need to receive prior to study approval and initiation. These efforts coincide with federal guidelines for education and training of clinical investigators, IRB members and associated IRB and institutional staff. These guidelines are needed since clinical research has become "increasingly complex and has been accompanied by an increase in new ethical and conflict-of-interest considerations" (HHS Fact Sheet, June 2000).

Patient-oriented research studies need to be approved by an IRB before any participant examination or data collection can begin. This applies to intervention studies such as clinical trials as well as epidemiological investigations, such as observational studies. All NIH, industry, foundation, and intramural sponsored studies must be approved by an IRB. Once a study has been approved, any additional information about the study that relates to participant safety (i.e., protocol changes, significant adverse events, changes in the consent form) also needs to be submitted to the IRB. Retrospective chart reviews with patient identifiers, as well as study recruitment ads, brochures, phone scripts and any materials that would be sent or given to potential participants must also be reviewed and approved by an IRB. NIH-funded extramural research, such as ACCORD, relies on local IRB review and approval at each site involved, rather than using a central NIH IRB process. All IRBs must follow national principles for assuring human subject safety, but each IRB is unique and may have specific requirements, for example on the structure of an informed consent document.

For local approval, the IRB will be provided all of the following documentation as deemed appropriate by the local institution.

- Study protocol and any future revisions or amendments
- Informed consent
- Any required local organizational approvals for the conduct of the study
- Research subject advertisement including posters, press releases, videos, Internet WEB page and flyers
- Patient brochures, pamphlets and guides, or form letters
- Phone call scripts (If any phone calls are made to prospective patients to tell them about the trial and solicit interest, the individual IRB should be given a "script" of what will be said to the person)
- Data Collection forms and explanation of electronic data transmission procedures
- Laboratory procedures including description of patient glucose testing equipment for home monitoring
- IND (if requested)

- Investigational drug forms describing study drugs, e.g., package inserts

1.7.2 Full versus Expedited Review/Approval

Any study involving more than minimal risk of harm to human participants needs to undergo a full review by the entire IRB committee. The term "minimal risk of harm" refers to being exposed to nothing more than everyday occurrences of routine procedures for standard health care. Studies involving only collection of blood samples from healthy individuals, collection of hair and nail clippings, and research involving data, documents of records that have already been collected, for example, may be eligible for expedited review. Other documents that may qualify for expedited review include recruitment brochures, advertisements, and form letters to participants.

1.7.3 Interim IRB Review/Approval

After initial approval, an IRB must be notified any time about:

- Recruitment Brochures and Advertisements
- Form Letters or Study information sent to participants
- Protocol Amendments
- Protocol Deviations
- Serious Adverse Events (SAEs)
- Consent Form Revisions
- Other issues required by local reporting requirements

In addition, an IRB must be notified of adverse events after DSMB review and discussion of those events. The Project Office and Coordinating Center will prepare a report after each DSMB discussion for PIs to convey this information to their IRBs.

1.7.3.1 Recruitment Brochures and Advertisements

Before circulating study brochures/fliers, placing ads in newspapers, in other publications, on a web page, or placing any kind of public service announcements about a study on TV or the radio, the ACCORD Coordinating Center as well as individual IRB's must approve the text/script of these materials. Key elements that the IRB members look for when reviewing these ads include:

- Use of the word "research"
- List of basic eligibilities
- No "overpromising" concerning results of the study

1.7.3.2 Protocol Amendments and Consent Form Revisions

All protocol changes must be sent to an IRB. Minor changes that do not affect participant care may be considered for expedited review. Call your site's research office to inquire about their specific, local requirements. Most amendments necessitating a change in the consent form need to undergo full IRB review. Changes in the consent form for clarification may be eligible for expedited review.

1.7.3.3 Adverse Events

The IRB must be notified about any serious or unexpected adverse events with the investigational drug or device. Serious adverse events refer to fatal or life-threatening events that may permanently disable the participant or that require hospital admission (or prolongation of hospitalization), that the PI feels is directly caused by a study medication. Also included would be congenital anomalies, cancer or overdoses due to the medication. Unexpected adverse events refer to adverse experiences that are not listed in the current labeling for the drug. These may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of the greater severity or specificity (e.g., hepatic necrosis constitutes an "unexpected event" by virtue of greater severity if labeling refers only to elevated hepatic enzymes or hepatitis). The ACCORD data collection process incorporates collection of information on adverse events.

1.7.4 Office for Human Research Protection (OHRP) Approvals and Assurances

1.7.4.1 What is Assurance and When is it Needed?

The Federal Policy (Common Rule) for the protection of human subjects requires that each institution "engaged" in federally supported human subject research file an "Assurance" of protection for human subjects. The Assurance formalizes the institution's commitment to protect human subjects. The requirement to file an Assurance includes both "awardee" and collaborating "performance site" institutions.

Under the Federal Policy, awardees and their collaborating institutions become engaged in human subject research whenever their employees or agents (a) intervene or interact with living individuals for research purposes; or (b) obtain, release, or access individually identifiable private information for research purposes.

In addition, awardee institutions are automatically considered to be engaged in human subject research whenever they receive a direct HHS award to support such research, even where all activities involving human subjects are carried out by a subcontractor or collaborator. In such cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award. The awardee is also responsible for ensuring that all collaborating institutions engaged in the research hold an approved Assurance prior to their initiation of the research.

1.7.4.2 Types of Assurance

Historically, OHRP has approved three basic types of assurances: Multiple Project Assurance (MPA), Cooperative Project Assurance (CPA), and Single Project Assurance (SPA). As of December 2000, OHRP implemented a new, simplified Assurance policy called Federalwide Assurance (FWA). The FWA covers all of an institution's federally supported human subject research, and eliminates the need for all other types of Assurance documents.

1.7.5 What Happens to Existing Assurances (MPAs, CPAs, SPAs)

Existing Assurances (MPAs, CPAs and SPAs) will remain in effect through their current expiration date, or December 31, 2003 (which ever comes first). Of course, coverage under these Assurances will be limited to that described in the Assurance.

Institutions holding MPAs, CPAs, and SPAs are encouraged to file new Federalwide Assurances at their earliest convenience.

Institutional Review Boards (IRBs) designated under currently approved MPAs will be Registered automatically. MPA institutions will receive a letter from OHRP requesting verification of information concerning their designated IRBs.

IRBs currently designated only under CPAs or SPAs will have to submit registration materials through the new system if they wish to be registered with HHS.

Note that each legally separate entity that engages in federally supported human subject research needs its own Assurance under the new system. Joint Assurances, and Inter-institutional Amendments have been eliminated. However, institutions are free to designate IRBs under their Assurances that are operated by other entities.

1.7.6 Which Sites Need Assurance?

If your site does not have an approved Multiple Project or Federal Wide Assurance on file with OHRP, you will need to apply for a Federal Wide Assurance. If you are unsure of your site's Assurance status, please contact your IRB Chairperson or an institutional official who is authorized to execute legal agreements for your site. If your site does not have an IRB, please contact the Coordinating Center to discuss options available to your clinic.

1.7.6.1 Domestic Sites Requiring FWA

If your site requires assurance, please contact the Coordinating Center. The Coordinating Center will send notification and an information packet to those sites that need FWA. The information packet will include the following items:

- Cover letter from Accord Coordinating Center
- Instructions from Coordinating Center
- Sample FWA document
- 45 CFR 46 (for informational purposes)
- The Belmont Report (for informational purposes)

1.7.6.2 Where to Find the FWA Application Form

The FWA form can be downloaded from the OHRP web site
http://ohrp.osophs.dhhs.gov/humansubjects/assurance/filasur.htm

1.7.6.3 How to Complete the FWA Form

- At the top of the form, please put an "x" to indicate whether this is a new filing or an update to a previous assurance.

Section 1

- Type in the full name of the institution, as well as the city and State where the institution is located.

- Type in the IPF or EIN number, if known. IPF and EIN numbers are assigned by Agencies other than OHRP. Some funding Agencies use these numbers for tracking purposes. OHRP has requested them simply to assist those Agencies. If your institution has no IPF or EIN number, just leave the items blank. These numbers are not necessary for an FWA and will not delay processing of your FWA.
- If this is an update to a previous filing (meaning that this assurance will replace a MPA or CPA) type in the "M" or "T" number where requested.

Section 2

- If your institution has legal authority over component sites that operate under different names, please list the name of those sites, as well as the city and State in which they are located. Components are generally defined as parts of your institution that may be viewed as separate organizations, but remain part of the legal entity or institution. For example, a ABC University can list its XYZ University Hospital, KLM School of Public Health, and EFG Institute for International Studies as components. In order to keep the listing of components manageable, only list the major components of your institution that are likely to be represented as either the applicant organization or as a research performance site. Please do not list all departments of your institution, as their participation in a study is likely to be represented by the name of the institution or one of the major components.
- If your institution does not have legal authority over any component sites, please put an "x" in the appropriate area above the table.

Section 3

- Domestic institutions (within the US) should indicate the ethical principle to which they adhere. Put an "x" next to only one choice. If you select "Other", you must attach a copy of that ethical principle to this application.

Section 4

- Section a - Domestic institutions must assure that they will comply with the terms of assurance as specified on the OHRP web site. Review the Terms of the Federalwide Assurance (FWA) for Domestic (U.S.) Institutions on the OHRP website http://ohrp.osophs.dhhs.gov/humansubjects/assurance/filasurt.htm
  These terms will give you a better understanding of the regulatory requirements that will be applied to federally-supported or -conducted human subjects research. You do not need to complete anything here.
- Section b - This section asks about the regulatory standards that your institution applies to all research, regardless of source of support. Indicate with an "x" whether your institution elects to apply 45 CFR 46 and all its subparts (A, B, C, and D) or the Common Rule (e.g., 45 CFR 46, Subpart A) to **all** human subjects research regardless of source of support. ***Completion of this section is optional.***

Section 5

- Please list the DHHS registration number and name of any IRB that your institution designates for review of research on a regular basis. To confirm if an IRB is registered with DHHS, please refer to the OHRP web site.
  http://ohrp.cit.nih.gov/search/asearch.asp#IORG
  If you are unsure of the DHHS registration number, please confer with the Chair of the IRB. If an IRB is not registered with DHHS or has not provided a membership roster to DHHS, please complete the IRB registration forms and attach them to the FWA application. To

register an IRB, refer to the following web page.
http://ohrp.osophs.dhhs.gov/humansubjects/assurance/regirbi.htm

Section 6

- The human subject administrator or contact person must complete this section. This can NOT be an IRB Chairperson. The Human Protections Administrator is an employee or agent of the FWA institution who exercises operational responsibility, on a day-to-day basis, for the institution's program for protecting human subjects. This individual's title and position within the institutional structure will vary from institution to institution. What is important is the individual's comprehensive knowledge of all aspects of the institution's systemic protections for human subjects. Every domestic FWA institution should have a Human Protections Administrator, even if the institution relies totally on IRBs from other organizations.

The Human Protections Administrator or contact person must provide their name, degree(s), institutional title, institution, phone, FAX, email address, and address in this section.

Section 7

- A Signatory official (i.e., a person who legally represents the institution or who can enter the institution into legal agreements) must complete this section. This person **cannot** be an IRB Chair or an ACCORD Investigator. This individual must also have the authority to assure compliance of the institution and all of its components to the Terms of the Assurance. Generally, this is someone at the level of President or Chief Executive Officer (CEO) of a company or Provost or Chancellor of an academic institution, unless another official has been specifically delegated with this authority.
- The Signatory official must also type in their name, degree, institutional title, phone, FAX, email, and address.

Section 8

- Do not complete this section. This section will be completed by OHRP

Once the site completes the FWA application, copies of the application, as well as copies of IRB approval letters, IRB approved consent forms, and IRB membership lists should be sent to Annemarie Lopina at the Coordinating Center. The Coordinating Center will review the applications and send them to OHRP. Once OHRP has approved the Assurance, the Coordinating Center will notify the site.

1.7.7 International (Canadian) Sites Requiring FWA

If your site requires assurance, please contact Annemarie Lopina at the Coordinating Center. The Coordinating Center will send notification and an information packet to those sites that need FWA. The information packet will include the following items:

- Cover letter from Accord Coordinating Center
- Instructions from Coordinating Center
- Sample FWA document
- 45 CFR 46 (for informational purposes)
- The Belmont Report (for informational purposes)

1.7.7.1 Where to Find the FWA Application Form

The FWA form can be downloaded from the OHRP web site http://ohrp.osophs.dhhs.gov/humansubjects/assurance/ifilasur.htm

1.7.7.2 How to Complete the FWA Form

- At the top of the form, please put an "x" to indicate whether this is a new filing or an update to a previous assurance. If this is a renewal, please type in the FWA number.

Section 1

- Type in the full legal name of the institution, as well as the city, State/Province and country where the institution is located.
- Type in the IPF or EIN number, if known. IPF and EIN numbers are assigned by Agencies other than OHRP. Some funding Agencies use these numbers for tracking purposes. OHRP has requested them simply to assist those Agencies. If your institution has no IPF or EIN number, just leave the items blank. These numbers are not necessary for an FWA and will not delay processing of your FWA.
- If this is an update to a previous filing (meaning that this assurance will replace a MPA or CPA) type in the "M" or "T" number where requested.

Section 2

- If your institution has legal authority over component sites that operate under different names, please list the name of those sites, as well as the city, State/Province or country in which they are located. Components are generally defined as parts of your institution that may be viewed as separate organizations, but remain part of the legal entity or institution. For example, a ABC University can list its XYZ University Hospital, KLM School of Public Health, and EFG Institute for International Studies as components. In order to keep the listing of components manageable, only list the major components of your institution that are likely to be represented as either the applicant organization or as a research performance site. Please do not list all departments of your institution, as their participation in a study is likely to be represented by the name of the institution or one of the major components.
- If your institution does not have legal authority over any component sites, please put an "x" in the appropriate area above the table.

Section 3

- International institutions should indicate the ethical principles to which they adhere. If you select "Other", you must attach a copy of that ethical principle to this application.

Section 4

- International institutions must assure that they will comply with the terms of assurance as specified on the OHRP web site. Review the Terms of the Federalwide Assurance (FWA) for Domestic (U.S.) Institutions on the OHRP website. http://ohrp.osophs.dhhs.gov/humansubjects/assurance/filasurt.htm
  These terms will give you a better understanding of the regulatory requirements that will be applied to federally-supported or -conducted human subjects research.
- This section asks about the regulatory standards that your institution applies to human subjects research. Indicate with an "x" the alternative regulatory standards available

on the FWA application for International Institutions (non-U.S.) that your institution elects to apply for U.S. federally-supported or -conducted human subjects research. Please note that the listed alternative regulatory standards are considered to be generally consistent to the U.S. Common Rule (i.e., U.S. Federal Policy for the protection of human subjects in research). However, for DHHS-supported or -conducted human subjects research item 7 of the Terms of the FWA for International (non-U.S.) Institutions may require additional protections for the involvement of pregnant women or fetuses, prisoners, or children.

- If "Other" procedural standards are named, a copy of those standards must be submitted with the FWA application.

Section 5

- Please list the DHHS registration number and name of any IRB or IEC that your institution designates for review of research on a regular basis. To confirm if an IRB or IEC is registered with DHHS, please refer to the OHRP web site. http://ohrp.cit.nih.gov/search/asearch.asp#IORG
- If you are unsure of the DHHS registration number, please confer with the Chair of the IRB or IEC. If an IRB or IEC is not registered with DHHS or has not provided a membership roster to DHHS, please complete the IRB/IEC registration forms and attach them to the FWA application. To register an IRB or IEC, refer to the following web page. http://ohrp.osophs.dhhs.gov/humansubjects/assurance/regirbi.htm

Section 6

- The human subject administrator or contact person must complete this section. This can NOT be an IRB Chairperson. The Human Protections Administrator is an employee or agent of the FWA institution who exercises operational responsibility, on a day-to-day basis, for the institution's program for protecting human subjects. This individual's title and position within the institutional structure will vary from institution to institution. What is important is the individual's comprehensive knowledge of all aspects of the institution's systemic protections for human subjects. Every domestic FWA institution should have a Human Protections Administrator, even if the institution relies totally on IRBs from other organizations.
- The Human Protections Administrator or contact person must provide their name, degree(s), institutional title, institution, phone, FAX, email address, and address in this section.

Section 7

- A Signatory official (i.e., a person who legally represents the institution or who can enter the institution into legal agreements) must complete this section. This person **cannot** be an IRB Chair or an ACCORD Investigator. This individual must also have the authority to assure compliance of the institution and all of its components to the Terms of the Assurance. Generally, this is someone at the level of President or Chief Executive Officer (CEO) of a company or Provost or Chancellor of an academic institution, unless another official has been specifically delegated with this authority.
- The Signatory official must also type in their name, degree, institutional title, phone, FAX, email, and address.

Section 8

- Do not complete this section. This section will be completed by OHRP.

Once the site completes the FWA application, copies of the application, as well as copies of IRB approval letters, IRB approved consent forms, and IRB membership lists should be sent to the Coordinating Center. The Coordinating Center will review the applications and send them to OHRP. Once OHRP has approved the Assurance, the Coordinating Center will notify the site.

1.7.8 Record Keeping of Regulatory Documents

It is the responsibility of the ACCORD Coordinating Center to assure the study sponsor that IRB review is being carried out in accordance with federal regulations. The Coordinating Center has the responsibility of monitoring the IRB approvals and annual re-approvals for all ACCORD CCNs .

IRB approvals must be renewed annually and proof of the renewal must be the submitted to the ACCORD Coordinating Center. This requirement is to provide documentation of the local IRB's notification and approval of participant recruitment activities, proposed interventions, and adverse events. The Coordinating Center will send information to the CCN offices if the annual renewals have expired.

ACCORD Study Document Binder

The Study Document Binder (Regulatory Document Book) is the administrative binder that serves as the regulatory record of your clinic's participation in the ***ACCORD*** study. It should be kept current and available for review by the Network Coordinators and/or representatives of regulatory agencies (i.e. FDA) during site visits or in the event of an audit. This book should include current copies of:

- The protocol and revisions
- FDA 1572 and curriculum vitae for the investigators, sub-investigator and study coordinator
- IRB/OHRP approvals, IRB renewals and IRB correspondence (adverse events reports)
- Copies of IRB approved informed consent document(s)
- Research participant advertisements, e.g. patient brochures, pamphlets
- Current correspondence (may keep separate correspondence file)
- Site visit log
- Enrolled patient log with pertinent identifier information (randomization number and acrostic if needed)

Other items that may also be included are: recruitment plans, a set of sample forms and travel documentation to investigator/training meetings.

1.7.9 Obtaining Consent from Participants

Informed consent is not just a form. Rather, it is a process that involves the following steps:

- Giving a participant adequate information about the study
- Providing adequate opportunity for the participant to consider all options
- Responding to the participant's questions
- Ensuring the participant has comprehended the information
- Obtaining the participant's voluntary agreement to enter the study
- Continuing to provide information as the participant or situation requires

In order to be effective, the process should provide ample opportunity for the investigator and the participant to exchange information and ask questions.

Below are some frequently asked questions about the consent process.

- **Who can obtain consent from potential participants?**
  FDA does not specify who can obtain consent from a potential participant. Some sponsors and IRBs require the clinical investigator to conduct the consent interview. Regardless, the person who conducts the consent interview should be knowledgeable about the study and able to answer questions. If someone other than the investigator obtains consent, the clinical investigator should formally delegate this responsibility and the person so delegated should have the appropriate training to perform this activity.

- **21 Code of Federal Regulations (CFR) 50.27(a) requires that a copy of the consent document be given to the person signing the form. Does this have to be a photocopy of the form with the participant's signature affixed?**
  No. The regulation does not require the copy of the form given to the participant to be a copy of the document with the participant's signature, although this is strongly encouraged. It must, however, be a copy of the IRB approved document that was given to the participant to obtain their consent.

- **Do you have to have a witness to the consent process?**
  An impartial witness is only required if the participant cannot read, if the participant is incapable of understanding the consent document, or if the participant does not speak English. Otherwise, a witness is not required.

- **When a witness is required, must they observe the entire consent interview or only the signature of the participant?**
  When a witness is required, they must be present throughout the entire consent interview. The intended purpose is to have the witness attest to the accuracy of the presentation and the apparent understanding of the participant, not just the validity of the participant's signature.

- **How do you obtain informed consent from someone who speaks and understands English but cannot read?**
  Illiterate persons who understand English may have the consent read to them and "make their mark," if appropriate under applicable state law. Federal regulations do permit the use of a short form for patients that cannot read. A short form is a document that states that the elements of informed consent as required by the Code of Federal Regulations have been presented orally to the participant. When this method is used, there must be an impartial witness to the oral presentation. Also, the IRB should approve a written summary of what is to be said to the participant. The participant must sign the short form. However, the witness must sign both the short form and a copy of the IRB approved summary. A copy of the summary and short form must be given to the participant. If you encounter an illiterate participant, consult with your IRB Chair to discuss your local guidelines.

- **How do you obtain consent from a person that does not speak English?**
  There are a couple of methods that are acceptable when obtaining consent from non-English speaking participants. Department of Health and Human Services regulations for the protection of human research participants require that informed consent information be presented in language understandable to the participant and, in most situations, that informed consent be documented in writing.

  Where informed consent is documented in accordance with federal regulations, the written consent document should embody, in language understandable to the participant, all the elements necessary for legally effective informed consent. Participants who do not speak English should be presented with a consent document written in a language understandable to them. The Office for Human Research Protections (OHRP) strongly encourages the use of this procedure whenever possible.

  Alternatively, the regulations permit oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. A witness to the oral presentation is required, and the participant must be given copies of the short form document and the summary.

  When this procedure is used with participants who do not speak English, there are several requirements:
- The oral presentation and the short form written document (see sample attached) should be in a language understandable to the participant
- The IRB-approved English language informed consent document may serve as the summary
- The witness should be fluent in both English and the language of the participant

At the time of consent, the participant should sign the short form document. The person obtaining consent must sign the summary (i.e., the English language informed consent document). The witness must sign the short form document and the summary. When a translator assists the person obtaining consent, the translator may serve as the witness.

The IRB must receive all foreign language versions of the short form document as a condition of approval. Expedited review of these versions is acceptable if the protocol, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

It is the responsibility of the IRB to determine which of the procedures is appropriate for documenting informed consent in protocols that it reviews.

Other Tips

- Use of the first person (e.g., "I understand that ...") can be interpreted as suggestive, may be relied upon as a substitute for sufficient factual information, and can constitute coercive influence over a participant. Use of scientific jargon and legalese is not appropriate. Think of consent as a teaching tool not as a legal instrument.
- Anyone who signs a consent form should personally date it.
- If consent is obtained the same day that the participant's involvement in the study begins, the participant's medical records should document that consent was obtained prior to participation in the research. The following statement could be included in the records; "All the required elements of informed consent were presented to the

patient. Voluntary consent was obtained and the patient's questions were answered prior to initiation of any research procedures."

- A copy of the consent document must be provided to the participant and the original signed consent should be retained in the study records.

ATTACHMENT: SAMPLE SHORT FORM WRITTEN CONSENT DOCUMENT FOR PARTICIPANTS WHO DO NOT SPEAK ENGLISH

THIS DOCUMENT MUST BE WRITTEN IN A LANGUAGE UNDERSTANDABLE TO THE PARTICIPANT

Consent to Participate in Research

You are being asked to participate in a research study.

Before you agree, the investigator must tell you about (i) the purposes, procedures, and duration of the research; (ii) any procedures which are experimental; (iii) any reasonably foreseeable risks, discomforts, and benefits of the research; (iv) any potentially beneficial alternative procedures or treatments; and (v) how confidentiality will be maintained.

Where applicable, the investigator must also tell you about (1) any available compensation or medical treatment if injury occurs; (2) the possibility of unforeseeable risks; (3) circumstances when the investigator may halt your participation; (4) any added costs to you; (5) what happens if you decide to stop participating; (6) when you will be told about new findings which may affect your willingness to participate; and (7) how many people will be in the study.

If you agree to participate, you must be given a signed copy of this document and a written summary of the research.

You may contact ____name____ at ___phone number__ any time you have questions about the research.

You may contact ____name____ at ___phone number__ if you have questions about your rights as a research participant or what to do if you are injured.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop.

Signing this document means that the research study, including the above information, has been described to you orally, and that you voluntarily agree to participate.

_____ _____

Signature of participant date

_____ _____

Signature of witness date

2. Recruitment of Study Cohort

2.1 General Issues of Recruitment

Patient recruitment is of prime importance to the success of this study. Listed below are points to consider on recruiting participants.

1. Emphasize the services provided. The trial provides a system of follow-up, which parallels the participant's private care, but does not conflict with it. This programmatic approach includes cooperation in general matters pertaining to medical care, special attention to risk factors, and the provision of health information. Approach potential participants more than once, if necessary. Emphasize the importance of the trial.
2. Be courteous and pleasant, and potential participants will respond positively.
3. Be professional and show interest and enthusiasm in the study.
4. Make sure that the potential participant fully understands the potential risks and benefits of the study. Explain all aspects of the study detailed in the participant brochure and informed consent document. Assure that the participant understands the information in the documents. Allow the participant sufficient time to consider and sign the informed consent document.
5. Potential participants may be told, "We don't know the answers, but here is a chance to help medical science."
6. Some potential participants will be motivated by stressing that the results may benefit their children and that they may have a chance to help society as well as themselves. Other advantages would be close follow-up from experts in relevant disciplines and increased knowledge and sense of involvement in their medical care.

2.1.1 Private Physician's Cooperation

1. Take the initiative in recruiting participants. Do not wait for referrals.
2. Mail a study brochure with a personal letter to physicians in the community requesting their cooperation.
3. Be non-threatening to the physicians. Ask permission to contact their patients and ask them to encourage their patients to enroll.
4. Don't expect these physicians to do the legwork for the trial.
5. Prepare a form letter to be sent out to private physicians thanking them for supporting the patient's interest in participation. Again, explain the objectives of ACCORD and discourage changes in study medications from those used as study interventions.
6. Provide unblinded laboratory results to the referring physician along with a summary of the participant's status.

It is important to reassure the referring physicians that their patients will be followed by ACCORD investigators for study purposes only and that they will be informed of the patient's status throughout the study. This will promote further referrals and cooperation during the study in notifying or obtaining information regarding events.

2.2 Contact with Referring Physicians

Investigator involvement and support is essential for successful recruitment in clinical trials. Although each clinical center will develop its own strategies, the most successful techniques involve personal contact with referring physicians. Possible strategies, which may be of assistance in recruitment on a study-wide basis, include:

- **Formal presentations** (Grand Rounds, Inservices, Research conferences)
- **Informal presentations** (housestaff rounds, informal clinic inservices)
- **Mailing of brochures, display of posters** in clinics and diagnostic labs,
- **Phone calls and /or conversations** with physicians soliciting referrals
- **Mass Mailings**-to targeted diabetic and or ethnic groups with high preponderance of diabetes
- **Consistent and frequent screening** in appropriate areas including setting up a system of logging in patients as staff sees patients and follow-up on regular basis with potential patients.
- **Data base searches** (ICD 9 codes, age and diagnosis, HbA1c values)

Again, it is important to reassure the referring physicians that their patients will be followed by ACCORD investigators for study purposes only and that they will be informed of the patients' status throughout the study. This will promote further referrals and cooperation during the study in identifying, notifying study personnel and obtaining information regarding events.

2.2.1 The Participant Brochure and Informed Consent

Multiple copies of a detailed patient recruitment brochure have been provided to each clinical site in ACCORD. The brochure describes in easy-to-understand language the purpose of ACCORD, what is expected of the patient, what the patient can expect from the study. You should carefully review the study requirements with the potential participant.

Some sites are using a separate informed consent for screening, which should be signed at the beginning of the first screening visit. The full study informed consent document must be signed at or prior to the first screening visit if a separate screening informed consent document is not being used. Principles of informed consent must be adhered to, which are described in section 4.5 of the ACCORD protocol and include a complete description of expectations, potential risks and benefits, and confidentiality. General informed consent guidelines are as follows:

1) Obtaining and documenting informed consent to IRB:
   a) The investigator should comply with applicable regulatory requirement(s) and should adhere to Good Clinical Practice.
   b) Written approval/favorable opinion of the written informed consent and any other written information provided to subjects.
2) Any revisions to the written informed consent form and written information should receive IRB approval/favorable opinion at each individual site.

3) The language used in the oral and written information, including the written informed consent, should be nontechnical and understandable to the subject or the subject's legally acceptable representative.
4) Offer ample time and opportunity for the participant to inquire about details of the trial and to decide whether or not to participate in the trial.
5) If either the subject or a legally acceptable representative is unable to read, an impartial witness (any competent person not affiliated with the study) should be present during the entire informed consent discussion. **Read all documents, including the informed consent.**
6) Obtain oral and if capable of doing so, a signed and dated consent from the subject or from the subject's legally acceptable representative.
7) The witness should also sign and date the consent form attesting to the accuracy of the document(s) and that coercion or undue influence was not used.

2.2.2 Posters for Publicizing ACCORD

These can be used in clinics, public spaces such as grocery stores, churches and pharmacies to encourage and remind participants about ACCORD.

2.2.3 Slide Set

Two generic slide sets will be provided. One will be directed to a professional audience and the other will be directed to a lay audience of either potential participants or advocacy groups.

2.2.4 Recruitment aids for minority and underserved populations

Minority/Women Recruitment -

Federal law mandates the proper inclusion of all racial and ethnic groups. Failure to include any racial ethnic groups is only acceptable if a disease process is not present in that specific racial ethnic group. The inclusion of all groups in an acceptable way presents a number of practical issues and problems.

Disease Burden -

The prevalence of many disease processes is frequently greater in racial and ethnic minorities. This is true of type 2 diabetes: there is an increased incidence of type 2 diabetes in Hispanics, Native Americans, and in Asians. It is quite appropriate to recruit these groups in excess of the specific proportions represented by these groups in the general population. This is a goal in ACCORD.

Barriers -

Credibility Gap - Medical establishment and government-sponsored projects frequently represent a credibility gap when members of minority groups are approached. Previous indignities and unethical medical studies have created an atmosphere of distrust and suspicion.

Language –

Every attempt must be made to make the language of consent forms and study forms as simple as possible so that language and level of education are not barriers for participant information gathering and participation.

Community -

It is important to have buy-in for ACCORD, especially in minority communities. In many minority communities there exists community-based organizations that served as power brokers between institutions such as University hospitals and research centers and residents. A negative attitude or response from those organizations can have a high negative impact on recruitment. However a positive response can be a huge benefit to recruitment and retention. Special attention should be paid to these organizations and extra attention given to the leadership in promoting ACCORD. Should the leader of any one of these organizations be a candidate for ACCORD, his/her participation should be encouraged.

Staff -

The inclusion of staff members who match up with the target population(s) by racial ethnic group represents one very concrete way in which trust building occurs. While these individuals need not have leadership roles, they must have meaningful roles on clinic staff. Especially in circumstances when new studies are being presented to communities with a preponderance of a specific racial ethnic group, public presentation (or a significant part of the program) should include a member of that racial ethnic group.

Volunteers -

All screenees are not enrolled in a clinical trial. Some of these people may be appropriate volunteers for clinical staff positions. There are documented roles for volunteers during recruitment and the follow-up portions of a clinical trial. These activities can be carried out in a good fashion and savings accrued with the use of volunteers. This may present an excellent opportunity to include members of a racial ethnic group in a visible role, or in a role with extensive contact with individuals considering enrollment in the study. Including these individuals in a meaningful role on the clinical staff should be an opportunity that is not lost. This is especially true if skilled members of a racial ethnic group are not available for employment on your staff.

2.2.5 Participant Identification /Medication Cards

The ACCORD ID card should be provided to the participant when enrolled and updated as needed with the instruction to keep it with them and to show it to other healthcare professionals who care for them. The card contains information about ACCORD, contact numbers, current medications, and important study values.

2.3 The Approach to Recruitment

2.3.1 Overview

It is anticipated that the majority of patients with treated type 2 diabetes will have been identified by chart review from the participating clinical centers in ACCORD in conjunction with the **Inclusion/Exclusion Summary Form.** It is also expected that much of the pertinent information (age, risk factor status, number of glycemic control drugs, etc.) will already be known. Any of the above information not attainable by chart review to determine a potential participant's eligibility will be considered part of the patient's routine medical management and will not be specifically reimbursed by the study.

Most of the information on exclusion and eligibility may already be in the patient's chart, and should be obtained prior to the patient's screening visit. Information that is unavailable or unable to be verified may be addressed during the first Screening Visit.

Screening visits with the ACCORD Study Staff will thus include introduction of the study to the patient, updating of the medical history, and reviewing glycemic, blood pressure and/or lipid eligibility. Visit time should be spent answering the patient's questions about the study.

2.3.2. ACCORD Recruitment and Retention Guidelines

RECRUITMENT STRATEGIES

Recruitment is challenging and vitally important to the success of a clinical trial. Retaining the participants for the remainder of the trial begins in the recruitment phase by enrolling the right participants.

Following is a brief description regarding development of a recruitment plan and strategies for recruiting and retaining ACCORD participants. In addition to this section, a manual called the ACCORD Survival Kit: Recruit – Retain – Resolve has been developed to assist you with valuable information and tools compiled from experience in other large clinical trials and the ACCORD Vanguard period. This manual will be provided to each site as an additional reference.

DEVELOP A RECRUITMENT PLAN

Identify staff involved with recruitment, review their responsibilities, and set regular meeting times.

Prepare an outline of your plan (brief but descriptive) in order to meet your designated randomization goal.

a. Determine the number of patients needed to screen per week in order to successfully enroll the specified amount (i.e., 2 per week plus number predicted to refuse or be ineligible).

Decide on the best system(s) at your site to promote referrals **FROM WITHIN** your office/clinic/institution.

a. Determine who will do chart reviews and when.
b. Flag the charts of possible eligible patients, as charts are pulled for routine visits the day of or day before. If eligible, notify coordinator – discuss ACCORD with patient.
c. Promote ACCORD among staff (See examples to follow)
d. Promote ACCORD among patients (See examples to follow)
e. If available, use computer lists of your age-eligible diabetic patients (by DM medications, HbA1C values, MI, CV surgeries, and various risk factors). Call, send letters, or flag charts for upcoming appointments.

Decide if **OUTSIDE PROMOTION** of ACCORD is appropriate. If so, prepare back-up strategies for utilizing various methods identified to follow (this includes deciding on a phone screening system and how to manage the new patients in your system). See the example within the ACCORD Survival Kit.

Discuss your plan with your Project Coordinator and Network Team, as they can provide extra assistance as needed.

Monitor your recruitment progress and revise your plan as needed.
a. Meet weekly as a team to discuss actual progress of your weekly goals. Increase the number of chart reviews each week as needed. Determine what is working and what is not. Review barriers and problems. Revise the plan as necessary.
b. Maintain a screening log for all patients screened. Input this via the web site to the Coordinating Center.

1. Stay involved and motivated – keep the momentum going!
   a. Keep your Network team informed. Share your ideas and problems. Keep your staff informed of your site's progress and thank them for their support and help. Recognize contributions of successful staff members.

The following are several strategies that may prove useful in recruiting and retaining ACCORD participants at your clinical site.

CHART SCREENING

Screen the charts of all scheduled patients to identify those who are of appropriate age according to ethnicity and seem to meet eligibility criteria for ACCORD.

- Use an ACCORD brochure to flag the charts of potential study participants and methods of contacting study personnel.

- Talk to the patient's health care provider (if you are not the primary provider) before the next appointment and offer to meet with the patient.

- Remind the patient of his/her appointment with a telephone call the day before the appointment.

- Make a notation of patients who seem to meet eligibility criteria for ACCORD but are not of appropriate age at this time but will be before the end of recruitment.

CLINIC SCREENING

- Make yourself available to talk about the project to the patient, friends, and family members while in clinic.

- Be prepared to provide the patient with information about ACCORD and set up a Screening Visit.

PHYSICIAN / NURSE REFERRALS

- Make physicians, nurses, and other health care providers inside and outside your practice aware of ACCORD. They can be a great source for participant referrals. Give out ACCORD eligibility pocket cards with clinical site contact numbers.

- Present ACCORD to your colleagues by placing flyers in their mailboxes, posters and brochures in common waiting rooms, clinic rooms, and nursing stations, as well as providing educational programs, grand rounds, and in-service meetings. Slide sets and/or overheads are available from the Coordinating Center or the web site.

- Obtain the appropriate permission/approvals before initiating recruitment efforts, particularly when screening outside practice. See sample letter to request support of physician to enroll patient.

- Establish a system for addressing referrals. Contact the patient promptly, and follow-up regularly with their health care provider, providing patient progress reports and appropriate test results.

- Post recruitment reports in prominent locations so colleagues are aware of your center's recruitment experience and its respective success on a regional and national level.

PARTICIPANT REFERRALS

- Encourage study participants to refer friends and family who appear to meet the study's eligibility criteria. Some of the most influential spokespersons for a study are the participants themselves.

- Provide general information and brochures to distribute to participants who are willing to tell friends and relatives about ACCORD.

- Insure that you discuss ACCORD with the primary care provider of any respondents from outside your practice. You must be sure that the potential participant and their health care provider are willing to make a long-term commitment to ACCORD.

TARGETED MAILINGS

- Discuss the topic of targeted mailings during your clinic's recruitment meetings and decide which clinic lists would be helpful (age-eligible diabetic patients by DM medications, HbA1C values, MI, CV surgeries, and various risk factors)

- Send potential eligible participants an ACCORD brochure and cover letter once you have gained the approval of the patient's primary health care provider.

- Follow-up with these patients while the project is fresh in their mind (no longer than a week after the original letter) to discuss ACCORD in more detail and to answer any questions that they may have. Do not leave it up to the patient to call you back.

- Send the potential participant a history and physical sheet to complete and bring back at their appointment so they can provide as much information about their medical and contact information as possible. Include a release of information form to obtain medical records from their primary care provider as well. See sample information sheets and release of information forms.

- Again, make sure to discuss the project with the patient's primary care provider before enrolling them in the screening process.

ADVERTISING WITHIN YOUR HEALTH CARE SETTING

- Make ACCORD a familiar name in your health care setting.

- Place articles in practice or hospital newsletters, hang posters and place flyers and brochures in clinics, cafeterias, lobbies, lounges and other areas where colleagues and staff gather. Also consider inter-office email and websites.

- Make use of any other source to continually bring ACCORD to the attention of the health care providers at your site so that ACCORD automatically comes to mind when they see patients.

- Provide ACCORD Eligibility Pocket Cards to all health care providers in clinic.

- Set up a display table in a high traffic area staffed by a study coordinator or physician offering study information.

EXTERNAL PROMOTION

- External promotion may be another method to recruit study participants although they must be more carefully screened than other methods.

- Remember that you must be sure that a potential screenee's primary care provider is supportive of their participation in the study before enrolling them in the screening process.

- Consider a paid advertising campaign or negotiate airtime for an ACCORD public service announcement (PSA) on radio and television stations in your area or arrange for a television/radio interview or newspaper article using the examples provided by the ACCORD Recruitment Subcommittee. It usually takes some time and effort to get PSAs on the air and to arrange for interviews and articles. If you are associated with a university, there may be a Public Relations department to assist you.

- Plan to provide adequate telephone coverage when using external promotions. You may not have the time to talk in detail to each person who responds to the promotion. At a minimum, however, you should thank them for calling, note their telephone number, and arrange to call them back for a more extensive discussion of ACCORD.

- Consider placing posters, when available, in various community sites where seniors or groups gather or conducting in-service programs or health fairs at the centers. Advertisements in local community newspapers, church bulletins, and targeted mailings of ACCORD brochures to residents in the community are other possibilities but again require more extensive screening for desirable participants than within your practice.

3. Screening and Baseline Visits

3.1 Initial Screening

Two sequences of screening or pre-randomization visits are described. One series would be used for those who are currently patients in the practices of the clinical centers within the network. A second sequence would be used for those who come from outside the clinical centers and are, therefore, less well known to the clinical center staff. A run-in procedure is required between the Screening Visits and the Randomization Visit.

3.2 Determining Eligibility

The patient's history must be thoroughly investigated and **applicable inclusion & exclusion clearly documented in the source documentation of the patient's study chart**. The criteria have been developed to define a particular patient population as well as protect the ineligible participants from unnecessary risks. Therefore careful consideration should be given to determining eligibility into the ACCORD trial. Costs of procedures and lab tests obtained to determine eligibility will not be covered by the study, with the exception of ECG and Point of Care (POC) HbA1c where the machines are provided for ACCORD participants. (If an HbA1c value is not available within the last 3 months prior to the randomization date, the Central Lab, DCA 2000, or an approved local lab can attain the HbA1c measure). ECG's and POC HbA1c's should not be billed. The following discussion provides an overview of the criteria contained on the Inclusion/Exclusion Summary Form that is used during the recruitment.

PART I. GENERAL INCLUSION CRITERIA

Applicable inclusion & exclusion clearly documented in the source documentation of the patient's study chart.

1. **Does the patient have a diagnosis of type 2 diabetes > 3 months as defined by 1997 ADA Criteria?**

   The participant must have source documentation of one of the following criteria with a copy filed in the patient's study chart to qualify for enrollment into ACCORD:

   - (fasting plasma glucose >126mg/dl (7.0mmol/l) **OR**
   - a 2 hour PC value in GTT > 200mg/dl (11.1 mmol/l)(confirmed by retesting) **OR**
   - symptoms of hyperglycemia plus history of PG > 200 mg/dL (11.1 mmol/L)

   a) Source documentation is not needed for anyone who says they have diabetes and whose history is compatible with type 2 diabetes, and has none of the secondary causes listed in Table 3.1 below and whose HbA1c is 7.5 % or higher. To be eligible for ACCORD, the participant must have type 2 diabetes. Patients with type 1 diabetes or other secondary type/causes of diabetes are not eligible.

Table 3.1:
Types of Diabetes Not Eligible for ACCORD*

Only patients with Type 2 diabetes are eligible for ACCORD.
Patients with the secondary type/causes of diabetes shown below are not eligible.

(*Adapted from Table 1 in: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 24 (suppl 1): S5-20, 2001.)

Type 1 diabetes

Other specific types of diabetes

A. Genetic defects of β-cell function
   1. Chromosome 12, HNF-1α (MODY3)
   2. Chromosome 7, glucokinase (MODY2)
   3. Chromosome 20, HNF-4α (MODY1)
   4. Mitochondrial DNA
   5. Other

B. Genetic defects in insulin action
   1. Type A insulin resistance
   2. Leprechaunism
   3. Rabson-Mendenhall syndrome
   4. Lipoatrophic diabetes
   5. Other

Diseases of the exocrine pancreas
   1. Pancreatitis
   2. Trauma/pancreatectomy
   3. Neoplasia
   4. Cystic fibrosis
   5. Hemochromatosis
   6. Fibrocalculous pancreatopathy
   7. Other

Endocrinopathies
   1. Acromegaly
   2. Cushing's syndrome
   3. Glucagonoma
   4. Pheochromocytoma
   5. Hyperthyroidism
   6. Somatostatinoma
   7. Aldosteronoma
   8. Other

Table 3.1 (continued): **Types of Diabetes <u>Not Eligible</u> for ACCORD**

Drug-or-chemical-induced

1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. β-adrenergic agonists
8. Thiazides
9. Phenytoin
10. α-interferon
11. Other

Infections

1. Congenital rubella
2. Cytomegalovirus
3. Other

Uncommon forms of immune-mediated diabetes

1. "Stiff-man" syndrome
2. Anti-insulin receptor antibodies
3. Other

Other genetic syndromes sometimes associated with diabetes

1. Down's syndrome
2. Klinefelter's syndrome
3. Turner's syndrome
4. Wolfram's syndrome
5. Friedreich's ataxia
6. Huntington's chorea
7. Laurence-Moon-Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader-Willi syndrome
11. Other

Gestational diabetes mellitus (GDM)

2. Has the patient's diabetes therapy been stable for > 3 months?

Diabetes therapy has been stable when the dose of any 1 antihyperglycemic drug has not changed by > two-fold (a dose can be doubled, just not more than doubled; and the dose can be halved, just not more than halved) and new agents have not been added within the previous 3 months. You may list the current therapy on the form in the shaded area to verify the regime. Note: A patient on no therapy can be considered to be on stable therapy if the time frame is 3 months or more. That is, the participant

does not have to be on pharmacological therapy. Any changes in the inclusion criteria influenced by Medical Nutrition Therapy (MNT) should be left to the discretion of the PI.

3. **Is the patient eligible by age and ethnicity?**
   - 40 to 79 years (inclusive) for anyone with a history of clinical cardiovascular disease (defined in protocol Chapter 2, Item #6A), or
   - 55 to 79 years (inclusive) for anyone without a history of clinical cardiovascular disease (defined in protocol Chapter 2, Item #6A).

4. **Does the qualifying HbA1c meet eligibility criteria by evaluation of the patient's current medication criteria? (Clinic POC or laboratory value within the last 3 months prior to the randomization date)**

   HbA1c:

   - 7.5 to 11%
     a) if on insulin $\leq$ 1 u/kg plus on 0 or 1 oral agent, or
     b) if not on insulin, on 0, 1, or 2 oral agents

   - 7.5 to 9%
     a) if on insulin $\leq$ 1 u/kg plus on 2 oral agents, or
     b) if not on insulin plus on 3 oral agents, or
     c) if on insulin > 1 u/kg plus 0 oral agents

     [Oral agents include: a) insulin secretagogues (sulfonylurea, meglitinides), b) biguanides, metformin c) insulin enhancers (thiazolidinediones) d) alpha glucosidase inhibitors]

   You will need to have the patient's qualifying HbA1c result as well as the patient's current medication regime to determine eligibility. If the patient does not fall into the categories listed above, even if the HbA1c is 7.5%, she/he is ineligible. For example, the patient is ineligible if taking insulin < 1 u/kg plus 3 oral agents, or if taking > 1 u/kg plus 1, 2, or 3 oral agents. The goal is to recruit patients who are likely to be able to achieve the ACCORD glycemic targets through further intensification of their pharmacologic therapy.

   The HbA1c result must be within the last 3 months prior to the randomization date. It will be evaluated at the clinic together with the glycemic medications the patient is currently taking to determine eligibility into ACCORD. [If there are 2 or more values available in the medical records, the most recent value takes precedence.] If a qualifying HbA1c value will expire before the randomization date (e.g. is older than 3 months prior to the randomization date) another HbA1c value must be obtained to determine eligibility.

CARDIOVASCULAR DISEASE HISTORY

The criterion in Part II are indicative of the presence of clinical cardiovascular disease demonstrated by previous events that classify the patients as secondary

prevention patients. **Applicable inclusion & exclusion criteria should be clearly documented in the source documentation of the participant's study chart.**

1. **Has the patient had a documented myocardial infarction > 3 months?**

   Documentation of an old or age-indeterminate myocardial infarction (MI) may be by one of the following: Q-waves on an ECG; akinesis or dyskinesis on echocardiogram, MUGA, or ventriculogram; prior hospital discharge diagnosis, significant cardiac enzyme test results. If enzyme tests for this particular MI were performed on more than one date, please enter the date of the total CPK, CK-MB, or Troponin-I that first document an MI, or verification from the primary or consulting physician that a MI has occurred. The date and location of the most recent MI may be listed on the source document.

2. **Has the patient had a documented stroke or cerebral vascular accident > 3 months?**

   Documentation of stroke may be by hospital discharge diagnosis, or by infarct on CT scan, a MRI, or verification from the primary or consulting physician that a stroke has occurred. Supportive evidence of the diagnosis (history and physical, discharge summary, or CT or MRI report) should be kept in the participant's chart.

3. **Has the patient had a documented coronary revascularization procedure > 3 months?**

   Identification of the specific type of coronary revascularization should be listed in the source documents with supportive evidence filed in the patient's chart. Some examples would be coronary artery bypass graft (CABG) surgery, stent placement, percutaneous transluminal coronary angioplasty (PTCA), rotoblation, or laser (LEAD) atherectomy.

4. **Has the patient had a documented peripheral carotid or arterial revascularization procedure?**

   Some examples would include carotid or peripheral endarterectomy, angioplasty, stent placement, atherectomy, bypass, or abdominal aortic aneurysm repair. Revascularization procedures not specifically listed under this criterion may be included under "other". The specific procedure, date, and location should be listed in the source documentation and copies of the hospital discharge summary procedure report kept in the participant's chart.

5. **Has the participant had angina with ischemic changes (ECG) or positive imaging on graded exercise treadmill (GXT) or pharmacologic stress study?**

   This can by identified with noninvasive cardiac diagnostic procedures such as:

   - Exercise testing- ST depression ≥ 1mm for ≥1 minute in 2 or more contiguous leads
   - Stress echocardiography- reversible wall motion abnormality
   - Stress nuclear perfusion study - fixed or reversible defect consistent with prior infarct or ischemia

   Note: These are largely semantic issues. When combined with GXT or pharmacologic stress, perfusion imaging can be performed with several nuclear

imaging agents, including Thallium, Myoview and others. SPECT refers to a type of image display, with computer generation to show the areas that do not take up the image agent. There is also a technique called planar image display that some diagnostic laboratories may use in some patients.

If a participant has had multiple tests of the same or different kind (e.g., a GXT and a thallium), use the most recent test result to answer this question.
A copy of the report should be kept in the participant's chart.

PART II. CARDIOVASCULAR SUBCLINICAL DISEASE HISTORY

The criteria in Part II are indicative of the presence of subclinical cardiovascular disease demonstrated by presence of the following conditions that also classify the patients as secondary prevention patients. **Applicable inclusion & exclusion criteria should be clearly documented in the source documentation of the participant's study chart.**

1. **Does the participant have evidence of micro or macro-albuminuria?**
   This is identified by protein in the urine as indicated on a urinalysis or dipstick of a urine sample within the past 2 years. The date and amount of protein should be indicated in the source document. The first step would be to check for macroalbuminuria by checking a spot urine sample. For the dipstick, if the reading is **1+** or higher, the patient would qualify for this criterion. If positive, continue screening. If negative, and needed to determine eligibility, send urine specimen for determination of microalbuminuria, payment for which will not be covered by study.
   (ADA guidelines indicate microalbuminuria can be determined by three methods):
   1. Measurement of albumin to creatinine ratio in a random, spot collection
   2. 24 hour collection with creatinine, allowing the simultaneous measurement of creatinine clearance
   3. timed (e.g. 4 hour or overnight) collection

2. **Does the patient have left ventricular hypertrophy (LVH) by ECG or echocardiogram criteria?**
   An ECG or echocardiogram used for this criterion must have been done within the last 2 years prior to randomization and a copy of the qualifying report kept in the participant's chart for verification.

LVH by ECG includes any one of the following:

- R amplitude in V_5 or V_6 > 26 mm.
- R amplitude in V_5 or V_6 plus S amplitude in V_1 > 35mm.
- R amplitude in aVL > 12 mm
- R amplitude in Lead I > 15 mm
- R amplitude in Leads II or III, or aVF > 20 mm
- R amplitude in Lead I plus plus S amplitude in Lead II1 > 25mm

- R amplitude in aVL plus S amplitude in V3 >28 mm for men or > 22 mm for women
- Computerized ECG machine documented LVH

For visual LVH reading, QRS amplitudes are measured in the *second to last complete normal beat* of the lead. A computerized reading indicating "borderline" or possible" LVH should be measured for the above listed voltage criteria and documented as such on the tracing. LVH by echocardiogram includes a combined wall thickness of 25 mm or more, which refers to the posterior wall plus the interventricular septum.

3. **Does the participant have a low ankle- brachial index (ABI) of < 0.9?**
   This ratio is indicative of advanced arterial obstruction and is obtained using Doppler ultrasound and a specific protocol. The measurements and date obtained should be listed in the source documents. If the procedure or report (performed in the past 2 years) is available to the clinic, this criterion can be utilized.

4. **Does the patient have ≥ 50% stenosis of a coronary, carotid, or lower extremity artery?**
   This would be documented by angiography, with the date and procedure listed in the source documents. A copy of the procedure report should be retained in the chart.

PART III. CARDIOVASCULAR RISK FACTORS HISTORY

The criteria in Part III are risk factors that indicate a high likelihood of a cardiovascular event in the future. Patients in this category are classified as primary prevention patients. **Applicable inclusion & exclusion criteria should be clearly documented in the source documentation of the patient's study chart.**

1. **Is the patient on lipid-lowering medication or has the patient had a LDL-C > 130mg/dL (3.38mmol/L) within the past 2 years?**
   List the most recent LDL-C result and date performed. Retain a copy of the report in the chart. If the patient is currently receiving lipid-lowering medication, be sure to document the therapy in the source documents. [If there are 2 or more values available in the medical records, the most recent value takes precedence].

2. **Does the patient have a low HDL, which is < 40 mg/dL (1.04 mmol/L) for males and < 50 mg/dL (1.29 mmol/L) for females, within the past 2 years?**
   List the most recent HDL result and date performed. File a copy of the qualifying result in the chart. (HDL and LDL values should both be taken from the same date.)

3. **Is the patient on BP lowering medication or has the patient had untreated SBP ≥ 140 mmHg or DBP ≥ 95 mmHg?**
   Refer to the patient's current BP medication status and currently measured BP to determine eligibility into the overall study. Additional criteria apply to qualify for the blood pressure arm of the study.

4. **Does the patient currently smoke?**

   If the patient is currently smoking cigarettes or has smoked in the past 30 days, the patient would meet these criteria. Document the patient's cigarette smoking history in the source documents. No other tobacco use qualifies.

5. **Does the patient have a Body Mass Index (BMI) of > 32 kg/m^2?**

   BMI is based on the weight/height ratio. You may also use the chart to calculate the BMI from the measurements you have taken on the patient. It is calculated by using the weight (in kg) and divided by the square of the height in meters. The formula to calculate BMI using a calculator is (Weight in kilograms)/Height in meters)^2 or BMI = [(Weight in pounds)/ 2.2046]/ [Height in inches)/39.37)^2] Document your calculations in the source notes.

PART IV. SUMMARY OF ELIGIBILITY CRITERIA

1. The patient must meet all of the criteria in Part 1 to be eligible. If not, the patient is ineligible at this time but you may consider re-screening at a later time.

2. The participant must have clinical CVD **or** at least one criterion from Part II, **or** at least two criterion from Part III in order to eligible for the trial. If not, the participant is ineligible at this time and you may consider be re-screening at a later time.

PART V. GENERAL EXCLUSION CRITERIA

The patient's history and physical must be verified to insure that none of the following exclusion criteria are present. Presence of at least one criteria must be documented. If any of the following are present, the patient is not eligible for ACCORD.

1. **Does the patient have a history of hypoglycemic coma/seizure within the past 12 months?**

   This indicates an unstable situation and the patient should not be enrolled at this time.

2. **Has the patient had hypoglycemia REQUIRING 3rd party assistance in the last 3 months WITH concomitant glucose < 60 mg/dl (3.3 mmol/l)?**

   This third party assistance may include family members, emergency medical staff (EMS) or emergency room personnel. The patient must have been unable to respond to the hypoglycemia without assistance. Remember both 3rd party assistance and documented hypoglycemia (< 60 mg/dl, < 3.3 mmol/l) must be present for exclusion.

3. **Is the patient's history consistent with Type 1 diabetes or types other than type 2?**

   A thorough review of the patient's medical record should detect this. It is important that we enroll only Type 2 diabetic patients. Patients with type 1 diabetes, (and/or those other types noted in Table 3.1), are not eligible for ACCORD.

4. **Is the patient receiving any ongoing medical therapy (systemic chronic use of corticosteroids and protease inhibitors) with known adverse interactions to the glycemic interventions**? If yes, then patient is ineligible.

5. **Has the patient had any cardiovascular event or interventional procedure, or been hospitalized for unstable angina within the last 3 months?**

   This would include MI, stroke, and revascularization. A 3-month waiting period insures clinical stability before initiating more aggressive treatment. If the answer is yes, patient can be rescreened after 3 months past the procedure or event if they meet all other criteria. (NOTE: An angiogram, is a diagnostic test rather than an interventional procedure, and therefore, by itself, does not render a patient ineligible).

6. **Does the patient currently have symptomatic congestive heart failure (CHF), or a history of NYHA Class III or IV CHF, or ejection fraction < 25% (by any method)?**

   Question the patient and review the records to insure that there are no symptoms or evidence of NYHA Class III or IV CHF, as listed below, at the time of enrollment.

   New York Heart Association CHF Classes
   Class I – No limitations of physical activity, ordinary activity does not cause symptoms.
   Class II – Slight limitation of physical activity, ordinary physical activity results in symptoms
   Class III – Marked limitation of physical activity, comfortable at rest but less than ordinary physical activity causes symptoms
   Class IV – Symptoms at rest

7. **Does the patient have any medical condition likely to limit survival to less than 3 years or a malignancy (other than non-melanoma skin cancer) within the last 2 years?**

   Patients with life-threatening diseases would likely lead to non-cardiovascular deaths during the study and therefore affect the power of the study to answer the questions.

8. **Is the patient on any immunosuppressive therapy (or had an organ transplant)?** If yes, the patient is ineligible. If a patient is on immunosuppressive therapy due to an organ transplant, the patient is ineligible. Patients with organ transplants may be placed on multiple medications to suppress organ rejection, some of which are known to have adverse interactions with glycemia interventions.

9. **Has the patient had > 10% weight loss in the last 6 months? If yes, then patient is ineligible.**
   If the answer is yes, this patient could conceivably be rescreened once patient's weight has stabilized if they meet all other criteria.

10. Does the patient have a Body Mass Index (BMI) of $\geq$ 45 kg/m^2?

These patients are considered morbidly obese and have a great deal of difficulty achieving the glycemic goals.

11. Does the patient have a serum creatinine > 1.5 mg/dL(132.6 μmol) obtained within the previous 2 months?

Since this is the upper limits for starting a patient on metformin, all patients should have a serum creatinine below this level to insure they can have any of the glycemic treatments allowed in the trial to achieve their goals.

12. Does the patient have a transaminase level > 2 times the upper limit of normal or active liver disease within the last 24 months?

Due to numerous medications used by these patients, it will be important to exclude people with active hepatitis cirrhosis and other causes of abnormal liver function studies.

13. Is the patient unwilling to do capillary blood glucose self-monitoring or unwilling to inject insulin?

It will be necessary for all participants, several times a day, to check their blood glucose levels at home and may be necessary for many participants to use insulin to achieve their glycemic goals.

14. Is the patient currently participating in another clinical trial?

Patients cannot be enrolled into ACCORD if already participating in another interventional clinical trial. Observational studies are acceptable. The screenee must wait until the completion of his or her activities in the other clinical trial before they may participate for ACCORD.

15. Is the patient living in the same household as an already randomized ACCORD participant?

People that reside in the same household cannot both be randomized into ACCORD.

16. Are there any factors likely to limit adherence to the trial interventions?

Examples would be dementia, history of alcohol or substance abuse in the last five years, plans to move or travel extensively within the next two years, history of unreliability in taking medications or keeping appointments, inability to commit to regular clinic visits over the course of the trial, significant concerns about participation in the study from the spouse, significant other, or family members, or lack of support from the primary health care provider. If the patient has any of these problems, please check (yes) and exclude the patient.

The importance of adherence to the protocol is crucial to the success of ACCORD. A patient may be eligible by all other criteria and will sign a consent form but be likely to subsequently refuse to take the prescribed medications or attend

clinic visits. It is in the patients' best interest as well as the study's that you evaluate their long-term commitment to carrying out the protocol.

17. Has the patient signed the informed consent for the ACCORD trial?

The full trial informed consent **MUST** be signed prior to or at Screening Visit 2 (the beginning of the run-in period).

18. Does the patient have recurrent requirement for phlebotomy or transfusion of red blood cells?

If yes, the patient is ineligible. Phlebotomy or transfusion changes the average life span of a red blood cell, limiting the hemoglobin HbA1c as an indicator of diabetes control.

3.2.1 Additional Eligibility Criteria for Participants in the Lipid Component of ACCORD

Patients eligible for the glycemic component of the trial will also be eligible for the lipid component:

- If the LDL-C 60 $\leq$ 180 mg/dl (1.55 mmol/l to 4.65 mmol) within the last 12 months, if not on lipid-lowering therapy or, if on a lipid therapy, less than the drug/dose-specific-cutpoints identified in Table 5.1 of Chapter 5 of MOP and on the Lipid Screening Form.

  and

- HDL-C less than 55 mg/dl (1.42 mmol/l) within the past 12 months for women or Black/African-Americans or HDL-C less than 50 mg/dl (1.29 mmol/l) for all other gender-race groups

  and

- Fasting triglycerides <750 mg/dl (8.47 mmol/l) within the last 12 months untreated or <400 my/dl (4.52 mmol/l) on lipid treatment.

NOTE: If these lipid values are obtained from a medical record, it should be documented as a fasting value. However, if the state is unknown and if the triglycerides < 750, the recorded values may be used. If the triglycerides $\geq$ 750, then a fasting sample needs to be drawn.

If 2 or more values are available in the medical record, the most recent value takes precedence.

The rationale for this limit is that patients with higher LDL-C often will require either the maximum dose of a statin (which might place them at higher risk for adverse events if randomized to a fibrate) or more than 20 mg of simvastatin to reach LDL-C goals. Thus, participants with baseline LDL-C levels $\geq$ 170 mg/dl (either untreated or estimated from the level on treatment) will be ineligible for the ACCORD lipid

intervention. The rationale for the HDL-C limits is that increasing HDL-C may have little effect among participants in whom HDL-C is already high. The triglyceride limits were selected for participant safety.

The additional exclusion criteria for the lipid intervention are:

- known hypersensitivity to statins or fibrates
- requirements for use of erythromycin, clarithromycin, or cyclosporine, systemic azole antifungals, or nefazodone or trazodone
- refusal to stop current lipid lowering drugs
- history of pancreatitis
- untreated or inadequately treated thyroid disease
- women who are breast-feeding or pregnant
- documented previous occurrence of myositis/myopathy
- pre-existing gallbladder disease in participants who still have a gallbaldder (e.g. history of gallstones)

SPECIAL NOTE: Do not forget that pregnancy and being of childbearing potential (and not using an effective method of birth control) are exclusion criteria for the overarching glycemia trial.

3.2.2 Additional Eligibility Criteria for Participants in the Blood Pressure Component of ACCORD

Patients eligible for the glycemic component of the trial will also be eligible for the blood pressure component: (See MOP Chapter 5, Section 5.3.1 for additional details)

- If the systolic blood pressure is between 130 and 160 mm Hg, inclusive, and the patient is on 0, 1, 2, or 3 antihypertensive medications, or
- If the systolic blood pressure is between 161 to 170 mm Hg, inclusive, and the patient is on 0, 1, or 2 antihypertensive medications, or
- If the systolic blood pressure is between 171 to 180 mm Hg, inclusive, and the patient is on 0 or 1 antihypertensive medication.

and

- If:
  dipstick protein in a spot urine is $< 2+$, or
  the protein-to-creatinine ratio in a spot urine is <700 mg/gm creatinine, or
  24-hour protein excretion is <1.0 gm/24 hours

For screenees who are not currently on blood pressure (BP)-lowering medication, there must be documentation of SBP ≥ 130 mm Hg on at least 2 occasions.

NOTE: Blood pressure eligibility is determined at the screening visits. Once eligibility has been determined, baseline values need not be consistent with the eligibility criteria (i.e. a baseline blood pressure is allowed to be out of range).

3.3 Tracking of Participants: Assignment of IDs and Acrostics

3.3.1 Overview

A label-generating program (called the Label Program) is contained on the Clinical Site computer and generates participant ID labels. This program is the only way that IDs can be obtained for participants in ACCORD. General descriptions of the capabilities of this program are contained in Sections 3.3.2 and 3.11.1. Section 3.11.3 contains specific details on how to use the ACCORD Label Program and figures containing examples.

Participant ID's take the form ABBC#####, where A is a number that references the Clinical Center Network (CCN) number, BB is a number that references Clinical Site (CS) number within CCN, and C##### is a 5-digit number preceded by an alphabetical character that references the participant within the study. A participant's ID follows the participant throughout ACCORD screening and follow-up visits. If a participant changes CCN or CS, then the first two prefixes (A and BB) will change to reflect the new status. Specifically, the last 6 digits of an ID will follow a participant throughout the study.

Clinical Site's are assigned a unique block of screening IDs used by the Label Program to generate labels. When using the Label Program, ID's for use in initializing participants into the study will be obtained from pages of labels containing 30 unique participant IDs (screening labels). An example of a valid ACCORD ID is 101A00001. This number would reference a participant screened in CS #01 within CCN #1.

An identifying acrostic will also be used within clinics to aid in situations where pages of forms become detached from the remainder of forms. The acrostic will consist of the first three letters of the last name, plus the first two of the first name, plus the middle initial. It should be hand written on the top of every form. If there is no middle initial, then the acrostic should be filled with a dash "-". An example of a valid acrostic for John S. Smith would be "smijos". If Mr. Smith did not have a middle initial, then the acrostic would be "smijo-".

You will be able to print additional labels containing a participant's ID. These can also be placed on each page of multi-page forms if placement of the labels does not interfere with data that has been written on the form.

3.3.2 Obtaining an ID for a Participant

The first step in assigning participant IDs requires you to print screening label batches or pages. The thirty sequential screening labels specific to each CS is printed per page. Each label contains a unique participant ID and a barcode that can be scanned. Each participant that is screened is given a screening label to be placed on the participant's Inclusion/Exclusion Summary Form.

When printing these labels you must identify the number of batches (pages) of 30 labels that should be generated. Once a page of unique IDs has been printed, you will be unable to reprint this group of unique participant IDs.

3.4 Existing populations in the clinical center practices

Medical record searches or reviews of existing data bases can be done initially by setting up the searches using the variables that match with the final list of the inclusion/exclusion criteria. Additional "hand searches" may be necessary using the remaining inclusion/exclusion criteria not already part of the data base but part of the patient's existing clinical record. It is expected that all or most all of the inclusion/exclusion criteria will be available in the medical record. Medical record review will be used to begin the process of completing the Inclusion/Exclusion Summary Form, the Blood Pressure Trial Screening Form and the Lipid Trial Screening Form.

3.5 Individuals recruited outside existing clinical center practices

Individuals identified by any media strategy or are otherwise identified outside of the practice of the clinical center will have to be appropriately screened. While it is recommended that no general screening of the population for abnormal fasting glucose levels be entertained until all other approaches are substantially exhausted, referrals from health fairs or community screenings conducted by others may be a useful source. The Inclusion/Exclusion Summary Form, the Blood Pressure Trial Screening Form and the Lipid Trial Screening Form can also be used to screen potential participants by telephone to determine who might be asked to attend a screening visit.

3.6 The Screening Visit

Participants will be scheduled to attend the initial screening clinic visit. Participant will be instructed to fast for Lipid profile if applicable and should bring current medications, any SMGB records, support person or significant other to the visit. During the visit, the following procedures will be conducted:

1. Review protocol and obtain full-scale informed consent.
2. Review all data collected during the prescreening process with the participant.
3. Determine eligibility status for the Glycemia, Blood Pressure, and Lipid trials.
   a. Review and record all current medications.
   b. Check BP, height and weight for use in screening.
4. Measure and record HbA1c. The qualifying HbA1c value must have been obtained within 3 months prior to the randomization date. For screening purposes, obtain HbA1c values from the following sources:
   - From medical records (value obtained within the last 3 months).
   - From a local laboratory that holds a CLIA-certificate.
   - From the ACCORD Central Laboratory
5. If provisionally eligible, explain the additional screening procedures to the participant. If ineligible, thank the participant for his/her time. Refer to Tracking Ineligible Screenees [See MOP Section 3.8]

6. Perform a phlebotomy to obtain blood samples, process and ship to the Local Lab for measurement of ALT, creatinine, and lipid profile to determine eligibility criteria. Measurements of ALT, and the lipid profile recorded in the clinical record during the previous year may be used for eligibility purposes. Measures of creatinine levels must be within 2 months of the anticipated date of randomization in order to determine eligibility. If no creatinine level is available, one can be drawn at the screening visit, which can be processed either locally or at the Central Lab. ACCORD does not reimburse for local tests done to determine eligibility.
7. Measurement of microalbuminuria recorded in the clinical record during the previous 2 years may be used to determine eligibility purposes. A spot urine sample dipstick test for proteinuria can be performed first to detect gross proteinuria. If negative and needed for eligibility a urine sample will be obtained, processed and submitted to the Local Lab for measurement of microalbuminuria. ACCORD does not reimburse for local tests done to determine eligibility.
8. Results from an ECG done during the previous 2 years may be used for eligibility purposes. An ECG will be obtained and reviewed locally as needed to determine eligibility criteria.
9. If eligible at this time, proceed with Run-in (if necessary; see Section 3.9) as follows:
   a. Instruct participants to measure and record SMBG values for the run-in period.
   b. Dispense glucose meter, Screening Period Glucose Diary, and sufficient strips for the run-in period. (**US Sites follow the NetGroup Diabetic Services procedures** found at the end of this chapter.)
   c. Make an appointment for the next visit. Instruct participant that the baseline visit will take 2-3 hours or longer if assigned to substudy.
   d. Remind participants to bring all their medications, logbooks, and meters to each visit.
10. Complete the following forms and enter data as required:
    a) **Participant Contact Information Form**
    b) **Inclusion/Exclusion Summary Form**
    c) **The Blood Pressure Trial Screening Form**
    d) **Lipid Trial Screening Form**
11. To save clinic time, it is recommended that the forms be completed and data entered prior to the participant returning for the baseline visit.
12. If eligibility criteria not yet complete (awaiting lab values or medical records), schedule Screening Visit 2 only when adequate documentation of criteria is available.

NOTE: For all potential participants who have an in person clinic visit for screening, the minimum data collection and data entry for screening data are items 1 through 11 on the **Inclusion/Exclusion Summary Form**. If the screenee is eligible at that point, continue to use the screening forms until the screenee is found to be eligible or ineligible and enter all data collected.

3.7 Re-Screening Previously Screened Participants

If a patient has been screened previously for the main trial and found to be ineligible, re-screening may be performed if in the judgment of the screener, the patient

may meet the eligibility criteria at a later date. The patient will retain the same ID number that was initially assigned for the main trial. No new ID number should be assigned.

If the patient was screened previously during the Vanguard Phase and is now being re-screened for the main trial, a new ID number must be assigned to the patient and retained for the remainder of the trial.

In instances where a patient is either re-screened or the screening process has been prolonged (i.e., more than 1 month), all eligibility criteria should be reviewed and updated if necessary. During this review, particular care should be taken to discern if diabetes therapy changed or if any new CVD events or procedures occurred since the time of initial screening. Remember that diabetes treatment must be stable for 3 months or more, and no new CVD events or procedures should have occurred within 3 months of randomization.

3.8 Tracking Ineligible Screenees

The **Inclusion/Exclusion Summary Form** is to be completed and data entered from items 1 through 11 for patients who are enrolled in ACCORD. It has been designed to serve as a worksheet to keep track of where potential participants are in the screening process. It will also serve to collect limited data on individuals who are screened for the study, but are not enrolled. These data will tell us some characteristics of the people who were NOT eligible for the trial, a requirement for describing the trial to other researchers and for journal publications.

For the Inclusion/Exclusion Summary Form for ineligible screenees, sites will be instructed to:

- Complete items 1-11 on the Inclusion/Exclusion Summary Form for every patient who comes in to the clinic for screening.
- If the patient is eligible through item # 11, continue until form is either complete (and patient is eligible) or until ineligibility is found.
- All Inclusion/Exclusion Summary Forms (partially or fully) completed should be data entered at the clinical sites.

3.9 Pre-Randomization Run-In Procedure

The extremely complex nature of the trial suggests that a pre-randomization adherence screening measure would be useful. Potential participants will be asked to provide evidence that they can routinely monitor their capillary blood sugars. This evidence may be from a diary, a self-monitoring blood glucose (SMBG) device that they bring to the clinic, or, if such retrospective data cannot be presented, then the screenee must prospectively go through a 2 to 4 week pre-randomization run-in period. If the data are obtained from a diary or from a SMBG device, then at least 2 weeks data must be available and the screening visit cannot occur on the same day as the randomization visit. Evidence of dietary and exercise regimen implementation will be expected although formal criteria on these issues for randomization are not identified. One recycling period should be allowed for appropriate indications in those individuals who fail to complete the run-in period on the first attempt.

If a prospective run-in is necessary, the patient should be instructed to take the glucose diary home and complete it for each day documenting the two times they tested their blood glucose each day and marking the value for each. An appointment will be made for approximately two weeks later and the patient will return with the diary completed. **To be considered a good candidate for ACCORD, it is suggested that blood glucose testing adherence be at least 80% of the prescribed times.** Adherence is calculated as:

Adherence = # times blood glucose is tested / # of times testing is expected

Ideally, the glucose meters used can be checked directly using the memory to assess adherence to the times prescribed by the study staff.

3.10 Baseline Visit

Participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening) They should not take their glycemia or lipid medications (if applicable) on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records, and support person or significant other with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic (if applicable). During the visit, the following procedures will be conducted:

1. All data collected during the screening process will be reviewed.
2. Verify eligibility status for Glycemia, Blood Pressure, and Lipid trials (including occurrence of events that may prohibit patient from participating).
   a) Review and record all current medications including OTC and herbal remedies.
   b) Review, evaluate and calculate the percentage of participant's compliance with at least 2 weeks of SMBG monitoring as part of the run-in procedures.
   c) Assure that the qualifying HbA1c value was obtained within the last 3 months prior to the randomization date.
3. If ineligible, the participant will be thanked for their time and dismissed from clinic.
4. If eligible, proceed with randomization process:
   a) Verify that the full-scale informed consent form has been obtained and signed and HIPAA authorization obtained.
   b) Obtain and perform baseline history and physical exam, including demographics, medical history, concomitant medications, weight, height, waist circumference, visual acuity, and foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
   c) Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completes all items before end of visit.
   d) Verify that all information on the **Inclusion/Exclusion Summary Form, Blood Pressure Trial Screening Form,** and **Lipid Trial Screening Form** is complete and correct both on the forms and in the computer.
   e) Click "Randomize pt" on data entry screen. A pop-up screen will appear to remind staff to provide the participant with Eye Sub-study and MIND Sub-study

(Canada, Western, Minnesota/Iowa, Ohio/Michigan, Northeast, and Southeast CCNs) introductory materials.

f) Input the percent of participant's report of compliance for SMBG.

g) Verify that the **Baseline History and Physical Exam Form** has been completed.

5. The participant will be assigned a treatment regimen. The randomization screen will display this information and list target dates for the follow-up visits. It is recommended that the participant's treatment assignment and visit schedule be printed out and filed in their research record.
6. **All Participants:** Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, ALT, Creatinine, Lipid Profile, CPK and for storage of additional aliquots (where approved).
7. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Lab.
8. An ECG will be obtained and sent to the ACCORD ECG Reading Center. Retain a copy for records.
9. Refer to appropriate randomization cell (Chapter 7) for further procedures required at this visit.

NOTE: If ACCORD is dispensing any study therapy (for any of the 3 interventions) to a participant, that participant is considered active and the respective management forms should be completed.

3.11 Initialization of Data Entry

Scanning the label on the top of the form initializes data Entry of all forms. This ensures that the ID is correctly placed in the database. Since both the label and the form have the acrostic written on them, comparison of these two entries is a good check that the correct label has been placed on a particular form. The data entry application checks the encoded acrostic versus the one that is entered at the top of the form and alerts the user if a discrepancy arises.

3.11.1 Initial Entry of Contact Information into the Label Program

Once a participant has been assigned a screening label, the next step is to enter the participant contact information. It is necessary to enter a minimal amount of information about the participant into the Label Program in order to generate labels for future visits. The only required information for the Label Program to print participant visit labels is the Patient ID, the acrostic, the date the form was completed and the identifier for the person entering the data. Other participant contact information can be entered at this time in the areas given. All the other information that is entered and saved can later be retrieved and is only for the local use of the Clinical Site. It is to be entered only if the Clinical Site finds this aspect of the program useful.

3.11.2 Printing of Visit-Specific Labels for Placement on Forms

After the participant contact information has been entered, the CS personnel have the option of printing a page of labels. These labels have the participant ID, acrostic and a visit ID encoded into the barcode. Also printed on the label will be the participant ID, acrostic and visit ID that corresponds to the barcode for easy identification.

The labels are to be placed on the top of all forms and one can be placed on the front of a participant's chart to facilitate easy scanning of the participant ID for generating labels for future visits.

3.11.3 Instructions for Use of the ACCORD Patient Identifier Labeling Program

1. Starting the Program

To start the ACCORD Label Program, use the mouse to place the cursor on the fox face (icon) located on the clinic PC screen and double click to start the program. This application is labeled "Shortcut to the acctrak". A blue screen with a menu bar will appear on the top of your screen. The first option on the menu bar will be "Action".

2. Choices

When the "Action" option has been selected by clicking on it, seven choices will appear. These choices include:

a) Print Screening Label Batches
b) Participant Contact Information
c) Print Participant Visit Labels
d) Print Participant Labels - Short
e) Software Setup
f) Print Software Setup Report
g) Exit

3. Printing Participant Screening Label Batches

The first step in assigning participant IDs requires you to print screening label batches or pages. The page contains thirty sequential screening labels specific to each CS. Each label contains a unique participant ID and a barcode that can be scanned. Each participant that is screened is given a screening label to be placed on the participant's Inclusion/Exclusion Summary Form (see Chapter 21 Forms).

To print these labels:

a) Select the *Print Screening Label Batches* option
b) Enter the number of batches (pages) to Print
c) Click Print
d) Make sure label stock is correct and answer yes when prompted

Once a page of unique IDs has been printed, you will be unable to reprint this group of unique participant IDs.

Figure 1 shows the screen of the Label program that is used to print screening labels and Figure 2 contains an example page of screening labels.

Figure 1. Screen for Printing Batches of Labels

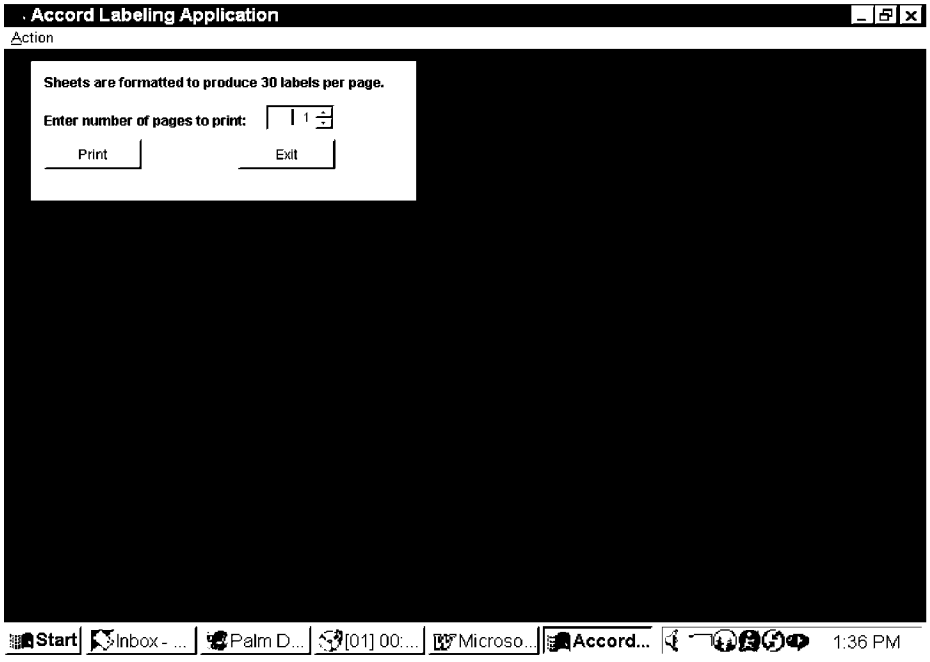
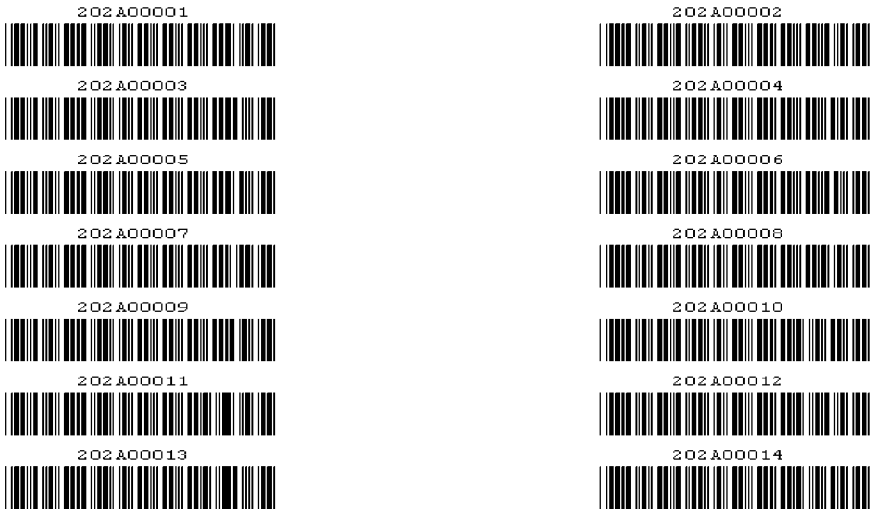


Figure 2. Example Screening Labels (CCN=2, CS=02, Patients A00001-A00014)



4. Entering Participant Contact Information

Once a participant has been assigned a screening label, the next step is to enter the participant contact information. To enter the contact information, select the *Participant Contact Information* option. It is necessary to enter a minimal amount of information about the participant into the Label Program in order to generate labels for future visits.

The steps to entering contact information for a participant are:

a) Select the *Participant Contact Information* option
b) Select Add to enter a new Participant ID (make sure your cursor is in the Patient ID field)
c) Scan in Participant ID from the Screening Label
d) Type in the Acrostic
e) Type in the date that the form was completed
f) Identify who the information was entered by (assigned number)
g) Enter other contact information
h) Click Save

The only required information for the Label Program to print participant visit labels is the Patient ID, the acrostic, the date the form was completed and the identifier for the person entering the data. Other participant contact information can be entered at this time in the areas given. All the other information that is entered and saved can later be retrieved and is only for the local use of the Clinical Site. It is to be entered only if the Clinical Site finds this aspect of the program useful.

In order to retrieve a participant from the Participant Contact Information:

a) Select the *Participant Contact Information* option
b) Select Find
c) Scan in the Participant's ID
d) Select the Participant to be retrieved
e) Click on Retrieve

Once the participant has been retrieved you may then edit the information by clicking on Edit.

Figure 4a. Part A of ACCORD Participant Contact Information Form

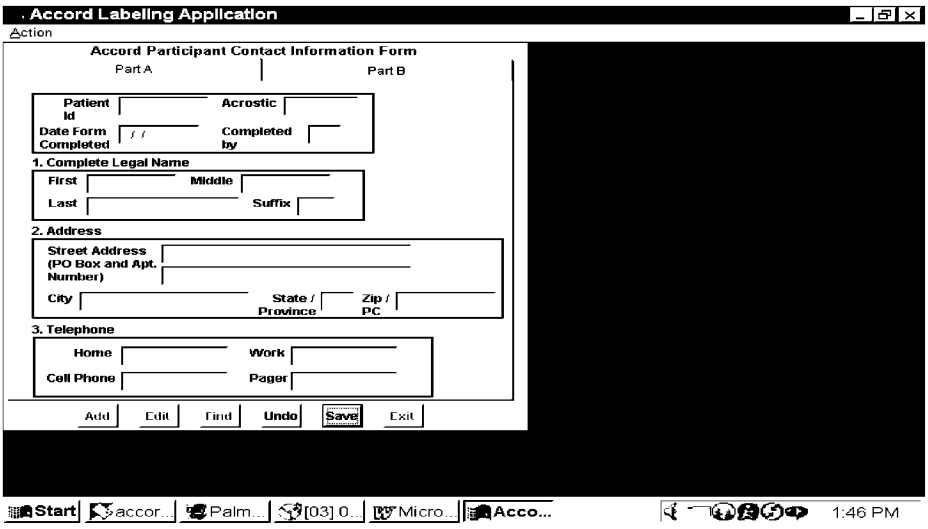
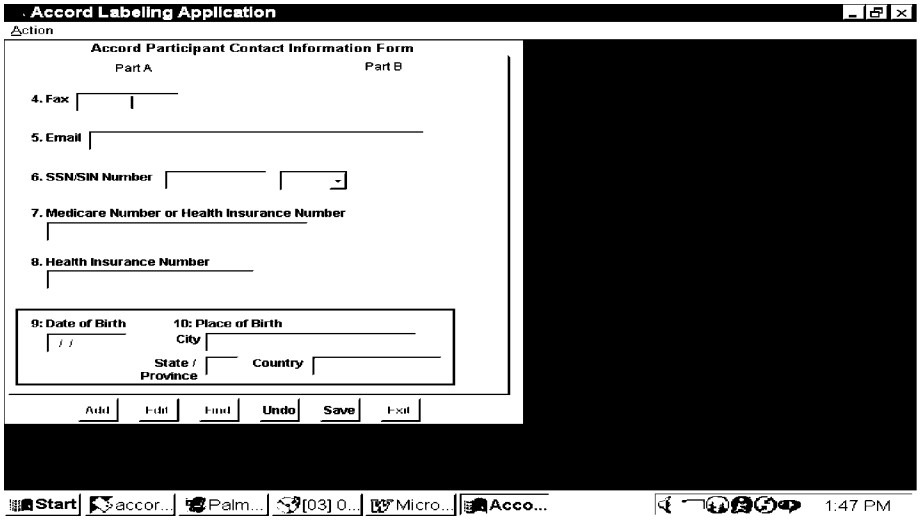


Figure 4b. Part B of ACCORD Participant Contact Information Form



5. Printing Participant Visit Labels

Once the participant contact information has been entered, the CS personnel have the option of printing a page of labels that is visit specific for use on all forms filled out at each visit. These labels have the participant ID, acrostic and a visit ID encoded into the barcode. Also printed on the label will be the participant ID, acrostic and visit ID that corresponds to the barcode for easy identification.

To print participant visit labels for all visits, following the process listed below:

a) Select the *Print Participant Visit Labels* option
b) Scan any previous participant label
c) Select the upcoming visit for the participant in the drop-down menu
d) Click *Print Labels* to print the page of visit-specific labels

The labels are to be placed on the top of all forms and one can be placed on the front of a participant's chart to facilitate easy scanning of the participant ID for generating labels for future visits. *Once labels are printed for a specific follow-up visit, these labels will not be printed again unless the user enters a previous visit code and overrides the decision of the computer.*

Figure 5. Screen for Printing Participant Visit Labels

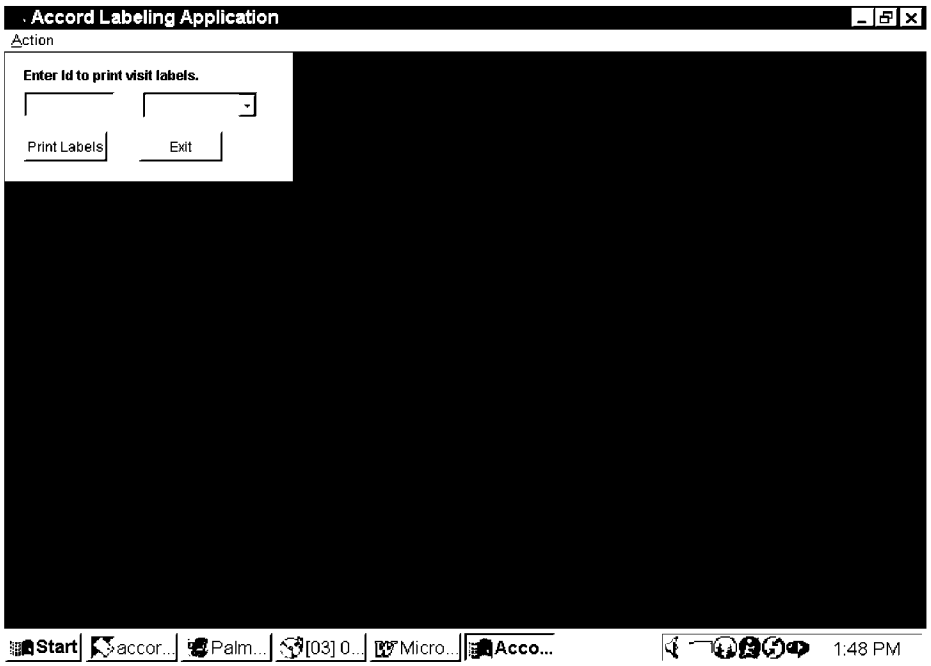


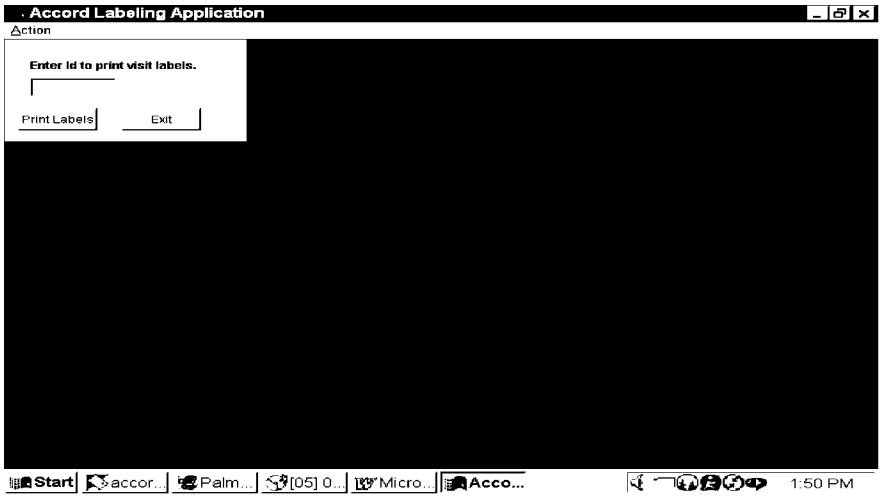
Figure 6. Example Visit Labels for the 8-Month Follow-Up Visit

6. Printing Participant Visit Labels - Short

The short participant visit labels are coded for the short visits (F00.5, F01.5, F02.5, etc.) only. All of the short visit labels are printed at one time. To print participant visit labels for all short visits, follow the process listed below:

a) Select the *Print Participant Visit Labels - Short* option
b) Scan any previous participant label
c) Click *Print Labels* to print the pages of short visit-specific labels

Figure 7. Screen for Printing Participant Visit Labels – Short



7. To Exit the Label Program

To exit the Label Program, click on *Exit* under the Action menu.

Action to Control Cardiovascular Risk in Diabetes
ACCORD

NetGroup Diabetic Services

ACCORD Blood Glucose Product Distribution Program

Site Coordinator Information

(revised 07/21/04)

ACCORD has entered into agreements with Abbott Laboratories, MediSense Products and NetGroup Diabetic Services for provision of Precision Xtra™ blood glucose monitoring supplies to ACCORD participants. Details of this mail distribution program follow. The Participant Information Sheets included in this mailing provide some additional detail as well.

- All participants who join this Program will receive a Precision Xtra Blood Glucose Monitor. Precision Xtra Test Strips, MediSense Control Solution and lancets will be shipped to each participant's home on a quarterly basis, regardless of their insurance coverage status. A new spring powered lancing device will be provided to each participant every six months and batteries will be provided every 12 months.

- Participants will be required to provide insurance information and sign an Assignment of Benefits (AOB) form. NetGroup will submit insurance claims for reimbursement. THE PARTICIPANT WILL NOT BE BILLED FOR ANY SUPPLIES, OR FOR CO-PAYS OR DEDUCTIBLES.

- ACCORD will provide meters, test strips and supplies to participants who are verified as uninsured.

- NetGroup has received a Department of Health and Human Services Advisory Opinion, which allows a waiver of co-pays and deductibles. This waiver will be applicable ONLY for ACCORD study participants who are participating in the NetGroup Distribution Program.

Site Coordinator Responsibilities

1. Provide each ACCORD participant with a Participant Information Sheet (provided to sites by NetGroup).

2. Assist study participants in completion of the Unified Form including all necessary insurance information and signing the Assignment of Benefits (AOB). NetGroup will provide all forms and instructions to your site.
3. Complete the physician information and medical order portions of the Unified Form and obtain a physician/NP/PA signature, UPIN, DEA# and date. Please note: If the participant is a member of the Vanguard group and has already received an Xtra meter, please check the box indicating "Vanguard meter provided" in the Notes/Special instructions area (Section 4). Please note: For qualified participants who don't have insurance, please check the box indicating "PUI" (Patient Uninsured) in the Notes/Special instructions area (Section 4). Please note: For VA sites whose participant(s) does not have insurance, please write VA in the Notes/Special instructions area (Section 4). Falsification on these requests (indicating patient is uninsured when they do have billable insurance) is a punishable offense.
4. Fax completed forms to NetGroup via the ACCORD designated Fax Line @ . The participant should receive their Precision Xtra monitor and beginning supplies at their home within approximately five (5) business days from receipt of the complete form.
5. Complete and return all NetGroup requests for shipment authorization (Refill Request Forms) (once per quarter for each participant) and renewal physician orders (annually).
6. If you need to change testing frequency prior to receiving an annual renewal of physicians orders, simply call and a new order will be faxed to you for documentation of changes. A blank DO form has been provided if you prefer to complete and fax to NetGroup instead of calling.

NetGroup Responsibilities

1. Provide appropriate product quantities for each participant. Quantities will be based upon the frequency of testing the physician has ordered.
2. Send shipments every three months to all qualified participants.
3. Answer all participant and site personnel questions as received on the 800 number.
4. Provide each site with a monthly list of study participants who are due to receive a quarterly shipment during the following month. Site

coordinators will select all participants who should continue to receive products and return the report to NetGroup.
5. Provide annual physician orders to sites for signature.

Qualified Participants who need a meter and supplies for run-in

1. Site Coordinators should contact NetGroup via telephone, email or fax with the name and participant ID# immediately when a Run-In meter is dispensed. A replacement meter will be shipped to the site by the next business day.

2. Determine that the patient has met all other eligibility criteria to be randomized. All screening forms must be completed and the ACCORD consent form must be signed. In addition, the patient must also complete the patient information needed on the NetGroup form, but this paperwork should not be sent in until after the run-in is complete.

3. Provide the patient with a meter, strips and lancets to complete a 2 week run-in from the supply at your site. This run-in can be repeated once if the patient does not demonstrate adequate SMBG testing.

4. **If the patient passes run-in then randomization can occur and the paperwork should be completed and mailed with "run-in meter provided" checked in the Notes/Special instructions area (Section 4). The rest of the form indicating frequency of testing should also be completed. This will generate a replacement meter to be sent to your site and will start the process of supplies going directly to the participant. In order to expedite replacement, you may notify NetGroup via fax, email or telephone. Please provide the patient's name and Participant ID#.**

5. **If the patient does not pass the run-in and will not be enrolled into ACCORD, the patient still keeps the meter and you should notify NetGroup via fax, email, or telephone. Please provide the patient's name and Participant ID#. Your meter will be replaced at your site.**

Action to Control Cardiovascular Risk in Diabetes
ACCORD

NetGroup Diabetic Services

Blood Glucose Products Mail Distribution Program

Under an arrangement with Abbott Laboratories, MediSense Products, the ACCORD study is able to make blood glucose testing supplies available to all study participants, regardless of insurance status. Using the designated mail distribution provider, NetGroup Diabetic Services, eligible participants will receive a Precision Xtra™ Blood Glucose Monitoring System and quarterly home shipments of Precision Xtra Test Strips, lancets and MediSense Control Solutions for the duration of their participation in the study.

In this mailing you will find an ACCORD Site Coordinator Information Sheet **that provides details of this unique program. Please read it thoroughly to acquaint yourself with how the program will work. This arrangement with MediSense makes it possible for all participants to initially obtain a Precision Xtra Blood Glucose Monitor at no charge and to receive ongoing supplies without responsibility for co-payments or deductibles related to glucose supplies. For those participants who do not have any coverage for glucose supplies, the study will be reimbursing NetGroup for the test strips provided. MediSense and NetGroup will provide free meters, lancets and control solutions for this population.**

Enrollment in the program is as simple as filling out the NetGroup Unified Form, a completed example of which is provided for you in the ACCORD NetGroup Binder.

- Have the participant fill out the Patient Information (section 1).
- Have the participant complete the Patient Insurance Information (section 2) OR attach a front/back copy of the participant's insurance card(s).
- Have the participant sign the AOB (Assignment of Benefits) statement (section 6) if they have insurance.
- Complete the Doctor's Information (section 3).
- Fully complete the Doctor's Order (section 7) and have it signed by a physician, nurse practitioner or PA.

- Send completed form to NetGroup in the postage-paid envelope provided. Upon receipt, an initial shipment will be processed for each participant and will arrive at their home by USPS Priority Mail.

If you were unable to attend one of the Glucose Product Mail Distribution Program training sessions at the recent Investigator's meeting in Charleston, please contact NetGroup ( ) to request a training binder with sample forms and complete instructions.

We are also providing copies of **Participant Information Sheets**. Every ACCORD study participant should be given one of these to read prior to completing the enrollment forms. This mail distribution program will be the only way for ACCORD participants to have their glucose monitoring devices and supplies provided by ACCORD. Any participant who elects to continue obtaining glucose monitoring supplies through their usual retail channels will also retain responsibility for all co-pays and deductibles.

Participation in this program is voluntary; however, you should be aware of the benefits for both individual participants and for the Study in general:

- ***Participants will not be responsible for co-pays or deductibles related to glucose supplies as long as they are participating in the ACCORD study.***
- ***Participants who do not have coverage for glucose testing products will receive all their needed supplies during the study.***

A Special Note:
Some sites will have a site supply of meters, strips and lancets to address the "2 week run-in" required prior to randomization for those people who do not already have a meter of their own, and meet all other eligibility criteria to enroll in ACCORD. Please refer to the Site Coordinator Information Sheet for this process.

Action to Control Cardiovascular Risk in Diabetes
ACCORD

NetGroup Diabetic Services

ACCORD Blood Glucose Product Distribution Program

Participant Information

What is the Program?

The Program consists of mail delivery of blood glucose supplies to your home every three months by NetGroup Diabetic Services. Approval for the waiver of co-pay which was granted by the Department of Health and Human Services, has made this program possible for individuals who have coverage. A claim will be sent to your insurance provider for the supplies provided to you. There will be no billing for deductibles or co-payments for glucose testing supplies because NetGroup has obtained an official waiver from the U. S. Government. If it has been verified that you do not have insurance coverage then ACCORD will also provide you with necessary strips and supplies.

Will I get any communication from my insurance company or Medicare?

Every time NetGroup files a claim on your behalf for the testing supplies it has shipped to you, your insurance carrier will send you an Explanation of Benefits (EOB). This document is intended to inform you whenever anyone files an insurance claim in your name. ***IT IS NOT A BILL!*** This document is intended to prevent fraud and is for your information and records only.

Why should I participate in this Program?

There are two very good reasons for you to participate.

1. The convenience of receiving all needed testing supplies right at your home.
2. People using the Program will not be responsible for any co-payments or deductibles related to glucose testing supplies.

What is NetGroup Diabetic Services?

NetGroup is a diabetes supplies provider, that have been chosen by the ACCORD study as the strips and supplies mail distribuor for ACCORD.

What brand of products will I be getting?

Each Program participant will receive a Precision Xtra™ Blood Glucose Monitor, manufactured by Abbott Laboratories, MediSense Products. Quarterly supplies will include Precision Xtra Test Strips, MediSense Control Solutions and lancets. Once every six months you will also receive a new spring-loaded lancing device.

What quantity of supplies will I receive?

The number of test strip and lancets you receive will depend on the frequency of testing ordered by your ACCORD physician when you sign up for the Program.

For example, if your physician wants you to test three times a day, you will need 270 test strips and lancets each quarter (3 months). Since Precision Xtra Test Strips come in boxes of 50, you will receive six boxes every three months. Lancets are packaged in boxes of 100, so you will receive three boxes each quarter.

What information will I need to provide to NetGroup company?

Each ACCORD participant who has insurance coverage and wishes to benefit from the Program must provide insurance information and give NetGroup permission to bill your insurance (Assignment of Benefits). The ACCORD clinical sites will have standard forms available for this purpose. After you have completed your information and signed the form, the clinical site coordinator will obtain the doctor's order information and signature and send the completed packet to NetGroup. If we verify that you do not have insurance, ACCORD will provide you necessary strips and supplies. Since this is a voluntary program, if you are unable, or unwilling to provide the contact information needed by Netgroup, supplies will not/can not be provided to you and you will be responsible for obtaining glucose monitoring supplies at your own expense.

When will I get my Precision Xtra monitor and supplies?

Once your completed forms are received and processed at NetGroup, your order will ship within 24 hours. It will be sent by US Postal Service Priority Mail and should arrive at your home within approximately five (5) business days. Following this first shipment, you will then receive a regular shipment of testing supplies every three months for as long as you remain in the study.

What if I prefer to continue using my current glucose monitoring system?

If your ACCORD clinical site coordinator agrees, you may continue to use your current system. However, you will have to obtain your testing supplies through your usual retail channel and you will be responsible for payment of all co-payments and deductibles.

4. Lifestyle Recommendations and Background Therapy

4.1 Overview

The lifestyle and background therapy section of the protocol addresses a broad range of therapies for patients with diabetes. The Lifestyle and Background Therapy protocol reflects national and (when available) evidence-based guidelines. These therapies are recommended in order to foster high-quality diabetes care in all ACCORD participants.

The background therapy recommendations include smoking cessation counseling, anti-thrombotic therapy, treatment of hypertension and dyslipidemia, use of angiotensin converting enzyme inhibitors, and diabetes-related general medical care. Please refer to the protocol (sections 3.5.c-g) for more extensive justification for these recommendations. Making uniform recommendations in these areas is intended to reduce bias by increasing the likelihood that background therapies that alter the risk of cardiovascular events, and that are not being studied in ACCORD, are utilized equally across all study arms. The background therapy recommendations should be provided to the participants and their physicians in written form (see section 4.3.6 below). Background therapy is considered part of usual recommended care for diabetes and, as such, is not covered by research study costs. The delivery of these background therapies will be left up to the participants' own physicians.

Lifestyle therapy, which includes medical nutrition therapy (MNT) and physical activity, is intended as an adjunct to drug therapy. It is anticipated that both lifestyle and medication interventions will be required to meet goals for glycemic control. Lifestyle and MNT recommendations are equivalent between the intensive and standard treatment arms but will differ in the intensity of reinforcement, as participants in the intensive treatment arm will have more frequent follow-up visits. Counseling in both MNT and physical activity is expected to be delivered by ACCORD staff.

General diabetes education should be carried out by the ACCORD clinics in accordance with national standards for diabetes self-management education programs. Clinics may use existing educational materials, but should avoid materials that give specific A1C, blood glucose, blood pressure and lipid targets, as these may differ between treatment arms in ACCORD. A general diabetes educational booklet entitled Type 2 Diabetes Basics will be available in English, Spanish and French for use in ACCORD. Additional educational materialssuitable for ACCORD participants in all treatment assignments are available from the Coordinating Center, and clinics will receive a packet including a sample of all items. These may be ordered individually using the form found at the end of this chapter on p. 15.

4.2 Lifestyle Recommendations

4.2.1 Medical Nutrition Therapy (MNT)

The overall goal of MNT is to assist individuals with diabetes in making changes in nutrition and exercise habits leading to improved metabolic (glucose, lipid and blood pressure) control. MNT consists of dietary modification and weight management. Participants in ACCORD should receive instruction in MNT at baseline and at least annually. Instruction should be delivered by the ACCORD clinic staff (nutritionist, diabetes educator,

or similarly qualified clinician.) The following recommendations and general principles will apply to all participants in ACCORD, regardless of randomized assignment. However, as stated above, participants randomized to the intensive glycemic control arm of the study may receive more intensive reinforcement of MNT, due to more frequent follow-up visits.

4.2.2 Weight Management

Moderate weight loss (5-9 kg [10-20 lb.], irrespective of starting weight, has been shown in short-term studies to reduce insulin resistance, hyperglycemia, dyslipidemia, and hypertension. Although long-term data assessing the extent to which these improvements can maintained is not available, several strategies can be recommended:

1. Moderate calorie restriction (250-500 calories less than average daily intake as calculated from a food history) and a nutritionally adequate food plan with a reduction of total fat, especially saturated fat.

2. Spacing of meals in which calorie intake is distributed in 3 or more meals/snacks throughout each day

3. Increase in physical activity (see section 4.2.4)

Participants who are considered overweight (BMI $\geq$ 25 kg/m^2) should be encouraged to lose 10% of their current weight or 5-9 kg, whichever is less, over a 6 month period of time. Once weight is lost, weight maintenance strategies should be implemented. Non-overweight participants should be encouraged to maintain weight. Weight will be measured at all clinic visits, providing an opportunity for feedback and counseling.

4.2.3 Dietary Modification

Dietary modifications will be recommended based both on glycemic control and control and prevention of CVD risk factors common in people with diabetes. The main focus of nutrition intervention will be the following three dietary components: carbohydrate, fat and sodium. Recommendations will also be made for alcohol intake.

- **Carbohydrate**

Percent of calories from carbohydrate (sugars, starch and fiber) will vary and is individualized based on the person's eating habits, glucose and lipid levels, and weight. Carbohydrate is the primary nutrient affecting blood glucose levels. Carbohydrate counting is a widely used food planning method used to achieve blood glucose control. Through controlling carbohydrate intake, or matching carbohydrate intake and insulin (exogenous or endogenous), better blood glucose control can be achieved on a more consistent basis. The total amount of carbohydrate consumed is more important than the source of the carbohydrate. The application of the carbohydrate counting method of food planning differs between insulin and non-insulin users.

For insulin users:

Carbohydrate intake is to be synchronized with the time-action of the insulin regimen being used.

For non-insulin users:

A moderate carbohydrate intake and spacing of meals (spreading nutrient intake, particularly carbohydrate, throughout the day) is a strategy that can maximize the effectiveness of an individual's endogenous insulin production.

A comprehensive discussion of carbohydrate counting is beyond the scope of this manual, however a few basic guidelines can be suggested. One "carbohydrate choice" is equivalent to 15 grams of carbohydrate. One slice of bread, ½ cup cooked pasta, 1 small potato, ½ banana, ½ cup fruit juice, ¾ cup Cheerios, 1 cup of skim milk, and 3 graham cracker squares all contain about 15 grams of carbohydrate. Because people often underestimate portion sizes, encourage the use of measuring cups or comparison to common objects. For example, ½ cup of mashed potatoes is about the size of a tennis ball. To maintain weight, most adult women need 3-4 carbohydrate choices per meal and 1-2 choices per snack, while most men need 4-5 choices per meal and 1-2 choices per snack. This may need to be adjusted downward for weight loss or upward for very active people.

- **Dietary fat**

The percent of calories from fat will also vary depending upon identified lipid problems and treatment for glucose, lipids and weight. Guidelines from the American Heart Association, National Cholesterol Education Program and American Diabetes Association differ in some details, but the major points are in agreement. These can be summarized as:

If elevated LDL cholesterol is the primary concern and is persistently elevated above 100 mg/dl (2.58 mmol/l)), or if cardiovascular disease is present, the intake of foods with cholesterol raising fatty acids should be limited. Lower LDL can be achieved by consuming:

- <7% of calories from saturated fats
- the minimum amount of *trans*-fatty acids (partially hydrogenated vegetable oils)
- <200 mg dietary cholesterol daily
- $\simeq$ 10% of calories from polyunsaturated fat
- 10-15% of fat calories from monounsaturated fat

People who are at a healthy weight and have normal lipid levels may consume a less restrictive diet that contains:

-
- <10% of calories from saturated fats
- the minimum amount of *trans*-fatty acids (partially hydrogenated vegetable oils)
- <300 mg dietary cholesterol daily
- $\simeq$ 10% of calories from polyunsaturated fat
- 10-15% of calories from monounsaturated fat

If obesity and weight loss are the primary concerns, a reduction in total dietary fat is recommended. If triglycerides and VLDL cholesterol are the primary concerns, moderately increase the monounsaturated fat, keep saturated fat to <10% of calories, and moderate carbohydrate intake to $\leq$50% of total calories. A total fat intake of 35% or less of energy is recommended; however higher fat intakes may be justified on an individual basis.

Food choices that are low in saturated fat and cholesterol include the following: skim or 1% milk, fruits and vegetables, steamed rice, baked potatoes, grains and pasta, chicken and turkey without skin, fish, and lean cuts of beef or pork. Meat should be trimmed of visible fat before cooking, and skin should be removed from chicken and turkey. Sauces, cream, and gravies should be skipped or used sparingly, as should butter or margarine on vegetables, potatoes and bread. Substituting low-fat or non-fat versions of sour cream, cream cheese, salad dressing, cheeses, lunchmeats and ice-cream should also be encouraged. Low-fat cooking methods include baking, broiling or grilling using nonstick cookware and cooking spray instead of oil, and saute′ing in broth or wine.

- **Sodium**

Dietary sodium intake should be reduced to less than 2400 mg/day for the ACCORD study population and to less than 2000 mg/day for those with nephropathy.

High sodium foods should be avoided, including chips, nuts, lunch meats, most canned foods, most fast foods, pickles and olives. Instead of adding salt to foods for flavor, encourage trying pepper, lemon juice, mustard, garlic, spices and herbs. Emphasize choosing more fresh foods - vegetables, fruits, grains, meats, and minimally processed foods. Encourage more home preparation of foods and reading food labels to help make lower sodium choices.

- **Alcohol**

It is recommended that trial participants limit daily alcohol intake to no more than one ounce (30 mL) of ethanol for men and 0.5 ounce (15 mL) for women. One ounce of ethanol is equivalent to 24 ounces (720 mL) of beer, (2 bottles of beer), 10 ounces (300 mL) of wine, (2 glasses), or two ounces (60 mL) of 100- proof hard liquor.

- **Dietary Assessment**

The means of assessing overall dietary intake will be individualized to the needs and abilities of the participants, as well as the resources of the ACCORD clinics. However, fat intake patterns will be assessed in a subsample of participants at baseline, year 1, 36-months and 48-months using the **ACCORD Diet Questionnaire Form.** Participants will be asked to fill out this form to the best of their ability if they are selected on the day of randomization. This sub-sample will be the same as the group completing the **ACCORD Modified CHAMPS Activities Questionnaire Form** (see section 4.2.4). Both forms are self-administered and are available in English, Spanish and French versions. They should be completed by the participant at a clinic visit, and checked for correct completion by clinic staff while the participant is in clinic. An acceptable alternative is to mail the forms to the participant in advance of the visit, and to collect the forms at the visit after checking for correct completion. Collection of the forms by mail after the clinic visit is discouraged, as errors or misunderstandings will be difficult to correct.

4.2.4 Physical Activity

Physical activity is a crucial component of lifestyle therapy for diabetes; thus, at least brief counseling for physical activity should be included in all clinic visits. Participants should be encouraged to accumulate 30 minutes or more of moderate-intensity aerobic

physical activity on 5 or more days of the week. Moderate-intensity aerobic activity is defined as repetitive motion using large muscle groups that increases the heart rate to 50-70% of maximal, is perceived as fairly light to somewhat hard, or is equivalent in perceived intensity to brisk walking (3-4 miles per hour for most people, or walking "as if you are in a hurry"). Maximal heart rate can be estimated by subtracting age from 220. For example, in a 60 year old the target heart rate range is (220 – 60) X (0.5) to (220 – 60) X (0.7), or 80 to 112 beats per minute. Persons on beta-blockers cannot use the heart rate criterion, as beta-blockers prevent the increase in heart rate, so perceived exertion or comparable intensity to brisk walking should be recommended.

Thirty minutes of physical activity may be accumulated in bouts of 8-10 minutes in a 24-hour period. Warm-up and cool-down activities should be encouraged. Participants should be instructed to drink plenty of fluids, to wear socks and appropriate footwear, and to inspect their feet on a daily basis. Clinics should develop and maintain lists of low cost or free local resources for safe physical activity to provide to participants. Physical activity will be assessed in a sub-sample of participants at baseline, year 1, 36-month and 48-month using the **ACCORD Modified CHAMPS Activities Questionnaire Form**. This sub-sample will be the same as the group completing the **ACCORD Diet Questionnaire Form**.

The general exercise prescription above may need to be modified for some participants. The following groups of participants will need tailored instructions:

- ACCORD participants who do little or no physical activity at baseline should be encouraged to increase their physical activity levels gradually, starting with lower-intensity, shorter-duration, and less frequent activities (e.g., moderately paced walking for 5 minutes twice a week) and increasing gradually over weeks or months to moderate-intensity and longer-duration activities until the goal of 30 minutes or more of moderate-intensity aerobic physical activity on 5 or more days of the week is achieved.

- Participants with proliferative retinopathy or peripheral neuropathy with loss of protective sensation should be advised to avoid vigorous or strenuous exercise, high-impact exercise (e.g., jogging, high-impact aerobics, racquet sports, competitive sports), or weight training. For those with advanced peripheral neuropathy and loss of protective sensation, recommended exercises include swimming, stationary cycling, and rowing.

- For ACCORD participants beginning an unsupervised exercise program or increasing their intensity of physical activity, screening for coronary heart disease should be considered. **Persons continuing their current regular physical activity or increasing duration of activity at the same intensity do not need this screening.** The recommended screening is an exercise stress test, or documentation of an exercise stress test within the previous 3 months, that is negative for ischemia and significant arrhythmias at a workload of 4-5 METS (i.e., moderate intensity, equivalent to brisk walking).

- Persons experiencing symptoms of ischemia during physical activity should undergo diagnostic evaluation.

4.2.5 Counseling approaches for behavior change

Behavioral counseling approaches are designed to help patients make changes in their lifestyles in order to achieve the recommendations for diet, physical activity, and weight. The underlying principle of these counseling approaches is to engage in an interchange where counselor and patient work together toward a common goal. The counseling is highly individualized based on the particular patient's motivation, past experience, knowledge, and personal circumstances.

Behavioral approaches shown to be effective include self-assessment, goal setting, self-monitoring, identifying barriers and influences, problem solving, and receiving feedback and reinforcement. A brief description of these approaches follows along with a description as to how to combine them.

Self-assessment: The patient determines their current motivation for making behavior changes. They also determine their current diet and physical activity behaviors and weight status and how close they are to the recommendations. Keeping a record of current diet and physical activity patterns is part of the initial self-assessment. Many people do not realize what their actual behavioral patterns are without engaging in some directed self-assessment activities. For example, one patient may not realize that she snacks in front of the television every evening until she writes down everything she eats and when and where she eats it.

Goal setting: The patient sets individualized, realistic goals for their diet and physical activity behaviors and their weight. For example for diet, one patient may select switching from whole milk to low-fat milk to reduce his/her calories from fat; another patient may select eliminating desserts. For physical activity, one patient may select walking for five minutes each day to start becoming more active, while another patient may select swimming twice a week. For weight, one patient may select calorie restrictions that should result in losing 2 pounds in the next month; another patient may decide not to work on weight yet, but to focus on achieving a more healthful diet. There are more successes in behavior change when small, achievable goals are selected first and then increased gradually to achieve the recommended diet and physical activity behaviors. Goal setting is revisited at each session.

Self-monitoring: Self-monitoring consists of keeping regular records of one's own behaviors, such as diet and physical activity patterns, or one's own weight. Diet and physical activity diaries can be kept by writing down everything an individual eats for 3 days in a row, or writing down all the moderate-to-vigorous physical activities he/she does for a week. These diaries should not only include what is eaten, or what activities are performed, but the time of day and context (for example, in the evening in front of the television, or after work). Self-monitoring helps the patient and counselor determine the patient's progress toward goals and identify specific issues that might need to be addressed. For example, one patient may see that she never completes her 15-minute walk on weekdays after work because her work demands are too high. This recognition can help the patient identify alternative approaches to obtaining physical activity, for example walking first thing in the morning before she goes to work. Continual self-monitoring has proven very effective in weight loss and in achieving dietary and physical activity changes.

Identifying Barriers and Influences: The patient identifies any personal barriers they might have to implementing changes, including lack of knowledge or skills, low motivation,

lack of social support, environmental constraints, etc. The patient also identifies any positive influences that might aid them in making changes. Two common barriers/influences are social support and environment. It is very difficult to make behavior changes in an unsupportive social environment, and engaging a person's spouse, other family member, or friend in providing support may be very important. For example, a husband can provide social support for physical activity by offering to go for a walk with his wife. It is difficult for some people to ask for social support, so practice in asking can be incorporated into a counseling session. The influence of the immediate environment is also very important. For example, if a patient keeps a supply of potato chips and beer in the house, he is more likely to snack on these when at home. Alternately, if grocery shopping is limited to only healthful foods, unhealthful foods will not be available in the home to eat on a whim. Similarly, buying exercise equipment and putting it in an obvious location, for example in front of the television, is an environmental cue to exercise that has been shown to be effective.

Problem solving: Problem-solving to overcome barriers or to increase positive influences follows the identification of the barriers and influences. The patient identifies possible things that can be done and then selects viable options to try. For example, one patient may say she cannot exercise because she has to take care of her grandchildren. One possible way to overcome that barrier is to take the children to the park and walk with them on the trails. The solutions should emanate from the patient, not be imposed by the counselor.

Feedback and Reinforcement: Feedback is simply providing back to the patient a description of what he/she is doing, e.g., describing the diet and physical activity patterns. For example, you may review a patient's diet diary with him/her and provide feedback that he/she is still eating dessert every night. Feedback is nonqualitative. Reinforcement, on the other hand, is a qualitative assessment of a patient's actions by giving praise or a small reward for goals achieved or positive efforts. The counselor can provide verbal reinforcement, and/or the patient can reinforce him or herself by some reward. For example, a patient could treat herself to buying a new dress when she achieves her weight goal.

These various approaches are combined in regular, ongoing counseling sessions. Each session should build on the previous one, and the sessions should continue throughout the patient's treatment. If the patient achieves the goals, then the sessions should focus on maintaining the changes. The effective use of behavioral counseling is an "art" and requires practice, but here is one scenario for the first three sessions.

Session 1: Self-assessment
Identify motivation for making changes
Have the patient start keeping track of their diet and physical activity behaviors in a diary

Session 2:
Review self-assessment diaries
Reassess motivation
Set short-term goals
Identify barriers to achieving the goals
Problem solve
Start self-monitoring

Session 3:
Review self-monitoring results
Assess progress toward the short-term goals
Provide feedback and reinforcement
Identify barriers and influences
Problem solve
Set new short-term goals, or confirm previous goals
Continue self-monitoring

In ACCORD, participants assigned to the intensive glycemic arm are scheduled to have more frequent visits to the clinic than participants assigned to the standard-care glycemic arm. Although the counseling approaches are the same in the two arms, the counseling is provided more often to participants in the intensive arm.

4.3 Background Therapy

4.3.1 Smoking Cessation

Cigarette smoking will be ascertained at baseline on the **ACCORD Baseline History and Physical Exam Form** and annually on the **Annual Follow-up and Physical Exam Form**. All participants who are tobacco users should be strongly encouraged to stop using a brief, unambiguous, strong and personalized message. Current smokers' willingness to quit may be assessed. Smokers who are interested in quitting may be provided with self-help materials, referred to their regular source of medical care or a smoking cessation program, or assisted by the ACCORD clinician.

4.3.2 Anti-thrombotic Therapy

Aspirin 75-325 mg daily is recommended for all ACCORD participants unless contraindicated by allergy, bleeding disorder, recent GI bleeding or need for anticoagulant therapy. Aspirin use will be assessed at baseline and annually thereafter.

4.3.3 Treatment of Hypertension and Dyslipidemia

Participants enrolled in the Glycemic/Lipid trial assignment will receive any necessary treatment for blood pressure from their usual source of medical care. Similarly, participants enrolled in the Glycemic/Blood Pressure trial assignment in ACCORD will receive any necessary treatment for dyslipidemia from their usual source of medical care. The recommended blood pressure and lipid goals for these patients are based on the ACCORD investigators' synthesis of clinical trial evidence. In some cases, these may differ from national consensus panel recommendations.

A blood pressure goal of < 140/85 mm Hg is recommended by ACCORD, as this goal is supported by evidence for cardiovascular disease prevention. Lower blood pressure goals are recommended for people with diabetes in guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (< 130/85 mm Hg) and the American Diabetes Association (< 130/80 mm Hg).

In ACCORD, an LDL-cholesterol goal of <100 mg/dl (2.58 mmol/l) is recommended. This goal is the same as that to be recommended by the American Diabetes Association and in the Adult Treatment Panel III of the National Cholesterol Education Program.

4.3.4 Angiotensin-Converting-Enzyme Inhibitors (ACE-Inhibitors)

ACE-inhibitors are recommended to reduce cardiovascular morbidity in people with type 2 diabetes at high risk for cardiovascular disease. ACE-inhibitor use will be assessed at baseline and annually thereafter.

4.3.5 Diabetes related general medical care

ACCORD participants should also receive diabetes related general medical care.

- Visual acuity will be checked at baseline and annual visits in ACCORD. In addition, all participants should receive an annual dilated eye and visual exam by an ophthalmologist or optometrist. This is considered part of usual recommended care for diabetes, and should be arranged by the participant's usual source of care.
- All participants will receive a foot examination at least annually in the ACCORD clinics. The standardized examination will include inspection for ulceration, testing of ankle reflexes, testing of vibratory sensation and testing with a 10 gm monofilament. Specific instructions for conducting the foot examination can be found in MOP Chapter 9, Section 9.6.
- All participants should receive annual influenza vaccine and, if previously unvaccinated, one dose of pneumococcal vaccine.

4.3.6 Communicating background therapy recommendations to the participant's usual source of medical care

For participants whose usual source of medical care is not an ACCORD clinic, it is recommended that the ACCORD clinic PI send an introductory letter to the non-ACCORD health care provider. The body of the letter will describe the participant's assignment to either the blood pressure or lipid trial. If the patient is not in the blood pressure trial the letter will give the recommended ACCORD blood pressure goal (<140/85 mm Hg). Likewise, if the patient is not in the lipid trial, it will give the recommended ACCORD LDL goal (<100 mg/dl [2.58 mmol/L]). Other national guidelines will be referenced. The letter will refer to an abstract that describes the ACCORD trial and the other components of recommended background therapy. It will close with an invitation to direct any questions or concerns to the clinic PI. (See following examples)

Example of a Background letter for a participant in the lipid trial:

Date

Dear Dr._____:

Your patient _____ is participating in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial. A brief description of the trial is enclosed.

Your patient is participating in the glycemic control and lipid control portion of the trial. Because of their high risk of cardiovascular disease, the ACCORD investigators recommend that all trial participants receive the enclosed components of high-quality background therapy under the supervision of their regular source of medical care.

Since your patient is not participating in the blood pressure portion of the trial, you will continue to provide medical care related to blood pressure. The ACCORD investigators recommend a blood pressure goal of <140/85-mmHg, based on their synthesis of clinical trial evidence for cardiovascular disease prevention. This goal differs from the recommended blood pressure goal for people with diabetes put forth by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (<130/85) and the American Diabetes Association (<130/80). You may wish to consider all these guidelines when individualizing treatment for this patient.

Please do not hesitate to contact me if you have any questions about the ACCORD Trial, or this patient's participation.

Best regards,

XXXXXXX

Example of a Background letter for a participant in the blood pressure trial:

Date

Dear Dr. _____:

Your patient _____ is participating in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial. A brief description of the trial is enclosed.

Your patient is participating in the glycemic control and blood pressure control portion of the trial. Because of their high risk of cardiovascular disease, the ACCORD investigators recommend that all trial participants receive the enclosed components of high-quality background therapy under the supervision of their regular source of medical care.

Since your patient is not participating in the lipid control portion of the trial, you will continue to provide medical care related to lipids. The ACCORD investigators recommend a LDL-cholesterol goal of 100 mg/dl [2.58 mmol/L] or below, based on their synthesis of clinical trial evidence for cardiovascular disease prevention. This goal is consistent with the recommendation of the American Diabetes Association and the forthcoming recommendations of the National Cholesterol Education Program for people with diabetes.

Please do not hesitate to contact me if you have any questions about the ACCORD Trial, or this patient's participation.

Best regards,

XXXXXXX

Action to Control Cardiovascular Disease in Diabetes (ACCORD)
ABSTRACT

Patients with type 2 diabetes mellitus die of cardiovascular disease (CVD) at rates two to four times higher than non-diabetic populations of similar demographic characteristics. They also experience increased rates of nonfatal myocardial infarction and stroke. With the growing prevalence of obesity in the United States, CVD associated with type 2 diabetes is expected to become an even greater public health challenge in the coming decades than it is now. Expected increases in event rates will be associated with a concomitant rise in suffering and resource utilization. Despite the importance of this health problem in the North American population, there is a lack of definitive data on the effects of intensive control of glycemia and other CVD risk factors on CVD event rates in diabetic patients.

The overall goal of the *Action to Control Cardiovascular Risk in Diabetes* (ACCORD) trial is to address this challenge by testing three complementary medical treatment strategies for type 2 diabetes to enhance the options for reducing the still very high rate of major CVD morbidity and mortality in this disease.

The design is a randomized, multicenter, double 2 X 2 factorial design in 10,000 patients with type 2 diabetes mellitus. The trial is designed to test the effects on major CVD events of intensive glycemia control, of treatment to increase HDL-cholesterol and lower triglycerides (in the context of good LDL-C and glycemia control), and of intensive blood pressure control (in the context of good glycemia control). All 10,000 participants will be in the overarching glycemia trial. In addition, one 2 X 2 trial will also address the lipid question in 5,800 of the participants and the other 2 X 2 trial will address the blood pressure question in 4,200 of the participants.

The three specific primary ACCORD hypotheses are as follow. In middle-aged or older people with type 2 diabetes who are at high risk for having a cardiovascular disease (CVD) event because of existing clinical or subclinical CVD or CVD risk factors:

(1) Does a therapeutic strategy that targets a HbA1c of < 6.0% reduce the rate of CVD events more than a strategy that targets a HbA1c of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%) ?

(2) In the context of good glycemic control, does a therapeutic strategy that uses a fibrate to raise HDL-C/lower triglyceride levels and uses a statin for treatment of LDL-C reduce the rate of CVD events compared to a strategy that only uses a statin for treatment of LDL-C?

(3) In the context of good glycemic control, does a therapeutic strategy that targets a systolic blood pressure (SBP) of < 120 mm Hg reduce the rate of CVD events compared to a strategy that targets a SBP of < 140 mm Hg?

The primary outcome measure for the trial is the first occurrence of a major cardiovascular disease event, specifically nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

The ACCORD study is designed to have:

- 89% power to detect a 15% treatment effect of intensive glycemic control compared with standard glycemic control,
- 87% power to detect a 20% treatment effect of lipid control through LDL-C treatment and fibrates compared with lipid control using LDL-C treatment alone,
- 94% power to detect a 20% treatment effect of intensive blood pressure control compared with standard blood pressure control.

Secondary hypotheses include treatment differences in other cardiovascular outcomes, total mortality, microvascular outcomes, health-related quality of life, and cost-effectiveness.

The 10,000 participants will be treated and followed for 4 to 8 years (approximate mean of 5.6 years) at approximately 60 Clinical Sites administratively located within 7 Clinical Center Networks in the United States and Canada. Recruitment will occur in two non-contiguous periods: an initial period that began in January 2001 for the Vanguard Phase of the trial (during which 1184 participants were randomized) and then a subsequent period beginning in January 2003 and ending in June 2005. Follow-up is scheduled to end in June 2009, with the primary results announced in early 2010.

Smoking Cessation

The Agency for Healthcare Research and Qualtiy guideline recommends the following steps:

1. ASK – each participant about tobacco use
2. ADVISE – smokers to quit using a brief, unambiguous, strong and personalized message
3. ASSESS – the smokers' willingness to quit
4. ASSIST –smokers who express willingness to make a quit attempt by developing a quit plan, encouraging adjunctive pharmacotherapy, and providing supplementary materials
5. ARRANGE -- follow-up, either by a health care provider or in a specialized smoking cessation program

Antithrombotic Therapy

Large-scale collaborative trials and meta-analyses of trials support the view that low-dose aspirin lowers the rate of recurrent cardiovascular events in men and women with diabetes and cardiovascular disease. The American Diabetes Association recommends low-dose aspirin as secondary prevention and as primary prevention in adults over the age of 40 with diabetes and one or more cardiovascular risk factors. All of the ACCORD participants will fall into one of these two categories. Aspirin is safe and effective across a dosage range from 75-325 mg daily. Therefore, aspirin 75-325 mg daily is recommended for all ACCORD participants unless contraindicated by allergy, bleeding disorder, recent gastrointestinal bleeding or need for anticoagulant therapy.

Angiotensin-Converting-Enzyme Inhibitors (ACE-Inhibitors)

Evidence for the effectiveness of angiotensin-converting-enzyme (ACE) inhibition in reducing adverse outcomes in patients with type 2 diabetes has been increasing, including mortality and sudden cardiac death in acute MI and hospitalizations for CHF. There is no clear consensus at the present time to use ACE-inhibitors over other antihypertensive treatments for hypertension. However, the Heart Outcomes Prevention Evaluation Study (HOPE) compared the ACE-inhibitor ramipril with placebo in participants at high risk for cardiovascular disease and found a 25% reduction in the combined outcome of MI, stroke, and cardiovascular death, which was not explained by the degree of blood pressure reduction. The effect was significant in participants with and without diabetes. There is evidence that ACE-inhibitors improve renal outcomes (nephropathy and albumin excretion) in type 2 diabetes. Therefore, the ACCORD study recommends ACE-inhibitors for reducing cardiovascular morbidity and mortality in patients who have experienced acute MI, congestive heart failure, nephropathy, and in patients with type 2 diabetes with at least one additional risk factor for cardiovascular disease.

Diabetes Related General Medical Care

The following recommendations are based on guidelines of the American Diabetes Association.

1. An annual dilated eye and visual exam by an ophthalmologist or optometrist.
2. An annual influenza vaccine and, if previously unvaccinated, one dose of pneumococcal vaccine.

ACCORD Lifestyle Educational Materials
Order Form

Requested Item	Check	Amount Needed
Diet Items In English:		
Eat Right to Help Lower Your High Blood Pressure		
My Food Plan		
My Food Plan Made Easy		
ACCORD Food Diary		
Fast Food Guide		
Diet Items In Spanish:		
Delicious Heart-Healthy Latino Recipes		
Protect Your Heart - Lower Your Blood Cholesterol!		
Cut Down on Fat - Not on Taste!		
Cut Down on Salt and Sodium!		
Watch Your Weight		
Mi Plan de Comidas (My Food Plan)		
Diet Items with African American Focus:		
Heart-Healthy Home Cooking (African American Style)		
Be Heart Smart! Eat Foods Lower in Saturated Fat/Choles.		
Spice Up Your Life! Eat Less Salt & Sodium		
Embrace Your Health! Lose Weight If You Are Overweight		
Physical Activity Items:		
Just Move		
Stay Active and Feel Better! (English/Spanish)		
Energize Yourself! Stay Physically Active (African American Focus)		
Smoking Cessation Items:		
You Can Quit Smoking		
Kick the Smoking Habit! (Spanish)		
Refresh Yourself! Stop Smoking (African American Focus)		
General Diabetes Care:		
Hyperglycemia/Hypoglycemia Sheet		
Diabetes & Stress		
Foot Care Dos and Don'ts		

5. Overview of Eligibility, Randomization, Available Drugs, and Treatment Algorithms

5.1 Overview

The ACCORD trial is being conducted to evaluate the effects of intensive glycemia control, intensive BP control and raising HDL-cholesterol and lowering triglycerides in the context of LDL-cholesterol treatment on cardiovascular disease (CVD) event rates in patients with type 2 diabetes. By using three complementary medical treatment strategies for type 2 diabetes, ACCORD will help to identify mechanisms for enhancing treatment options to reduce the cardiovascular morbidity and mortality associated with this disease.

5.2 Glycemia trial (all 10,000 participants)

5.2.1 Glycemia Eligibility Criteria:

Participants with type 2 diabetes meeting the ACCORD eligibility criteria (MOP Chapter 3), having given their informed consent and successfully completed the run-in phase, will be eligible for randomization.

5.2.2 Randomization and Initiation of Glycemia Therapy

Eligible participants will be randomized to one of two different HbA1c strategies: a strategy that targets a HbA1c < 6% (intensive group) versus a strategy that targets a HbA1c of 7.0% to 7.9% (standard group). Treatment approaches, monitoring and follow-up of participants will be determined by their randomization assignment and are described in MOP Chapter 7 by treatment assignment.

5.3 Blood Pressure Trial (a subset of 4,200 participants)

5.3.1 General Blood Pressure Eligibility Criteria (including which drugs are considered antihypertensive medications)

Participants eligible for the glycemia component of the trial will also be eligible for the BP component if:

1) SBP is between 130 mm Hg and 160 mm Hg, inclusive, and the patient is on 0, 1, 2, or 3 antihypertensive medications

   OR

   SBP is between 161 mm Hg and 170 mm Hg, inclusive, and the patient is on 0, 1, or 2 antihypertensive medications

   OR

   SBP is between 171 and 180 mm Hg, inclusive, and the patient is on 0 or 1 antihypertensive medication

AND

2) Dipstick protein in a spot urine is < 2+

   OR

The protein – to – creatinine ratio in a spot urine is < 700 mg/gm creatinine

OR

24-hour protein excretion is < 1.0 gm/24 hours

Screenees with BPs outside these parameters would be excluded from the BP intervention.

If previously untreated for hypertension, a participant should have documentation of SBP readings ≥ 130 mm Hg on at least two occasions (i.e., visit averages) by or at the randomization visit in order to be eligible for the BP portion of the trial. Blood pressures obtained at the screening visits may satisfy this requirement.

(See Section 5.3.1.1 for additional details for screenees not currently on BP medication).

There are no diastolic blood pressure (DBP) inclusion criteria.

For the purpose of eligibility, it should be noted that BP- lowering medications, even if given for a purpose other than BP-lowering, are to be considered antihypertensive medications, such as:

- Beta-blockers
- Alpha-blockers
- Alpha-beta-blockers
- ACE-inhibitors
- Thiazide diuretics
- Calcium channel blockers (CCB).

Loop diuretics are considered blood pressure lowering medications if used at doses/frequency known to reduce blood pressure, specifically:

- Furosemide greater than or equal to 20 mg BID
- Bumetanide greater than or equal to 0.5 mg BID
- Ethacrinic Acid: greater than or equal to 25 mg BID
- Torsemide: any dose

Nitroglycerine is not considered a blood pressure lowering medication.

For eligibility for the ACCORD Blood Pressure Trial, combinations of 2 diuretics (e.g., Maxide, Dyazide, and Moduretic) are considered one drug. However, for combinations of different classes, each class will be counted as a separate blood pressure-lowering agent.

NOTE: Blood pressure eligibility is determined at the screening visits. Once eligibility has been determined, baseline values need not be consistent with the eligibility criteria (i.e., a baseline blood pressure is allowed to be out of range).

If an informed consent has been obtained and signed, medications may be adjusted prior to the randomization visit to allow a participant's BP to rise or fall to meet the BP criteria. **After adjusting the antihypertensive medication, no more than two visits will be permitted to allow a participant to meet the entry criteria for the BP component of the trial.**

For those screenees that are on BP lowering medication at the ACCORD Screening visit, refer to Figure 5.1. For those screenees not on BP lowering medication at the ACCORD Screening visit, refer to Section 5.3.1.1 below and Figure 5.2. (It should be noted in Figure 5.2 that medications/doses may be increased or decreased to see if screenee can become BP-eligible: e.g., if on 3 drugs, but SBP < 130 mm Hg, stop a drug and see if BP comes in range. If SBP > 180 mm Hg and patient is on 1 drug, add 1-2 drugs to see if SBP can be within range).

5.3.1.1 BP Criteria for Screenees Not Currently on a BP-lowering Medication

For participants being screened who are not currently on blood pressure (BP)-lowering medication, there must be documentation of SBP ≥ 130 mm Hg on at least 2 occasions (per JNC VI Guidelines), with the last screening visit SBP also being no greater than 180 mm Hg for the participant to be eligible for the BP portion of ACCORD. Any one ACCORD screening visit SBP less than 130 mm Hg is sufficient to make participant ineligible for the BP portion of the trial, unless the participant is rescreened.

If a participant, who is not currently on treatment for hypertension, presents at his/her first screening visit and the average of their 3 SBP measurements is at least 130 mm Hg, the participant will be eligible for the BP portion of ACCORD if one of the following criteria are met.

1. The current screening SBP is no greater than 180 mm Hg and one of the following conditions is met:

    a. At least one SBP ≥ 130 mm Hg can be found in the screenee's medical record within past 3 months. The SBP documented in the medical record must not have been taken during an acute event/illness.

    b. If there is no SBP ≥ 130 mm Hg within the past 3 months documented in the medical record, a second ACCORD screening visit will be required to determine eligibility for the BP intervention. The SBP at the second screening visit must be at least 130 mm Hg and no greater than 180 mm Hg for the screenee to be eligible for the BP portion of ACCORD. If BP lowering medication is initiated prior to the second screening visit, the participant must meet on-treatment SBP eligibility criteria at the second screening visit.

2. If the current ACCORD screening SBP is greater than 180 mm Hg, a second ACCORD screening visit will be required to determine eligibility for the BP intervention, regardless of the presence or absence of chart data regarding previous SBP values. The SBP at the second screening visit must be at least 130 mm Hg and no greater than 180 mm Hg for the screenee to be eligible for the BP portion of ACCORD. If BP lowering medication is initiated prior to the second screening visit, the participant must meet on-treatment SBP eligibility criteria at the second screening visit.

Otherwise, the participant is ineligible for the BP intervention.

Screenees not being treated with anti-hypertensive medications whose SBP is less than 130 mm Hg at their first screening visit are ineligible for the BP intervention.

If a second screening visit is required, the second screening visit cannot occur on the same day as the first screening visit, although the time difference between the visits need not be 24 hours.

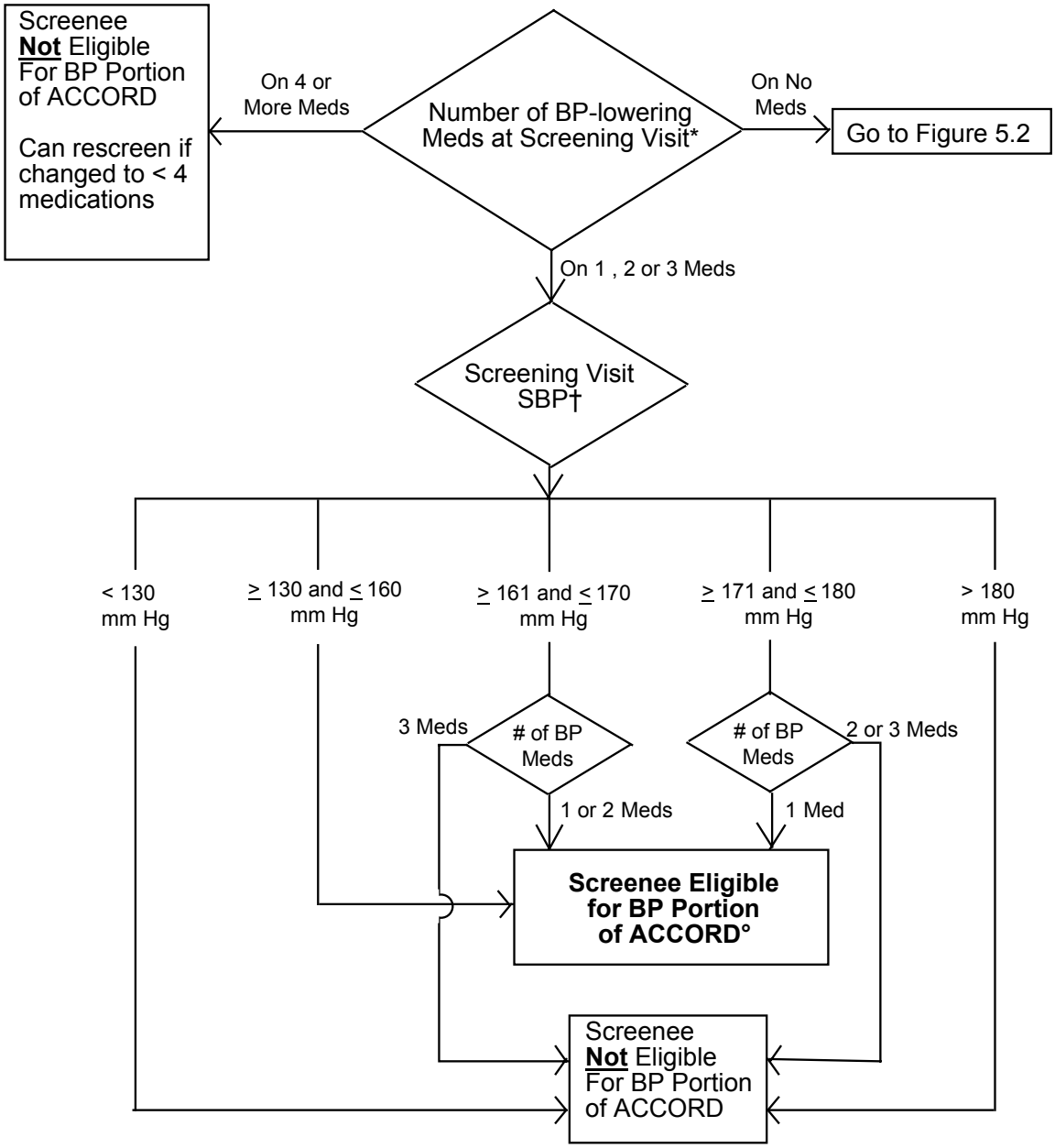
The randomization visit may occur on the same day and during the same visit as the 2nd BP screening visit, but baseline BP must be determined separately from and subsequent to the 2nd screening BPs.

If a screenee is not being treated for hypertension but is on BP-lowering medications for another indication (for example, beta-blockers, alpha-blockers, ACE-inhibitors), then the SBP eligibility criteria for persons on antihypertensive medication will apply.

5.3.2 Randomization and Initiation of Blood Pressure Therapy

Eligible participants for the BP component will be randomized to two different SBP goals: < 120 mmHg (intensive group) versus < 140 mmHg (standard group). The BP intervention will begin at the randomization visit. The investigator may choose from among the available ACCORD agents. It is recommended that the regimen include a drug class associated with reduced cardiovascular events in diabetes (ACE-inhibitor, beta-blocker, calcium channel blocker or diuretic). Treatment approaches, monitoring and follow-up of participants will be determined by their randomization assignment and are described in MOP Chapter 7 by treatment assignment.

Figure 5.1: Blood Pressure (BP) Eligibility Criteria for Screenees on BP-Lowering Medication at ACCORD Screening Visit

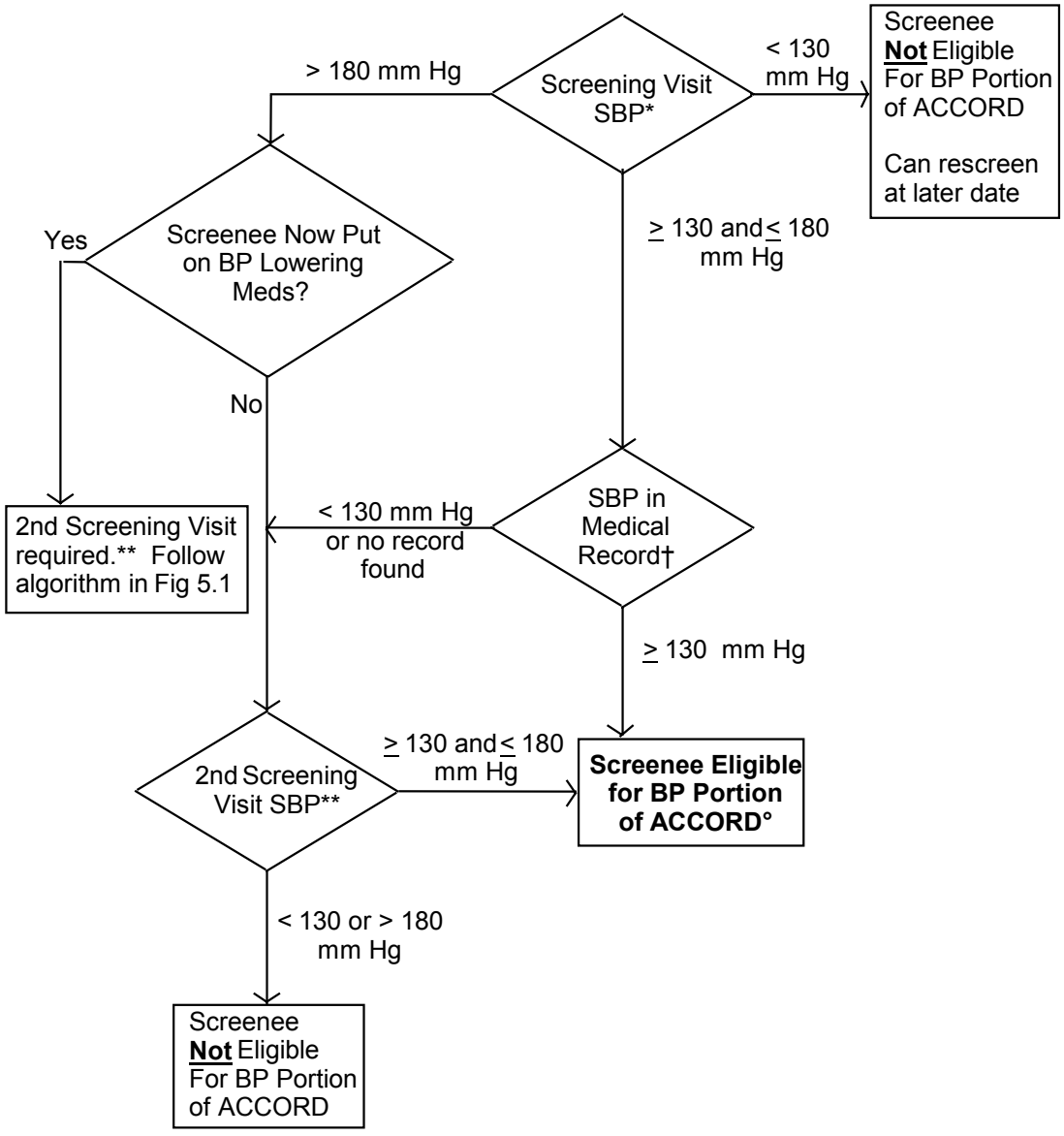


* Note: if a screenee is not being treated for hypertension, but is on a BP lowering medication for another indication (e.g., beta-blockers, alpha-blockers, ace-inhibitors), then this medication also counts as a BP lowering medication.

† All official Screening Visit BP values are the average of 3 measurements

° Randomization Visit may occur during same visit as BP Screening Visit, but baseline BP must be determined separately from and subsequent to screening BPs.

Figure 5.2: Blood Pressure (BP) Eligibility Criteria for Screenees Not on BP-Lowering Medication at ACCORD Screening Visit



* All official Screening Visit BP values are the average of 3 measurements.

† BP recorded within 3 months of Screening Visit Date and not associated with an acute event/illness

** 2nd Screening Visit cannot occur on same day as 1st Screening Visit, although the time difference between the visits need not be 24 hours

° Randomization Visit may occur during same visit as 2nd BP Screening Visit, but baseline BP must be determined separately from and subsequent to screening BPs.

5.4 Lipid Trial (a subset of 5,800 participants)

5.4.1 Lipid Eligibility Criteria

5.4.1.1 Lipid Inclusion Criteria

Participants eligible for the glycemia trial will also be eligible for the lipid component if their screening lipids are:

a) 60 mg/dl $\leq$ LDL cholesterol $\leq$ 180 mg/dl (1.55 to 4.65 mmol/l) if not on lipid lowering therapy during screening or **if on a lipid therapy**, less than the drug/dose-specific-cut points identified in the Table 5.1 below

AND

b) HDL cholesterol < 55 mg/dl (1.42 mmol/l) for women or Blacks/African Americans, or HDL cholesterol < 50 mg/dl (1.29 mmol/l) for other gender- race groups

AND

c) Fasting triglyceride < 750 mg/dl (8.47 mmol/l) untreated or < 400 mg/dl (4.52 mmol/l) on lipid treatment.

Screening lipids may either be measured at a local laboratory or obtained from medical records. If obtained from medical records, use the most recent values recorded within the **previous 12 months**. If there are no lipid values recorded in the medical records within the previous 12 months, a blood test must be performed by the local laboratory.

5.4.1.2 Lipid Exclusion Criteria

Participants eligible for the overarching glycemia trial will be ineligible for the lipid component if the following exclusion criteria are found:

a) known hypersensitivity to statins or fibrates or history of intolerance to statins or fibrates (depending on the nature of the reaction or reason for intolerance, individuals with a history of intolerance to statin or fibrate other than simvastatin or fenofibrate may be entered into the study at the discretion of the clinic investigator).
b) requirements for use of erythromycin, clarithromycin, cyclosporine, or systemic azole antifungals, or nefazodone or trazodone.
c) refusal to stop current lipid lowering drugs.
d) history of pancreatitis.
e) untreated or inadequately treated thyroid disease.
f) women who are breast-feeding or pregnant.
g) documented previous occurrence of myositis/myopathy.
h) Pre-existing gallbladder disease (NOTE: If the gallbladder has been removed, this is **not** an exclusion criterion)

SPECIAL NOTE: Do not forget that pregnancy and being of childbearing potential (and not using an effective method of birth control) are exclusion criteria for the overarching glycemia trial. Women should not become pregnant while taking statin or fibrate. If they do become pregnant while on these medications, the medications should be discontinued and they should be referred to a GYN/OB specialist for care.

Table 5.1: LDL-C Eligibility Ranges for Screenees on a Lipid-Lowering Agent (By Agent and Dose) (08/03/04 Revision)

Lipid Lowering Agent		Dose	Estimated % LDL-C Reduction	In **mg/dl**, the LDL-C Must Be Between (inclusive):	In **mmol/L**, the LDL-C Must Be Between (inclusive):
Atorvastatin	(Lipitor)	2.5 mg	25	45 - 135	1.16 - 3.49
Atorvastatin	(Lipitor)	5 mg	29	43 - 128	1.10 - 3.30
Atorvastatin	(Lipitor)	10 mg	39	37 - 110	0.95 - 2.84
Atorvastatin	(Lipitor)	20 mg	43	34 - 103	0.88 - 2.65
Atorvastatin	(Lipitor)	40 mg	50	30 - 90	0.78 - 2.33
Atorvastatin	(Lipitor)	80 mg	60	24 - 72	0.62 - 1.86
Simvastatin	(Zocor)	5 mg	26	44 - 133	1.15 - 3.44
Simvastatin	(Zocor)	10 mg	30	42 - 126	1.09 - 3.26
Simvastatin	(Zocor)	20 mg	38	37 - 112	0.96 - 2.89
Simvastatin	(Zocor)	40 mg	41	35 - 106	0.92 - 2.75
Simvastatin	(Zocor)	80 mg	47	32 - 95	0.82 - 2.47
Lovastatin	(Mevacor)	10 mg	18	49 - 148	1.27 - 3.82
Lovastatin	(Mevacor)	20 mg	24	46 - 137	1.18 - 3.54
Lovastatin	(Mevacor)	40 mg	30	42 - 126	1.09 - 3.26
Lovastatin	(Mevacor)	80 mg	40	36 - 108	0.93 - 2.79
Pravastatin	(Pravachol)	10 mg	22	47 - 140	1.21 - 3.63
Pravastatin	(Pravachol)	20 mg	32	41 - 122	1.06 - 3.17
Pravastatin	(Pravachol)	40 mg	34	40 - 119	1.02 - 3.07
Pravastatin	(Pravachol)	80 mg	40	36 - 108	0.93 - 2.79
Fluvastatin	(Lescol)	20 mg	22	47 - 140	1.21 - 3.63
Fluvastatin	(Lescol)	40 mg	24	46 - 137	1.18 - 3.54
Rosuvastatin	(Crestor)	5 mg	40	36 - 108	0.93 - 2.79
Rosuvastatin	(Crestor)	10 mg	46	32 - 97	0.84 - 2.51
Rosuvastatin	(Crestor)	20 mg	52	29 - 86	0.74 - 2.23
Rosuvastatin	(Crestor)	40 mg	55	27 - 81	0.70 - 2.09
Rosuvastatin	(Crestor)	80 mg	58	25 - 76	0.65 - 1.96
Ezetimbe	(Zetia)	10 mg	17	50 - 149	1.29 - 3.86
Fenofibrate		any	5	57 - 171	1.47 - 4.42
Niacin		any	10	54 - 162	1.40 - 4.19
Resin		any	10	54 - 162	1.40 - 4.19
All Others		any	0	60 - 180	1.55 - 4.65

SPECIAL NOTE: The general exclusion (part IV, Chapter 3 of MOP) of transaminase level > 2x upper limit of normal or history of liver disease also applies here.

For example, suppose a screenee is being treated with simvastatin 20 mg and a cholesterol absorption inhibitor (ezetimibe). First note that the LDL-C limits for simvastatin/20 alone are 37 and 112 mg/dl (0.96 and 2.91 mmol/l), and the LDL-C limits for ezetimibe alone are 50 and 149 mg/dl (1.30 and 3.67 mmol/l). The revised eligibility cut points for someone on these two drugs are 37 – 60 + 50 = 27 mg/dl for the lower and 112 – 180 + 149 = 81 mg/dl for the upper. (In international units, the revised cut points would be 0.96 – 1.56 + 1.30 = 0.70 mmol/l for the lower and 2.91 – 4.68 + 3.87 = 2.10 mmol/l). Thus, such an individual, the on-treatment LDL-C value for the study entry must be between 27 and 81 mg/dl, inclusive (or between 0.70 and 2.10 mmol/l, inclusive).

These calculations assume additive effects of the agents. Such subjects would also be required to meet a serum triglycerides entry criterion of < 400 mg/dl (4.4 mmol/l). Note that participants on combined

fibrate and niacin therapy may have experienced substantial reductions in triglycerides. If the screenee is currently on 3 or more lipid lowering medications, contact your CCN's Lipid Group representative or the Coordinating Center for advice as to how to proceed.

Other agents: If a participant is on a lipid-lowering agent that is not listed in the table, the expected percent reduction in LDL-C should be ascertained (e.g., from the package insert, if available, or current PDR). Use the expected percent reduction to calculate lower and upper LDL-C cut point critical values. To obtain the lower and upper critical values, multiply $\left[1 - \%\text{Reduction}/100\right]$ times 60 mg/dl (1.55 mmol/l) and 180 mg/dl (4.65 mmol/l), respectively. If you do not know the expected % reduction for the current therapy or combination of therapies, contact your CCN's Lipid Working Group representative or the Coordinating Center for advice as to how to proceed.

5.4.2 Randomization and Initiation of Simvastatin and Fibrate/ Placebo Therapies

Participants who were on a lipid-lowering agent at screening must agree to stop treatment and be changed to simvastatin.

The starting dose of masked fenofibrate/placebo medication will be determined by the calculated glomerular filtration rate (GFR) using the baseline serum creatinine level and the abbreviated MDRD equation (Levey 2003). Those participants with a baseline GFR $\geq$50 ml/min/1.73m^2 will begin at a starting dose of 160 mg of fenofibrate or identical placebo tablet. Those with a calculated GFR between 30 and <50 will start at the reduced dose of 54 mg/day fenofibrate or placebo (or will be placed on 160 mg tablet every other day if the 54 mg dose is unavailable). The masked medication should be administered with the morning meal.

Participants in the lipid trial will have serum creatinine measured every four months during follow-up. If the participant had started on the 160 mg dose of the masked medication, this dose will be down-titrated if the participant's estimated GFR falls between 30 and <50 mL/min/1.73m^2 on two consecutive measurements taken four months apart. Participants with GFRs in this range will receive either 54 mg/day (or 160 mg every other day) of fenofibrate or matching placebo.

If the estimated GFR falls below 30 mL/min/1.73m^2 at any time, the Coordinating Center will notify the clinic site that a confirmatory blood draw for repeat estimated GFR will be required within 2 weeks. If the confirmatory estimated GFR is below 30mL/min/1.73m^2, the masked study medication will be permanently discontinued, regardless of fenofibrate or placebo assignment.

The starting dose of open-labeled simvastatin is 20 mg/day, administered once daily after the evening meal or at bedtime. If the LDL-C is greater than 100 mg/dl (2.59 mmol/l) on two consecutive follow-up visits, the daily dose of simvastatin will be increased to 40 mg.

During follow-up, if the LDL-C is > 120 mg/dl (> 3.10 mmol/l) on two consecutive measurements following titration of simvastatin to 40 mg/day, the participant will be referred to their own physician for individualized treatment.

The order of therapy will be simvastatin first (at randomization), with the fenofibrate/placebo started at the next monthly visit (i.e., at the 1 month post-randomization visit). Participants and physicians will be masked to the fibrate/placebo assignment, and to LDL-cholesterol, triglyceride, and

HDL-cholesterol levels throughout the trial. This will be the only fully masked part of the ACCORD study.

5.5 The Role of Insulin in the ACCORD Study

The document below is meant to be a discussion paper that can be provided to participants prior to signing the consent form. It deals with anxieties that people may have about using insulin if they are randomized to the intensive group. It also answers questions that they may have about using insulin and could be a useful discussion document to ensure that patients have their insulin related questions answered prior to being consented.

ACCORD Information Sheet

The Role of Insulin in the ACCORD Study

The ACCORD trial will determine if glucose control that targets an A1c less than 6% - a level of glucose control found in people without diabetes - will safely reduce cardiovascular risk for people with type 2 diabetes. To do this, 5,000 people in North America are having their diabetes medications adjusted to try and achieve a "normal, non-diabetic" level of 6%, and 5,000 people are having them adjusted to maintain a level between 7% and 7.9%.

To achieve an A1c level below 6%, most participants assigned to the group targeting an A1c below 6% will need to take insulin to reach this goal. Because many people worry about taking insulin, and fear it may be too hard, too painful, or too dangerous, everyone entering the trial should know several things about insulin treatment today.

1) Taking insulin is not painful.
You can give yourself insulin using either modern insulin syringes or insulin pens. The pen devices are easy to use and deliver the right dose accurately. Both the syringe and the pen use tiny, very sharp needles which make the injection almost pain-free. You will find that injecting insulin is actually less uncomfortable than doing glucose tests.

2) Taking insulin is not hard.
Most people only need one injection a day when they start insulin, using a new long-acting insulin preparation called glargine. Later, more injections (before meals) are likely to be needed, but they can be added one at a time and are also easy to take.

3) Taking insulin is safer than most people think.
Like other glucose lowering drugs, insulin can cause dangerously low blood glucose levels (hypoglycemia). However, the use of newer insulin preparations in combination with oral treatments leads to less hypoglycemia than the older insulin preparations. In general, hypoglycemia is much less frequent in type 2 diabetes than type 1 diabetes. Also, the safety of ACCORD is being carefully monitored by a group of experts outside of the study.

4) Taking insulin does not increase eye and kidney disease – it actually reduces the risk of these diseases.

5) Taking insulin does not increase cardiovascular risk -- and probably reduces it.
The reason we are doing ACCORD is to determine if vigorous treatment of type 2 diabetes, with insulin and with other treatments, can reduce cardiovascular risk. There is no evidence at all that taking insulin increases the risk of heart attacks or other vascular events.

6) Use of insulin in ACCORD is going smoothly.
We are now well along in doing the ACCORD trial. Experience so far suggests our assumptions about the safety and effectiveness of insulin treatment for lowering blood glucose, and the way we are doing it, are correct. We will be able to answer the question posed by the trial: will intensive treatment to lower blood glucose levels with therapies that include insulin provide even more cardiovascular protection than standard treatment?

5.6 Treatment Options to Achieve an A1c < 6%

The document below was designed as a discussion document to be provided to people who have questions about options that may be available to achieve a normal HbA1c. It may not be appropriate for all participants, but for those participants who have high level questions, we thought it would be a useful one for the sites to have.

ACCORD Information Sheet
Treatment Options to Achieve an A1c Less than 6%

The ACCORD study will determine if lowering blood sugar (glucose) to normal will safely lower the chance that people with type 2 diabetes will ever have a cardiovascular event (heart attack, stroke, etc.) You have been assigned to the intensive treatment group. This means that we need to work together to achieve normal blood glucose levels and an A_{1c} level that is less than 6.0%. To do this, you will need to know more about your diabetes and its treatment than you might ever have learned until now.

- People with diabetes have glucose levels that tend to be higher than glucose levels in people without diabetes for 5 main reasons:
  1. your pancreas may not make enough insulin during the night or between meals when you are fasting;
  2. your pancreas may not make enough insulin when you eat a meal;
  3. your liver may pump too much glucose into your bloodstream overnight (when you are fasting);
  4. your muscles may not remove enough glucose from the bloodstream in response to the insulin that is present;
  5. glucose from foods that contain carbohydrates may be absorbed into your blood too quickly after eating.

- We have drugs that attack each of these problems:
  1. long-acting insulins like glargine (Lantus) or NPH take care of problem #1;
  2. fast-acting insulins like aspart insulin or regular insulin, or certain pills such as repaglinide (Prandin) or glimepiride (Amaryl) take care of problem #2;
  3. the metformin (Glucophage) pill lowers the amount of glucose the liver makes and helps problem #3;
  4. pills like rosiglitazone (Avandia) or pioglitazone (Actos) help insulin move glucose into your muscles and improve problem #4;
  5. pills like acarbose (Precose) slow conversion of carbohydrates into glucose and help problem #5.

- To achieve normal blood glucose levels, we usually have to use several of these 5 types of drugs together. This is called "combination therapy". In particular, insulin is usually needed and will likely be started early in your ACCORD diabetes treatment. In fact, you can think of all the pills as aids to the action of insulin in your body because insulin by itself is not enough to control glucose levels in many people with type 2 diabetes. Remember, ACCORD is using insulin at an earlier stage than is customary in many doctors' offices to ensure that your body has enough insulin to maintain normal glucose levels.

If you test your blood glucose frequently enough, you will be surprised and pleased at how close to normal you can safely maintain your blood glucose levels.

5.7 Randomization Visit

At or before the randomization visit, the investigator or study coordinator will data enter the screenee's eligibility criteria for the glycemia trial and the lipid and/or BP trial. The trial's main computer at the Coordinating Center will review the eligibility (inclusion and exclusion) criteria for each intervention and verify that a signed informed consent has been obtained. Using the web-based data entry system, the participant can then be randomly assigned to each of the intervention arms. The assignments for the Glycemia Trial and the Lipid or BP Trial are as follows:

Glycemia: intensive versus standard control
Lipid trial: fibrate versus placebo (masked)
BP trial: intensive versus standard control.

Only the lipid trial assignment will be masked from both the study personnel and participant.

Following the randomization process, the remainder of the visit will be completed per randomization cell in MOP Chapter 7.

The glycemia interventions and lifestyle recommendations (Chapter 4) will begin at randomization. Participants in the BP component will also begin the BP interventions at randomization. ***The first doses of the study drugs should begin the day of randomization.*** All glycemia and, if necessary, blood pressure drugs should begin on that day. For Lipid Trial participants, simvastatin should also begin on the day of randomization, with the blinded fibrate/placebo beginning at the one- month follow-up visit.

5.8 Drug Accountability

Information on study drug ordering, receiving, packaging, storage, disposal and accountability records will be provided by the study Drug Distribution Center and is described in MOP Chapter 17 – Central Drug Distribution Procedures.

5.9 Trial Medications

Tables 5.4, 5.5, and 5.6 list the study medications (and doses) that are available for the trial though the Drug Distribution Center.

Table 5.4: Glycemia Medications Available for ACCORD

(01/15/01)

Drug Class	Generic Name	Trade Name (Canadian Names in Parentheses)	Strength	Dosing
sulfonylurea	glimepiride	Amaryl	2mg	QD
sulfonylurea	glimepiride	Amaryl	4mg	QD
metformin	metformin		500mg	QD-TID
metformin	metformin		1000mg	QD-TID
TZD	rosiglitazone	Avandia	4mg	QD or BID
TZD	rosiglitazone	Avandia	8mg	QD
meglitinide	repaglinide	Prandin (Gluconorm)	0.5mg	TID w/meals
meglitinide	repaglinide	Prandin (Gluconorm)	1mg	TID w/meals
meglitinide	repaglinide	Prandin (Gluconorm)	2mg	TID w/meals
insulin	insulin glargine	Lantus	100U/ml	QD
insulin	aspart	NovoLog (NovoRapid)	100U/ml	VARIABLE
insulin	human mixed	Novolin 70/30 (NovoLog 70/30)	100U/ml	VARIABLE
insulin	human, zinc suspension	Novolin L (NovoLog L)	100U/ml	VARIABLE
insulin	human NPH	Novolin N (NovoLog N)	100U/ml	VARIABLE
insulin	human regular	Novolin R (NovoLog R)	100U/ml	VARIABLE

Table 5.5: Lipid Medications Available for ACCORD

(01/15/01)

Drug Class	Generic Name	Trade Name	Strength	Dosing
Blinded Med	placebo	placebo	---	OD
Blinded Med	fenofibrate	Tricor	200mg	OD
statin	simvastatin	Zocor	5mg	QPM
statin	simvastatin	Zocor	10mg	QPM
statin	simvastatin	Zocor	20mg	QPM

Table 5.6: Blood Pressure Medications Available for ACCORD

(01/15/01)

Drug Class	Generic Name	Trade Name	Strength	Dosing
diuretic	chlorthalidone	Thalitone	15mg	QD
diuretic	chlorthalidone	Thalitone	25 or 30mg	QD
ACE-I	benazepril	Lotensin	10mg	QD or BID
ACE-I	benazepril	Lotensin	20mg	QD or BID
ACE-I	lisinopril	Zestril	10mg	QD
ACE-I	lisinopril	Zestril	20mg	QD
ACE-I	lisinopril	Zestril	40mg	QD
ACE-I	ramipril	Altace	2.5mg	QD
ACE-I	ramipril	Altace	5mg	QD
ACE-I	ramipril	Altace	10mg	QD
CCB(non-DHP)	diltiazem	Cardizem CD	120mg	QD
CCB(non-DHP)	diltiazem	Cardizem CD	180mg	QD
CCB(non-DHP)	diltiazem	Cardizem CD	240mg	QD
CCB(non-DHP)	diltiazem	Cardizem CD	300mg	QD
BB(cardiosel/non-ISA)	metoprolol	Toprol XL	50mg	QD
BB(cardiosel/non-ISA)	metoprolol	Toprol XL	100mg	QD
BB(cardiosel/non-ISA)	metoprolol	Toprol XL	200mg	QD
AII RB	candesartan	Atacand	4mg	QD or BID
AII RB	candesartan	Atacand	8mg	QD or BID
AII RB	candesartan	Atacand	16mg	QD or BID
AII RB	candesartan	Atacand	32mg	QD or BID
AII RB	valsartan	Diovan	80mg	QD
AII RB	valsartan	Diovan	160mg	QD
alpha-beta blockers	carvedilol	Coreg	3.125mg	BID
alpha-beta blockers	carvedilol	Coreg	6.25mg	BID
alpha-beta blockers	carvedilol	Coreg	12.5mg	BID
alpha-beta blockers	carvedilol	Coreg	25mg	BID

Continued on Next Page

Table 5.6 (continued)**: Blood Pressure Medications Available for ACCORD**
(01/15/01)

Drug Class	Generic Name	Trade Name	Strength	Dosing
reserpine	reserpine	reserpine	0.1mg	QD
reserpine	reserpine	reserpine	0.25mg	QD
vasodilator	hydralazine	hydralazine	25mg	BID
vasodilator	hydralazine	hydralazine	50mg	BID
vasodilator	hydralazine	hydralazine	100mg	BID
alpha blocker	terazosin	Hytrin	1mg	QD or BID
alpha blocker	terazosin	Hytrin	5mg	QD or BID
alpha blocker	terazosin	Hytrin	10mg	QD or BID
loop diuretic	furosemide	Lasix	20mg	QD or BID
loop diuretic	furosemide	Lasix	40mg	QD or BID
loop diuretic	furosemide	Lasix	80mg	QD or BID
ACE-I/diuretic	benazepril & HCTZ	Lotensin HCT	10mg/12.5mg	QD
ACE-I/diuretic	benazepril & HCTZ	Lotensin HCT	20mg/12.5mg	QD
ACE-I/diuretic	benazepril & HCTZ	Lotensin HCT	20mg/25mg	QD
ACE-I/diuretic	lisinopril & HCTZ	Zestoretic	10mg/12.5mg	QD
ACE-I/diuretic	lisinopril & HCTZ	Zestoretic	20mg/12.5mg	QD
ACE-I/diuretic	lisinopril & HCTZ	Zestoretic	20mg/25mg	QD
AII RB/diuretic	candesartan & HCTZ	Atacand HCTZ	16mg/12.5mg	QD
AII RB/diuretic	candesartan & HCTZ	Atacand HCTZ	32mg/12.5mg	QD
AII RB/diuretic	valsartan & HCTZ	Diovan HCT	12.5mg/80mg	QD
AII RB/diuretic	valsartan & HCTZ	Diovan HCT	12.5mg/160mg	QD
DHPccb/ACE-I	amlodipine & benazepril	Lotrel	5mg/10mg	QD
DHPccb/ACE-I	amlodipine & benazepril	Lotrel	5mg/20mg	QD
K sparing diuretic/thiazide	triamterene & HCTZ	Dyazide	50mg/25mg	QD
betablock/diuretic	metoprolol & HCTZ	Lopressor HCT	100/25mg	QD or BID
betablock/diuretic	metoprolol & HCTZ	Lopressor HCT	50/25mg	QD or BID

5.8 Treatment Algorithms

Figures 5.3 to 5.5 represent the treatment algorithms for the Intensive and Standard Glycemia groups.
Figures 5.6 to 5.7 represent the treatment algorithms for the Intensive and Standard Blood pressure groups.

Figure 5.3
Treatment Algorithm for Intensive Glycemic Therapy Group (Goal: HbA1c<6%)

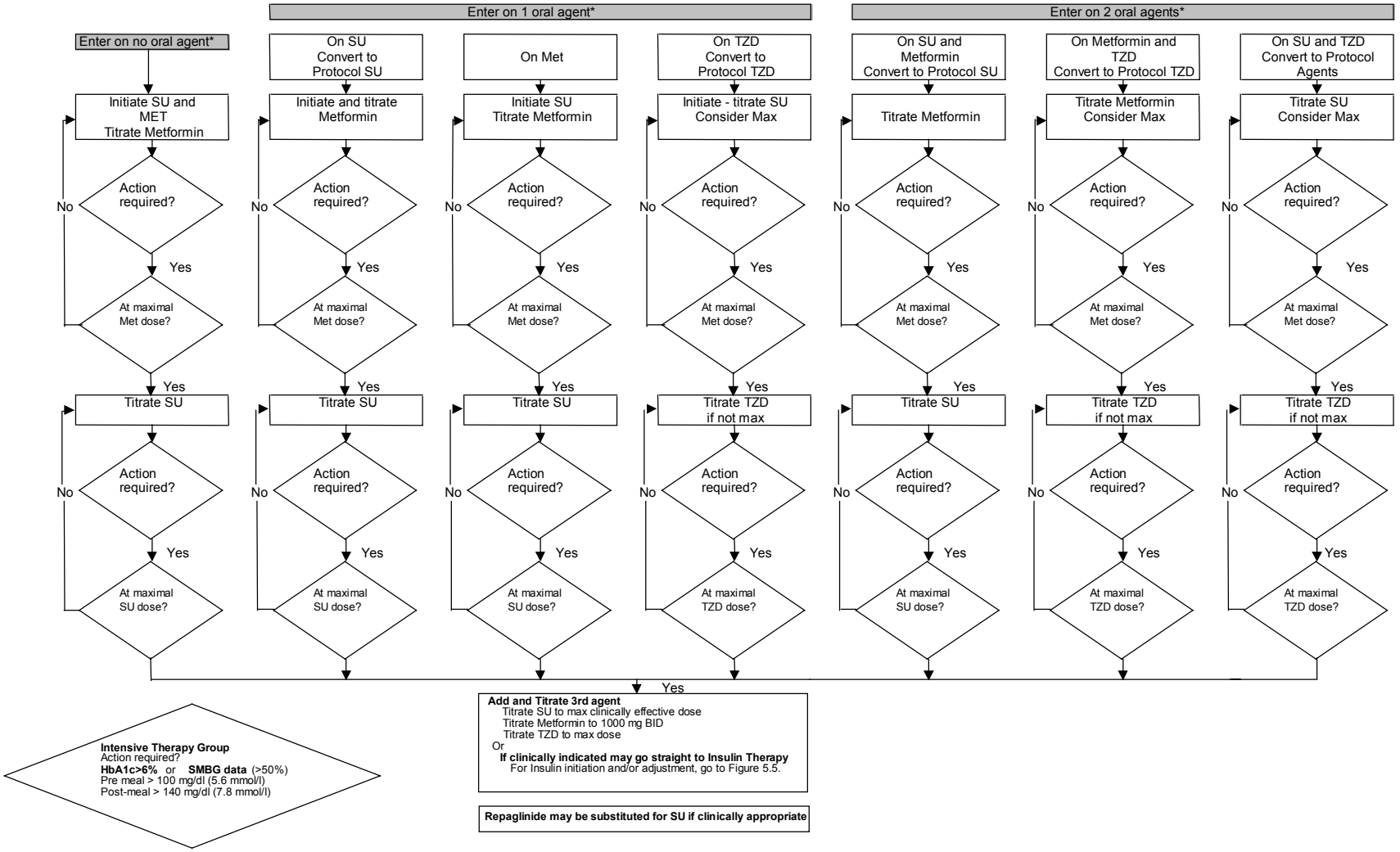


Figure 5.4:
Treatment Group Algorithm for Standard Glycemia Therapy Group (Goal: HbA1c 7% to 7.9%)

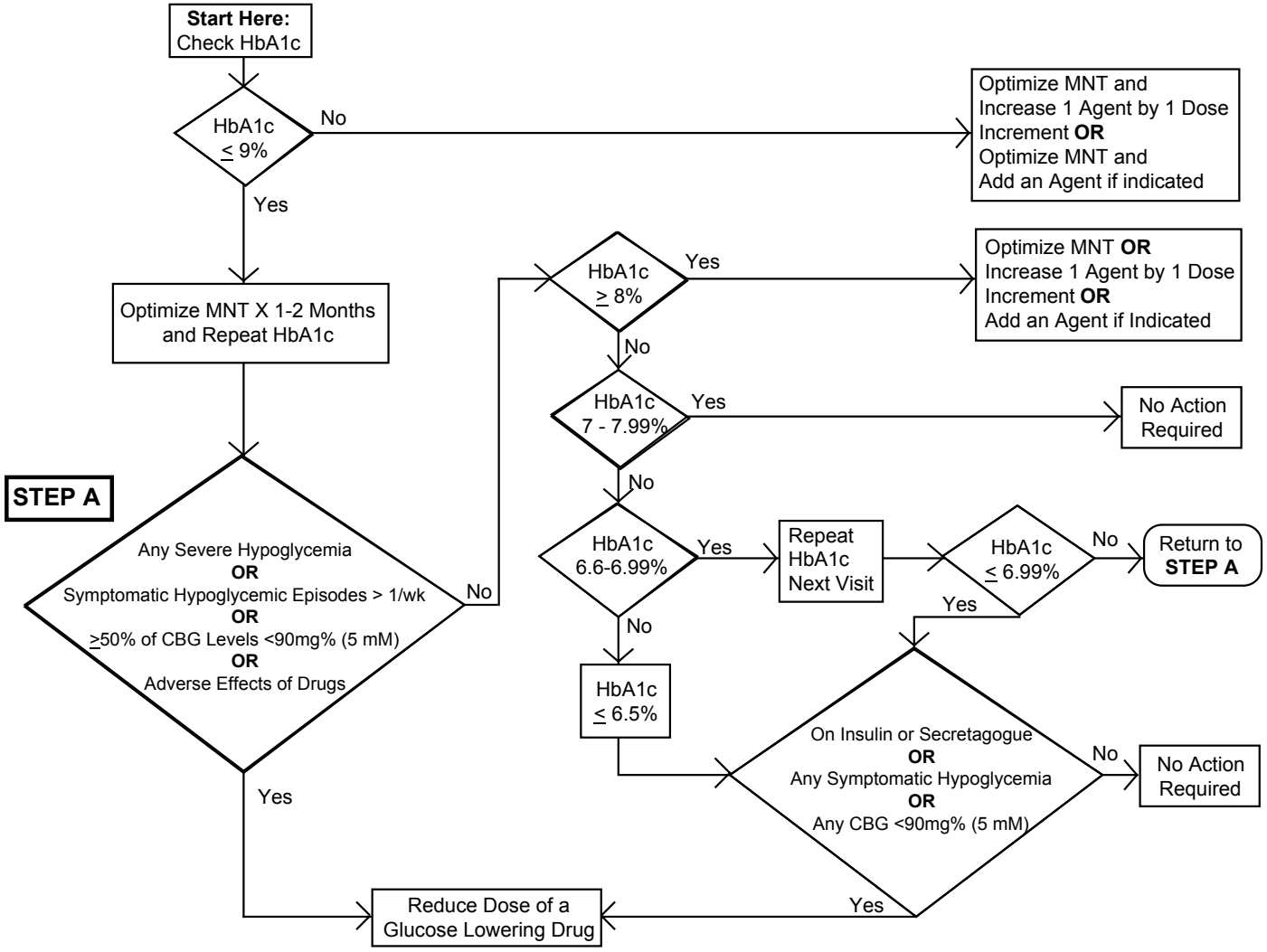
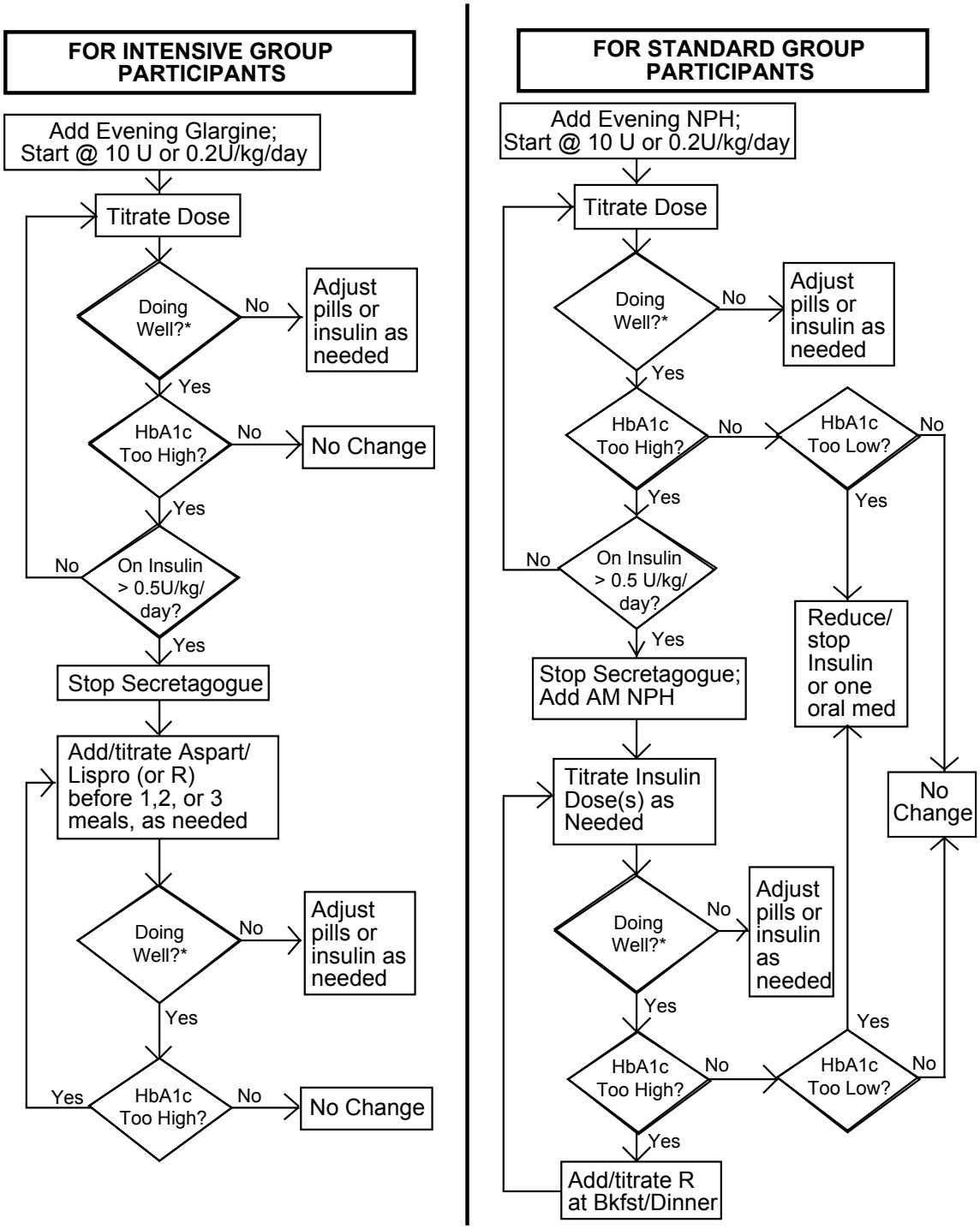
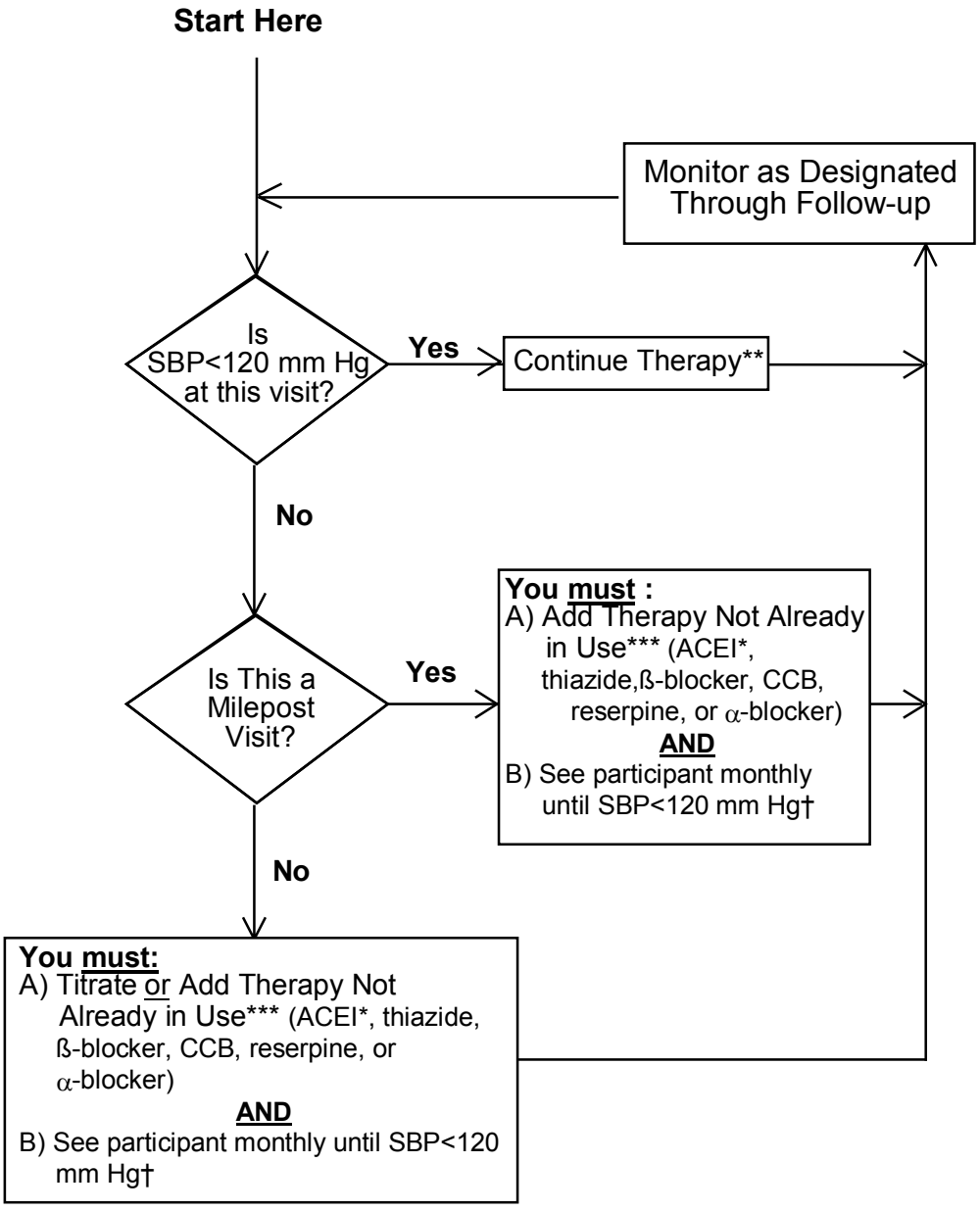


Figure 5.5:
Use of Insulin for Participants On Maximal Oral Therapy



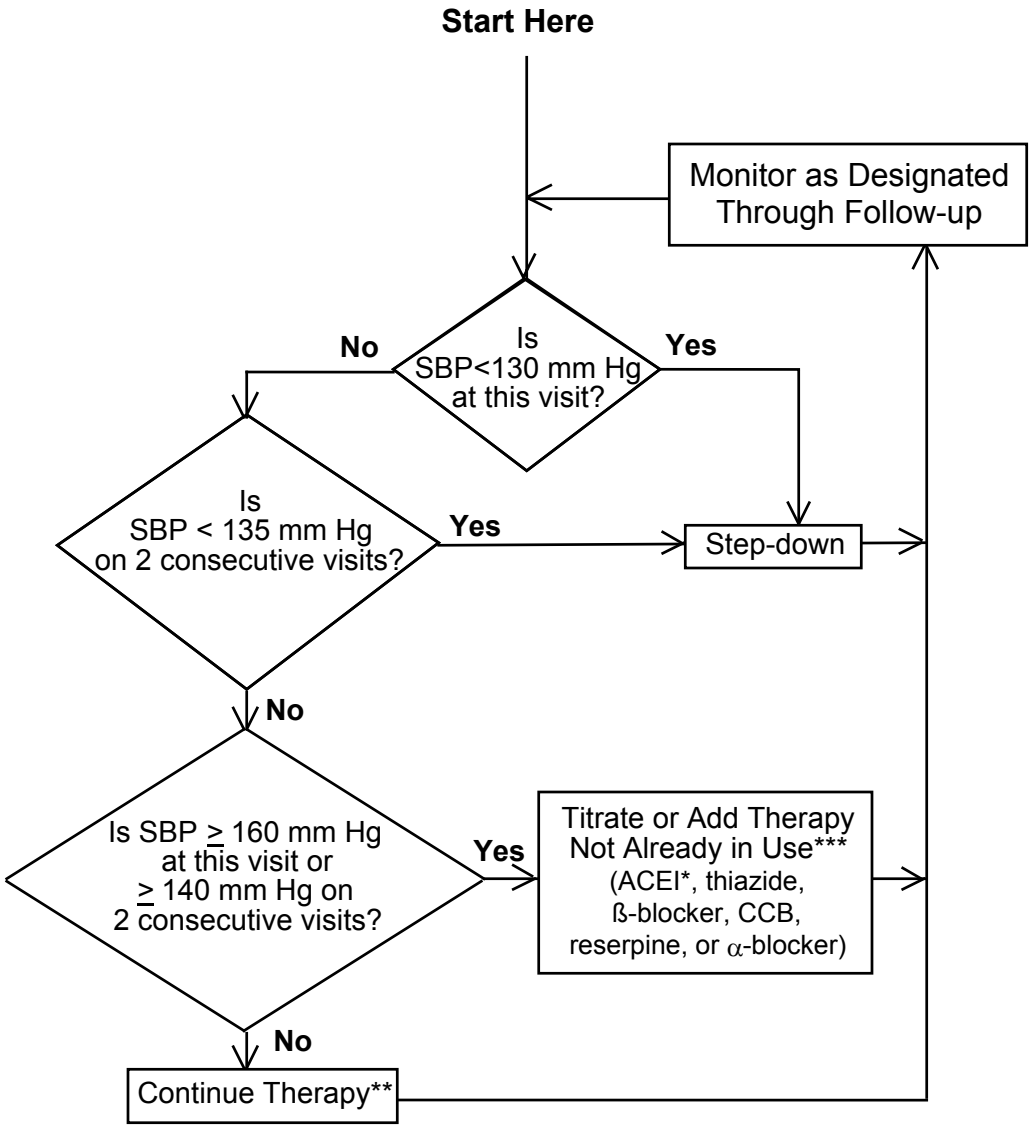
*Doing well: no severe hypoglycemic or adverse event or no reason to reduce therapy (as described in Figure 5.4)

Figure 5.6: Treatment Algorithm for Intensive Blood Pressure Group (Goal: SBP < 120 mm Hg)



* ARB can be considered as a substitute for participants who do not tolerate ACEI therapy
** Unless side effects warrant change in therapy
*** Consult with the Clinical Center Network before adding a fifth antihypertensive medication
† or until a clinical decision is made that therapy should not be increased further

Figure 5.7: Treatment Algorithm for Standard Blood Pressure Group (Goal: SBP < 140 mm Hg)



* ARB can be considered as a substitute for participants who do not tolerate ACEI therapy
** Unless side effects warrant change in therapy
*** Consult with the Clinical Center Network before adding a fifth antihypertensive medication

6. Adjusting Therapy and Dealing with Side Effects for all Three Interventions

6.1 Glycemia Intervention

6.1.1 Overview

One of the key aims of the ACCORD study is to determine if a therapeutic strategy that targets a HbA1c of < 6.0% reduces the rate of cardiovascular disease (CVD) events more than a strategy that targets a HbA1c of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%) in high risk middle-aged or older people with type 2 diabetes. The approaches used to implement these targets, suggested algorithms for the use of pharmacologic agents and follow-up schedules are described in Chapters 2 and 3 of the protocol.

6.1.2 Algorithms for Glycemic Control/ Choice of Agents

Figures 5.3, 5.4 and 5.5 (see Chapter 5) in the MOP are algorithms to guide changes in glycemic therapy for the intensive and standard groups. The exact changes to be made whenever glycemic therapy needs to be intensified on the basis of the HbA1c or the SBGM results will be determined by the individual site using Figures 5.3 through 5.5 as guides.

The point at which to start insulin in individuals not taking insulin at randomization is not explicitly defined. Nevertheless, evening basal insulin should be added to any intensive group participant on maximal oral therapy whose glucose values are in the "Action Required" range (see Table 6.1 below).

Table 6.1: Glycemic Targets and Thresholds for Action for ACCORD

		"Action Required" Threshold	
Group	HbA1c Targets	**HbA1c**	**> 50% of SMBG Results/4 days**
Standard Therapy	7 – 7.9%	> 7.9%* or ≤ 6.5%[#] (anytime) or 6.6%-6.9% [#] (twice consecutively)	fasting/ac < 90 mg/dl (5.0 mmol/l)[#]
Intensive Therapy	< 6.0%	≥ 6.0%*	fasting/ac > 100 mg/dl (5.6 mmol/l) or 2 hrs pc > 140 mg/dl (7.8 mmol/l)*

pc: postcibal; ac: antecibal; SMBG: self monitoring of blood glucose;
*antihyperglycemic therapy will be advanced if either the HbA1c or the SMBG "action required" criteria are met at any participant encounter [#] therapy with drugs that increase

the risk of hypoglycemia (e.g. insulin, sulfonylureas, meglitinides) will be reduced to avoid hypoglycemia if these criteria are met

6.1.3 Reducing Glycemic Medications/ Contraindications to Intensifying Glycemic Therapy

Antihyperglycemic therapy will not be reduced for participants in either group whose HbA1c is within or above the target range (noted in Table 6.1) unless required because of severe hypoglycemia or adverse effects.

Antihyperglycemic therapy will be reduced for participants in the standard group for the following reasons (MOP Chapter 5 Figure 5.4):

1. any severe hypoglycemia
2. more than 1 episode of symptomatic hypoglycemia per week
3. $\geq$ 50% of SMBG levels < 90 mg/dl (5 mmol/l)
4. adverse effects of antihyperglycemic drugs
5. HbA1c < 6.5% on one occasion or 6.6-6.99% on 2 consecutive occasions and either on insulin or a secretagogue, a history of 1 or more episodes of symptomatic hypoglycemia since the previous visit, or 1 or more SMBG levels below 90 mg/dl (5 mmol/l) since the previous visit.

Whenever an intensive group participant's therapy is not intensified when either the Point of Care (POC) HbA1c or the SMBG results indicate that intensification is required, the reason for not complying with the protocol needs to be documented and justified. Reasons may include:

a) any episode of loss of consciousness/seizure within the previous year, or severe hypoglycemia since the last visit (See Section 6.1.5);
b) > ¼ (25%) SMBG values < 70 mg/dl (3.9 mmol/l) within the 2 weeks before a contact;
c) intercurrent illness or hospitalization that accounts for temporarily raised glucose levels.

6.1.4 If a Supplemental (prn) Visit is Required for Hyperglycemia in an Intensive Group Participant

This can be a phone call or visit at the discretion of the site.

1. Review the previous 2 weeks SMBG log and assess for glycemia intervention.
2. Optimize MNT and Lifestyle modification as necessary.
3. Complete **Intensive Glycemia Management Form**. Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See MOP section 6.1.5). If any severe hypoglycemia, fill out **Severe Hypoglycemia Action Form**.

4. Record current glycemic medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record appropriate information on the **Intensive Glycemia Management Form**.
5. Adjust or maintain therapy according to the following:
   a) If POC HbA1c < 6% **AND** < 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
      - Maintain current therapy.
   b) If POC HbA1c < 6% **BUT** $\geq$ 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** $\geq$ 50% of the 2 hour postprandial levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See Section 6.1.3) to intensify therapy:
      - Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).
      2. If POC HbA1c is $\geq$ 6.0% and there is no contraindication (See Section 6.1.3) to intensify therapy:
   c) Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).
6. Reinforce appropriate SMBG Frequency according to Table 3.2 in the protocol (at least $\geq$ 2 times/day if and 4 times/day if glucose is > target (2 ac and 2 pc results/day) if diet /oral therapy. At least 4-8 times/day (2 ac and 2 pc results/day and occasional 3 am test prn) if on insulin.
7. Instruct participants on when and how to self titrate therapy. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.
8. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication if necessary. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
9. Complete the following form and enter data as required:
   a) **Glycemia Medications Log**
   b) **Intensive Glycemia Management Form**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   d) **Encounter and Disposition Form**
   e) **Drug Dispensing Form (as necessary)**
   f) **Study Status Form (as necessary)**

6.1.5 Adjusting Therapy for Hypoglycemia

Hypoglycemic events may occur in individuals in either the intensive or standard group. Severe hypoglycemia is not common in people with type 2 diabetes (even when normoglycemia is targeted). Mild episodes of hypoglycemia are, however, likely to occur. For example, in the UKPDS, the highest rate of major hypoglycemia (defined as hypoglycemia requiring medical intervention or third party assistance) was 2.3% year; it was noted in the subgroup of intensive therapy individuals on insulin. The rate of any hypoglycemic episode (defined as either major episodes or minor, self-treated episodes) in these patients was 36.5%/year.

All participants will be instructed to check their glucose levels regularly as described in the protocol. They will also be taught how to recognize and self-treat hypoglycemia (see MOP Section 6.1.6), and will be instructed to keep glucose available at all times (as tablets). Moreover, any participant who has had an episode of severe hypoglycemia will be provided with glucagon and they and any cohabiting partner will be taught how to administer it.

Severe hypoglycemia is defined as any episode of loss of consciousness/seizure or documented hypoglycemia (glucose < 50 mg/dl or 2.8 mmol/l) that also requires hospitalization or treatment by emergency personnel. If this occurs:

- Adjust medications to target fasting and 2 hour postprandial glucose levels between 100 - 140 mg/dl (5.5 - 7.8 mmol/l) and ≤ 180 mg/dl (10 mmol/l) respectively for at least 4 weeks.
- Ensure that a complete medical assessment by the physician is completed to identify other potential causes (e.g. pituitary or adrenal insufficiency)
- Ensure that the physician reassesses the glycemic goals at subsequent visits.
- Ensure that the participant has received glucagon and that the participant and cohabitant know how to administer it.
- Have telephone contact with participant before the next visit to assess blood glucose records and freedom from hypoglycemia.

Minor hypoglycemia is defined as self-reported transient symptoms such as lightheadedness, tremor, shaking, sweating, tingling, blurry vision, trouble concentrating etc., that are self-treated by ingestion of carbohydrates and resolve on their own. All participants will be asked to note such episodes in their glucose logbooks and to confirm them whenever possible. The estimated frequency (of confirmed and suspected minor hypoglycemia) will be recorded at every visit.

6.1.6 Self-Treatment of Hypoglycemia

1. If the glucose value is < 50 - 70 mg/dl (3.9 mmol/l), it should be treated by ingestion of 15 grams of CHO (e.g. 3-4 glucose tablets, 5 Lifesavers, 4-6 oz. of a regular – [non-diet] – soft drink, or 8 oz. low fat milk);
2. If the glucose value is < 50 mg/dl (2.8 mmol/l), it should be treated by ingestion of 20-30 grams of CHO (e.g. 6-8 glucose tablets);
3. Blood glucose should be self-tested 15-20 minutes after therapy and therapy repeated if the level is still low (as above)
4. If no meal will be eaten within 1-2 hours, a mixed nutrient snack, including CHO, protein, and fat should be ingested right after the initial therapy to prevent another episode
5. If the glucose value was low or there was significant cognitive or motor impairment, individuals should treat and re-test glucose value. The glucose value should be > 70 mg/dl (3.9 mmol/l) before driving a car or operating heavy machinery.

6.1.7 Education and Minimization of Hypoglycemia in Participants

Hypoglycemia is an inherent risk in the treatment of diabetes. It is important to inform participants of the signs and symptoms of hypoglycemia, techniques to minimize the risk and appropriate methods of treatment. Several tools are available for use in educating participants:

1. Hypoglycemia Cartoon
2. Participant Wallet Card
3. Primer on Hypoglycemia
4. Participant Newsletters

All participants must be provided with the written material listed above at the beginning of the study. Study staff should review verbally the signs and symptoms with the participant and family members. Both participants and family members should be educated on the appropriate treatment for symptoms, and provided with glucose tablets. Those participants suffering one severe hypoglycemic event should be provided with a glucagon kit and both the participant and the family member taught how to use it. This material must be reviewed annually with all participants and after every reported hypoglycemic event.

6.1.8 Dealing with Liver Function Test Issues

Patients with known chronic active liver disease other than fatty liver without evidence of cirrhosis should not be treated with thiazolidinediones (TZD). All patients should have a baseline ALT level prior to initiating TZD therapy. Patients with ALT levels between 1.0 and 2.5 times the upper limits of normal should have an evaluation of common liver disorders (hemochromatosis, hepatitis B, hepatitis C, autoimmune hepatitis including liver ultrasound) before considering TZD therapy. Therapy with TZD's in patients with mildly elevated liver enzymes may be initiated with caution and should include the appropriate clinical follow-up, which may include more frequent liver enzyme monitoring. Patients with ALT levels > 2.5 times the upper limits of normal should not be started on TZD's.

During therapy with TZD's ALT should be measured every two months during the first year and intermittently thereafter (generally recommended every 3-6 months). Patients who display ALT levels at 1 to 2.5 times the upper limit of normal any time during therapy with TZD's should be evaluated to determine the cause of the liver enzyme elevation. Therapy with TZD's in patients with mildly elevated liver enzymes may continue with caution and include appropriate clinical follow-up, which may include more frequent liver enzyme monitoring. If ALT exceeds 2.5 times the upper limit of normal, liver function tests should be evaluated more frequently (weekly was suggested with troglitazone) until the levels return to normal or pretreatment values. If ALT levels exceed 3 times the upper limit of normal, the test should be repeated as soon as possible and if ALT levels remain > 3 times the upper limit of normal or if the patient is jaundiced, TZD therapy should be discontinued.

6.1.9 Thiazolidinediones (TZD) and Heart Failure

As TZDs are contraindicated in people with stage 3 or 4 heart failure, if a participant who is taking a TZD does develop heart failure, the TZD should be stopped and the heart failure treated and investigated. Depending on the results of these investigations the investigator may reconsider cautiously reinstituting TZD therapy if the heart failure resolves, and was judged to have not been directly cause by the TZD alone.

6.2 Blood Pressure Intervention

6.2.1 Overview

The ACCORD blood pressure (BP) trial component is designed to test whether a therapeutic strategy that targets a systolic blood pressure (SBP) of < 120 mm Hg reduces the rate of cardiovascular events in a middle-aged or older type 2 diabetic population at high risk for cardiovascular events compared to a strategy that targets a SBP of < 140 mm Hg in the context of good glycemic control.

6.2.2 Research Design

The BP intervention is an unmasked, open label, randomized component of participants entered into ACCORD. The recruitment goal for the BP portion of ACCORD is 4,200 participants.

6.2.3 Intensive BP Group (and Milepost Evaluations)

The BP goal for the Intensive BP Group is SBP < 120 mm Hg. Participants in this group should be initiated on at least two antihypertensive medications, one of which is a thiazide-type diuretic. Visits should occur at least monthly until SBP goal is achieved or until a decision is made by the investigator to not add further medications or increase doses, which should be a rare exception.

Drug doses should be increased and/or additional medications added at each visit, usually at one-month intervals until the participant's goal is reached. Once a participant has achieved SBP < 120 mm Hg, the regimen should be reviewed and reinforced with the participant. Compliance with their medications, diet, exercise and other risk reduction therapy should be encouraged. If the participant's BP increases above goal, drug regimens may be adjusted (doses increased or drugs added) as needed until the goal BP is re-established.

At randomization all participants in the intensive group of the BP trial will automatically be assigned a series of "milepost" dates. Milepost dates will be assigned for the entire duration of the study. "Milepost visits" will occur at 4 month intervals for the first 2 years of follow-up and annually thereafter.

Between these dates, antihypertensive medications should be adjusted and/or additional antihypertensive medications should be added within the recommended dose range to achieve the target BP. However, **once a milepost date has been reached and if the participant's BP remains above goal, the investigator is required to add an additional drug class** to the existing regimen, **and see the participant monthly until the SBP goes below 120 mm Hg.**

The site will be notified before a participant's milepost date that adding a drug will be required if the BP is above goal at that visit. In situations where the investigator believes that the ***addition of another drug may potentially be harmful to the participant, the requirement may be waived***. This decision must be **justified with a Milepost Blood Pressure Drug Exception Form that is data entered at the clinical site**. The number of Milepost exception forms will be closely monitored in each ACCORD clinic and regular feedback provided to the clinic for the degree of adherence to the drug protocol.

Action is required at each milepost visit throughout the duration of the study for those intensive group participants who remain above their initial goal pressure of < 120 mm Hg.

6.2.4 If a Supplemental (prn) Visit is Required for Blood Pressure in an Intensive Group Participant:

1. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self-report of adherence in source documents.
   c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
   d) If the SBP is at the desired goal of < 120 mm Hg, maintain current therapy
   e) If the SBP $\geq$ 120 mm Hg, an upward dose titration or an additional drug (not already in use) should be added. Participants should be seen at monthly intervals until at goal.
   f) Record name, dose, and adherence of all blood pressure medications on the **Blood Pressure Medications Log.**
2. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
3. Remind participant to take blood pressure medications the morning of next visit.
4. Complete the following forms and enter data as required:
   a) **Intensive Blood Pressure Management Form**
   b) **Blood Pressure Medications Log**
   c) **Encounter and Disposition Form**

d) **Drug Dispensing Form (as necessary)**
e) **Study Status Form (as necessary)**

6.2.5 Standard BP Group

The BP goal for the standard BP group is SBP < 140 mm Hg. Participants in this group may or may not be on treatment with one or more antihypertensive medications, based on their baseline SBP and prior therapy. The treatment algorithm (MOP Fig 5.7) should be used at the initial visit and subsequent visits to decide on the appropriate regimen. If antihypertensive medication(s) is indicated per protocol, consideration should be given to include a thiazide-type diuretic as initial therapy or as part of the regimen.

6.2.6 Antihypertensive Therapy

All study antihypertensive agents (except carvedilol and hydralazine) are once daily preparations of the representative agent. See MOP Table 5.6 for antihypertensive agents that are available from the Drug Distribution Center.

The investigator may select among the available ACCORD antihypertensive medications for initiation of therapy. Other drugs not supplied by the trial may be used as the investigator determines appropriate. However, all antihypertensive regimens should include a drug class associated with reduced cardiovascular events in diabetic participants: diuretic, beta-blocker, calcium channel blocker, or ACE inhibitor, and consideration should be given to include a thiazide-type diuretic as initial therapy or as part of the regimen. Based on currently completed trials, some experts believe that monotherapy with a calcium channel blocker may be less desirable in a participant with diabetes. If an alpha-blocker is used, it should be used in combination with at least one agent proven to reduce cardiovascular events in hypertensive participants with diabetes. For participants in the intensive BP group (Figure 5.6 in Chapter 5 of the MOP), a combination of a diuretic and either an ACE inhibitor, a beta-blocker, a calcium channel blocker, or an angiotensin II receptor blocker (ARB) is strongly encouraged for initial therapy at randomization. For this group, doses should be increased and/or additional antihypertensive medications should be added at each visit, until the participant's goal has been reached. "Milepost Visits" will occur at 4-month intervals in the intensive therapy group for the first 2 years of follow-up. After 2 years of follow-up, these visits will occur annually in the intensive therapy group. If the SBP is not less than 120 mmHg at a "Milepost Visit," then an antihypertensive drug from an additional class must be added (unless there are compelling reasons to wait) and the participant seen monthly until the SBP goes below 120 mm Hg.

6.2.7 Treatment algorithm

The algorithms, for both the standard and intensive BP groups, (See MOP Figures 5.6 and 5.7) call for an assessment of the participants' antihypertensive medication regimen at baseline to determine the starting point on the decision tree for future monitoring and medication adjustments needed to achieve their assigned BP goals. (See MOP Section 5.5).

The standard participants' BP should be monitored as indicated. If the SBP for a standard group participant is < 140 mmHg, one should continue the therapy and monitoring as prescribed by the protocol. Should the SBP fall under 135 mm Hg on two consecutive clinic visits or 130 mmHg at a single visit, step-down therapy (a reduction of dose or number of antihypertensive drugs) is allowed at the discretion of the ACCORD therapist, after consultation with the participant. However, if the SBP is $\geq$ 160 mm Hg at a single visit or $\geq$ 140 mmHg on two consecutive visits, upward dose titration or an additional drug (not already in use) is indicated.

For the intensive BP group, initiation of study therapy is the same, independent of the participant's medication status at baseline. Regardless of whether the participant was or was not receiving any antihypertensive therapy at baseline, the participant will begin a study drug combination (at least thiazide + some other agent) and be monitored at least monthly until SBP<120 mm Hg. If the SBP remains $\geq$ 120 mm Hg upward dose titration or an additional drug (not already in use) must be considered (and must be done if this is a milepost visit). If the SBP has reached the desired goal and remains < 120 mm Hg, therapy and monitoring will continue as per protocol.

6.2.8 Add-on or Substitution Therapy

Investigators may use their discretion in selecting agents to refine the participant's regimen in attempting to achieve the assigned SBP goal. Most multi-drug regimens are more effective if a diuretic is included and if drugs from several classes with different mechanisms of actions are used. It is expected that most ACCORD participants in the intensive BP intervention will require at least 2 and up to 5 medications to achieve their BP goal. If a participant is not at goal on 4 drugs, consultation with your CCN office or your CCN BP Working Group representative is recommended. Once a participant is receiving 5 drugs at optimal doses and the BP remains above goal, a different drug class may be substituted instead of adding another drug.

6.2.9 Consultation with CCN Office (PI)

Consultation with your local CCN Office or your CCN BP Working Group representative about a participant's regimen may be requested at any time for any concern relative to the participant, protocol or regimen. It is strongly recommended that such contact occur, if a participant is on 4 or 5 antihypertensive agents and remains above their assigned goal, or prior to discontinuing study therapy because of non-serious adverse effects.

6.2.10 Evaluation and Management of Symptomatic Orthostatic Hypotension

Definition

Orthostatic hypotension (OH) is usually defined as a decline of systolic blood pressure (SBP) ≥20 mm Hg or a decline of diastolic BP ≥10 mm Hg that occurs within 3 minutes after moving from a supine or seated to a standing position.

Symptoms

OH may be asymptomatic or may be accompanied by dizziness, lightheadedness, feeling faint, or syncope. Generally, asymptomatic OH should not change adherence to the ACCORD protocol, although medication classes may be adjusted to continue appropriate sitting BP control while minimizing postural hypotension.

Predisposing Conditions

In epidemiologic studies OH is more likely to occur in older individuals with high SBP. Diabetes mellitus and other autonomic neuropathies, volume depletion, varicose veins, alcoholism, and certain medications are also associated with OH.

Note: Occasionally, hypotension occurs if a patient previously nonadherent to prescribed medications begins taking the medications. Because BP typically declines after a meal due to splanchnic blood pooling, standing BP should not be measured within 90 minutes after a meal if possible.

Predisposing Medications

Some classes of medications are more likely to cause OH than others. The most frequent offenders are alpha-blocking drugs, such as prazosin, terazosin, or doxazosin, and central alpha agonists, such as clonidine, methyldopa or guanfacine. Although beta-blockers are perhaps least likely antihypertensive class to cause OH, one of the most common adverse effects of combined alpha-beta blockers, such as labetolol or carvedilol, is OH or dizziness, primarily because of the alpha-blocking component of these drugs. Rarely, beta-blockers may cause OH because of severe bradycardia (e.g., <40-50 BPM) and inability to increase heart rate/cardiac output on upright posture, especially if other drugs or conditions have lowered BP excessively. Occasionally, reserpine, nitrates, or calcium channel blockers may contribute to or cause OH. Certain psychotropic drugs, most notably phenothiazines, can also cause OH.

Thiazide diuretics rarely cause OH, unless the patient is significantly volume depleted or another agent is added to a diuretic that may cause first-dose hypotension (e.g., a short-acting ACE inhibitor like captopril or a short-acting alpha blocker like prazosin). High dose loop diuretics, such as furosemide, may lead to excessive volume depletion and hypotension, with or without OH.

Management

Patients with poor oral intake, dehydration from whatever cause, GI or renal causes for excessive fluid loss, or hemorrhage, may need to have their diuretic or other antihypertensive medications stopped temporarily until the volume-depletion is corrected. If a participant with symptomatic OH has no obvious cause of excessive volume depletion, the medication regimen should be reviewed. Psychotropic drugs may need to be changed or reduced in dose. If the patient is on an alpha-blocker, alpha-beta blocker, or central alpha agonist, the dose should be reduced or the potentially offending agent

discontinued and, if necessary for BP control, replaced with another class of antihypertensive drug less likely to cause symptomatic OH. If the participant requires an alpha-blocker for BPH/bladder outlet obstructive symptoms, a more selective alpha-blocker (e.g., tamsulosin) may be considered.

Patients with symptomatic OH should eat small meals and avoid standing up rapidly after eating. Such individuals should avoid hot showers and other excessive heat exposure. An increase in sodium intake may be considered in patients without hypertension or heart failure. In those with large varicose veins, fitted elastic hose or compression stockings may reduce venous pooling in the legs. In refractory cases of symptomatic OH, drug therapy with vasoconstrictors such as midodrine or dihydroergotamine or with mineralcorticoids may be considered.

6.3 Lipid Intervention

6.3.1 Overview

The ACCORD lipid component is designed to test whether a therapeutic strategy that uses a fibrate to raise HDL-C/lower triglyceride levels and uses a statin for treatment of LDL-C reduces the rate of CVD events compared to a strategy that only uses a statin for treatment of LDL-C. The specific fibrate to be used in ACCORD is fenofibrate and the specific statin is simvastatin. All participants in the lipid portion of ACCORD will be on at least 20 mg of the simvastatin.

6.3.2 Design of the Lipid Trial

The question under study in the ACCORD Lipid Trial is: In the face of appropriate LDL-C control, does the addition of fenofibrate to reduce triglycerides and increase HDL reduce cardiovascular events? ACCORD is using a statin to obtain LDL-C control and the specific statin available for use is simvastatin (although sites are not limited to simvastatin- see section 6.3.10 below).

Appropriate LDL control is defined as an LDL less than 120 mg/dl. Because the upper limit for entry LDL-C is 180 mg/dl, and because 40 mg simvastatin (the maximum dose available for use with the blinded study medication) should provide about an average 40% reduction in LDL-cholesterol, it is expected that few participants will have an on-treatment LDL-C of more than 120 mg/dl. However, as noted below, if a participant has an LDL-cholesterol level that is persistently greater than 120 mg/dl, ACCORD will, consistent with NCEP guidelines, take the participant off the masked study medication and continue treatment with simvastatin until placed on a non-study statin by his/her primary caregiver.

6.3.3 Determination of Statin Dose

The starting dose of simvastatin is 20 mg/day for those who do not have a history of a cardiovascular event (primary prevention) and 40 mg for those who have had a previous cardiovascular event (secondary prevention). For ACCORD purposes, a cardiovascular event (defined in the protocol in Chapter 2, Section 2.1.a.6.A) is a myocardial infarction, stroke, coronary revascularization (e.g., coronary artery bypass graft surgery, stent placement, percutaneous transluminal coronary angioplasty, or laser atherectomy), carotid or peripheral revascularization (e.g., carotid endarterectomy, lower extremity atherosclerotic disease atherectomy, repair of abdominal aorta aneurysm, femoral or popliteal bypass), and angina with ischemic changes (resting ECG changes, ECG changes on a graded exercise test (GXT), or positive cardiac imaging study). Simvastatin should be administered once daily after the evening meal or at bedtime.

Participants may have their simvastatin dose increased from 20 mg to 40 mg in two circumstances. The first is an LDL-C greater than 100 mg/dL (2.59 mmol/L) on two consecutive occasions. If a participant has an LDL level above 100 mg/dl (2.59 mmol/l) at an annual visit after the first year, the following steps occur (**see Figure 1**):

- The clinical site is sent an automated email from the Coordinating Center
- The Clinical Site draws another fasting lipid profile at the participants next scheduled visit in 4 months. This lipid panel should be sent to the Central Lab.
- If the LDL>100 mg/dl (2.59 mmol/l) is confirmed, the clinical site is sent another automated email. The clinical site should place the participant on 40 mg dose of simvastatin.
- Once the participant has been placed on the increased dose of simvastatin, a blood sample for ALT and CPK should be drawn at the next regular 4 month visit after the increase.

The second circumstance that requires an increase in the dose of simvastatin is when a participant requires secondary cardioprotection. **ACCORD participants receive 40 mg of simvastatin if they have had a cardiovascular event unless the most recent LDL-C is less than 40mg/dl (1.03 mmol/l)**. For ACCORD purposes, a cardiovascular event (defined in the protocol in Chapter 2, Section 2.1.a.6.A) is a myocardial infarction, stroke, coronary revascularization (e.g., coronary artery bypass graft surgery, stent placement, percutaneous transluminal coronary angioplasty, or laser atherectomy), carotid or peripheral revascularization (e.g., carotid endarterectomy, lower extremity atherosclerotic disease atherectomy, repair of abdominal aorta aneurysm, femoral or popliteal bypass), and angina with ischemic changes (resting ECG changes, ECG changes on a graded exercise test (GXT), or positive cardiac imaging study). Should a participant have qualifying event during the ACCORD trial, the following will occur:

- The Clinical Site will complete and data enter the Preliminary Event Form.
- The Coordinating Center will send an email to the Clinical Site upon receipt of the Preliminary Event Form informing the Clinical Site that the participant now qualifies for secondary protection and should be placed on 40 mg of simvastatin. This information is also posted on the web site home page for each participant.
- The Clinical Site contacts the participant and increases the dose of simvastatin upon receipt of the alert. A blood sample for ALT and CPK should be drawn at the next regular 4 month visit after the increase.

If the measured LDL-C goes above 120 mg/dl (3.10 mmol/l) after titrating simvastatin to 40 mg/day the Coordinating Center will send an automated email to the Clinical Site PI and Coordinator, and the CCN PI and Coordinator who should confirm compliance with the study statin, refer the participant to a nutritionist for dietary instruction/reinforcement (if appropriate), and schedule a blood draw for the visit four months from the visit at which the LDL-C was above 120 mg/dl (3.10 mmol/l). This blood specimen needs to be sent to the ACCORD Central Chemistry Laboratory for lipid analysis.

If the participant has an LDL-C above 120 mg/dl (3.10 mmol/l) on two consecutive visits 4 months apart after titrating simvastatin to 40 mg/day (even after compliance review and dietary counseling), other lipid lowering medications can be considered (see section 6.3.10 for allowed medications). If other lipid medications are used in conjunction with the masked study medication, a blood sample for ALT, CPK and fasting lipid level should be drawn at the next regular 4 month visit after the start of the new medication and sent to the central lab. If the participant is to be put on a combination not allowed by MOP 6.3.10 then the following will occur (**see Figure 2**):

- The CC will send an automated email to the Clinical Site PI and Coordinator, and the CCN PI and Coordinator.
- The participant will be taken off the fibrate/placebo pills.
- The participant will remain on simvastatin 40 mg/day until placed on non-study statin by his/her primary caregiver. [The site needs to contact the CCN office if any participant needs non-study simvastatin].
- The site staff will make an appointment with the participant's doctor for follow-up.
- The site staff will also provide a letter for the participant to take to his/her physician for the follow-up visit. This letter will include the blood lipid values and describes the medication regimen the participant was on when the blood was drawn.
- The site staff will confirm that the participant had visited their physician.
- From that point on, the participant would be treated for their lipids by his/her personal physician and given results of any ACCORD lipid determinations to share with this physician.

If the centrally measured LDL-C is ever less than 40 mg/dl (1.03 mmol/l) during follow-up, clinic personnel should determine compliance with study statin and fibrate/placebo (to make sure that the participant is not taking more than the prescribed number of pills daily) and refer participant to nutritionist for dietary counseling to ensure that the participant is eating a balanced, adequate diet. If the centrally measured LDL-C is ever less than 40 mg/dl (1.03 mmol/l) on two consecutive measurements taken 4 months apart, the following will occur (**see Figure 3 and 4**):

- The CC will send an automated email to the Clinical Site PI and Coordinator, and the CCN PI and Coordinator.
- If the participant is on 40 mg of simvastatin, the Clinical Site will reduce the dose to 20 mg. Another centrally measured LDL-C should be checked at the next 4 month visit. If this LDL is still below 40 mg/dl (1.03 mmol/l), the participant should be taken off their simvastatin (**see Figure 3**).

- If the participant is already on the 20 mg dose of simvastatin, the participant should be taken off simvastatin (**see Figure 4**).
- The participant may remain on masked study medication.

6.3.4 Determination of Masked Study Medication Dose

The starting dose of masked fenofibrate/placebo medication will be determined by the calculated glomerular filtration rate (GFR) using the baseline serum creatinine level and the abbreviated MDRD equation (Levey 2003). Those participants with a baseline GFR $\geq$50 ml/min/1.73m^2 will begin at a starting dose of 160 mg of fenofibrate or identical placebo tablet. Those with a calculated GFR between 30 and <50 will start at the reduced dose of 54 mg/day fenofibrate or placebo.

The dose of masked study medication may be adjusted during the study if the participant has a reduction in renal functioning. Participants in the lipid trial will have serum creatinine measured every four months during follow-up. If the participant had started on the 160 mg dose of the masked medication, this dose will be down-titrated if the participant's estimated GFR falls between 30 and <50 mL/min/1.73m^2 on two consecutive measurements taken four months apart. Participants with GFRs in this range will receive either 54 mg/day of fenofibrate or matching placebo (**see Figure 5**).

Implementation of ongoing blinded study medication dose adjustment based on GFR:

- The ACCORD Coordinating Center (CC) will monitor GFR values obtained on participants at routine 4-month blood draws. **NO** automated email is sent to the clinic at the first occurrence of decreased GFR.
- The CC will notify the Clinical Site PI and Coordinator, the CCN and Coordinator, and the Drug Distribution Center (DDC) when a participant has met the criteria for down titration of masked study medication (two reduced GFR 4 months apart).
- The DDC will send a new box of reduced dose masked study medication for the participant to the Clinical Site.
- The dose of blinded study medication will be listed on the participant main page below the "Lipid Bottle ID" (e.g. REDUCED).

If the estimated GFR falls below 30 mL/min/1.73m^2 at any time, the Coordinating Center will send an automated email to the clinical site that a confirmatory blood draw for repeat estimated GFR will be required within 2 weeks. If the confirmatory estimated GFR is below 30mL/min/1.73m^2, the masked study medication will be permanently discontinued, regardless of fenofibrate or placebo assignment.

Implementation of discontinuation of blinded study medication for GFR less than 30ml/min/1.73m^2 for both active and placebo Lipid Trial participants (**see Figure 6**):

- The CC will notify the Clinical Site PI and Coordinator, and the CCN PI and Coordinator when a participant has a Central Lab calculated GFR less than 30ml/min/1.73m^2.
- Clinics must schedule a repeat blood draw for creatinine within 2 weeks. This should be sent to the Central Lab. The participant should remain on blinded medication during the 2-week interval.
- Upon receipt of the second blood sample, the CC will determine if the participant meets the criteria to stop the blinded study medication or whether a dose reduction is required.
- An automated email will be sent from the CC to the Clinical Site at this time with dosing instructions. If the participant is on full dose and the repeat GFR is greater than 30ml/min/1.73m^2, the participant will be placed on reduced dose. If the participant is on reduced dose, then the participant may remain on the current dose.
- If Clinical Sites become aware of a participant who had an elevated creatinine at an outside blood draw, they should bring the participant in for an ASAP prn visit and recheck the creatinine using the ACCORD Central Lab. The Clinical site should send the outside creatinine level to the Safety Officer at the CC at the time of Central Lab blood draw. The CC will then notify the clinic if the participant should have a reduced dose or have their blinded medication discontinued.

6.3.5 Monitoring Lipid Treatments

Participants will be seen by staff according to the schedule of visits for the glycemia intervention. For participants in the lipid component of the ACCORD study, lipid measurements will be taken at 4, 8, and 12 months post-randomization, and annually thereafter. Creatinine measures will be taken every 4 months. Also, blood samples for ALT, and CPK measurements will be obtained at 1, 4, 8, and 12 months and then annually thereafter. If at any time the participant has relevant symptoms or signs suggestive of drug-induced toxicity, liver function tests and/or CPK levels will be obtained through the Central Laboratory.

If an ACCORD participant requires an increase from 20 mg to 40 mg in their dose of simvastatin during the study (for either secondary prevention or because of LDL level above 100 mg/dl (2.59 mmol/l), a blood sample for ALT and CPK should be drawn at the next regular 4 month visit after the increase. Similarly, if the participant has their simvastatin (or other statin medication) increased to 40 mg (or equivalent) by a physician outside the ACCORD study for a non-protocol reason and the participant remains on blinded study medication, a prn blood sample for ALT and CPK should be drawn at the next regular 4 month visit.

Clinical sites have the option of checking additional labs on their participants during the study and are encouraged to do so in particular clinical situations. The following sections describe the procedures to be followed if abnormalities occur.

6.3.5.1 What to do if Triglyceride Exceeds 750 mg/dl (8.47 mmol/l)

If the centrally measured triglyceride ever exceeds 750 mg/dl (8.47 mmol/l) but is less than 1000 mg/dl during follow-up, the CC will send an automated email to the Clinical Site PI and Coordinator, and the CCN PI and Coordinator. Clinic personnel should contact the participant and assess for signs and symptoms of pancreatitis. If the participant has any complaints consistent with pancreatitis, they should immediately be referred for urgent medical care. If no signs or symptoms of pancreatitis are present, study staff should determine compliance with study statin and fibrate/placebo, refer participant to nutritionist for dietary instruction/reinforcement (if deemed appropriate) and determine and modify potential exacerbating disorders i.e. alcohol or simple sugar intake, hypothyroidism, hyperglycemia. A follow-up blood draw should be done at the next scheduled visit.

If the triglyceride exceeds 750 mg/dl (8.47 mmol/l) but is less than 1000 mg/dl on two consecutive measurements 4 months apart, even after the above measures have been conducted, the following will occur (**see Figure 7**):

- The CC will send an automated email to the Clinic Site PI and Coordinator, and the CCN PI and Coordinator.
- The participant will be taken off the simvastatin and the masked fibrate/placebo medication.
- The participant will be dispensed a 160 mg/day tablet of fenofibrate or 600 mg BID of gemfibrozil until placed on non-study fibrate by his/her primary caregiver. [The site needs to contact the CCN office if any participant needs non-study fenofibrate].
- The site staff will make the appointment for follow-up by the participant's physician and will confirm that the appointment was kept.
- The site staff will also provide a letter for the participant to take to their physician for the follow-up visit. This letter will include the blood lipid values and describes the medication regimen the participant was on when the blood was drawn.
- From that point on, the participant will be treated for their lipids by his/her personal physician and given results of any ACCORD lipid determinations to share with this physician.

If the centrally measured triglyceride ever exceeds 1000 mg/dl during the follow-up the CC will send an automated email to the Clinical site PI and Coordinator and the CCN PI and Coordinator. Clinic personnel should contact the participant and assess for signs and symptoms of pancreatitis. If the participant has any complaints consistent with pancreatitis, they should immediately be referred for urgent medical care. If no signs or symptoms of pancreatitis are present, study staff should determine compliance with study statin and fibrate/placebo, refer participant to nutritionist for dietary instruction/reinforcement (if deemed appropriate) and determine and modify potential exacerbating disorders i.e. alcohol or simple sugar intake, hypothyroidism, hyperglycemia. A follow-up blood draw should be done within 2 weeks.

If the triglyceride exceeds 1000 mg/dl on two consecutive measurements, even after the above measures have been conducted, the following will occur (**see Figure 7**):

- The CC will send an automated email to the Clinic Site PI and Coordinator, and the CCN PI and Coordinator.
- The participant will be taken off the simvastatin and the masked fibrate/placebo medication.
- The participant will be dispensed a 160 mg/day tablet of fenofibrate or 600 mg BID of gemfibrozil until placed on non-study fibrate by his/her primary caregiver. [The site needs to contact the CCN office if any participant needs non-study fenofibrate].
- The site staff will make the appointment for follow-up by the participant's physician and will confirm that the appointment was kept.
- The site staff will also provide a letter for the participant to take to their physician for the follow-up visit. This letter will include the blood lipid values and describes the medication regimen the participant was on when the blood was drawn.
- From that point on, the participant will be treated for their lipids by his/her personal physician and given results of any ACCORD lipid determinations to share with this physician.

If the masked fibrate/placebo study medication is stopped for any reason, neither the participant nor the clinic staff needs to be unmasked regarding the study medication's true identity, unless there are other circumstances dictating unmasking.

6.3.6 What to do if Non-protocol Specified Lower Dose of Simvastatin or Blinded Medication is Used

If the protocol specifies the provision of the 40 mg dose of simvastatin and the participant either refuses or does not tolerate, or if the investigator feels that a lower dose is warranted, the participant may be given the 20 mg dose of simvastatin and still remain in the Lipid Trial as an active participant. Please specify on the Lipid Medication Management Form the reason for the lower dose.

If the study investigator wishes to reduce the dose of blinded study medication for a non-protocol specified reason, they must first contact their CCN Lipid Working Group representative and discuss the case. If the Lipid Working Group Representative agrees with the decision to lower the blinded study medication dose, the site principle investigator should then contact the Safety Officer at the Coordinating Center by e-mail, provide the ACCORD participant's study ID, the reason for the lower dose and the confirmation of the CCN Lipid Working Group Representative of the need for the lower dose. The Coordinating Center will then make arrangements for the lower dose to be sent to the clinical site. The ACCORD participant remains in the Lipid Trial as an Active Participant.

6.3.7 What to do if the Participant Complains of Muscle Pain

Participants are advised to report unexplained muscle pain, tenderness, or weakness, or abnormal urine color, particularly if accompanied by fever or malaise. Additionally, participants are asked on the Interval History Follow-up Form and the Annual History

and Physical Follow-up Form about out of the ordinary severe muscle aches and pains. If a participant reports out of the ordinary severe muscle aches and pains, the clinical staff should do the following (**see Figure 8**):

- Assess the participant for signs/symptoms of myostitis. If the participant reports symptoms congruent with myositis, clinic staff should discontinue study lipid medication (statin and masked study drug) and encourage the participant to increase their intake of fluids.
- Draw blood for a CK level and send to the Central Lab. Clinical sites may consider obtaining a creatinine level and urine myoglobins to rule out rhabdomyolysis.
- If the participant appears acutely ill or if changes in creatinine occur or myoglobin is present in the urine, consistent with a diagnosis of rhabdomyolysis, they should be immediately referred for inpatient IV hydration, steroid therapy and monitoring of renal function.

If the initial CK is greater than 10X the upper limit of normal, an automated email will be sent to the clinic site. The site should take the following actions (**see Figure 9**):

- The ACCORD Lipid medications should be temporarily discontinued.
- The CK level should be rechecked within one week. This blood draw should be sent to the Central Lab.
- Clinic staff should ascertain whether there is another explanation for the possible elevation.
- If the CK elevation is associated with out of the ordinary muscle symptoms, the event should be reported as a Serious Adverse Event.
- If at the second blood draw, the CK level remains > 5X ULN, another automated email will be sent to the clinical site. The participant should be permanently taken off the ACCORD lipid medications and monitor CK levels at least weekly until at least 2 consecutive levels are within 3 times the upper limit of normal. CK should then be monitored at 6-week intervals (or more frequently) until at least 2 consecutive measurements are within the normal range. The participant should be referred to their primary care doctor for further lipid management.
- If the second Central Lab CK level is less than 5x ULN, the clinical site may rechallenge the participant with ACCORD Lipid Medications. The order of rechallenge is masked study medication followed by simvastatin 1 month later. CK levels must be monitored and sent to the Central Lab after each lipid study drug addition.

If the initial CK is greater than 5x ULN but less than 10x, the following will occur (**see Figure 10**):

- An automated email will be sent to the Clinical site from the Coordinating Center.
- The participant may continue the ACCORD Lipid medications.
- The CK level should be rechecked within one week. This blood draw should be sent to the Central Lab.

- Clinic staff should ascertain whether there is another explanation for the possible elevation.
- If at the second blood draw, the CK level remains > 5X ULN, another automated email will be sent to the clinical site. The participant should be permanently taken off the ACCORD Lipid medications.
- If at the second blood draw, the CK level is less than or equal to 5x the ULN, the participant may continue their ACCORD lipid medications. The clinic staff should assess the participant for the use of other medications that may interact with the lipid medications and determine if the participants has other underlying causes of the elevation. At the next clinic visit, the participant should be assessed for muscle symptoms. Consider checking a prn CK level in 2-4 weeks.

If the initial CK is less than 5x the upper limit of normal, the participant should continue on their current lipid therapy. The clinic site should assess the participant for the use of other medications that may interact with the lipid drugs and should determine if the participant has another possible cause for the muscle symptoms. The participant should be assessed for symptoms at the next visit. Clinic staff should consider checking a prn CK level 2-4 weeks after the first abnormal value.

If participants report persistent muscle pain despite normal or mildly elevated CPK values (<3X ULN), the study lipid medication may be temporarily discontinued (fibrate/placebo or statin alone or both fibrate placebo and statin) to determine if symptoms resolve. Such participants may be rechallenged with study drug at the investigator's discretion.

6.3.8 What to do if a Routine CK is Abnormal but the Participant Does Not Have Muscle Symptoms

If a CPK value > 10x ULN (**see Figure 9**) is encountered during routine laboratory follow-up, the Clinic Site will receive an automated email from the Coordinating Center. The staff should have the participant return for a repeat blood draw in one week which should be sent to the Central Lab. The participant should temporarily discontinue their ACCORD lipid medications.

If the repeat CK is greater than 10x ULN, the following will occur:

- An automated email will be sent to the Clinic Site from the Coordinating Center
- The participant will have ACCORD Lipid medications permanently discontinued.
- CK levels should be monitored at least weekly until at least 2 consecutive levels are within 3 times the upper limit of normal. CK should then be monitored at 6-week intervals (or more frequently) until at least 2 consecutive measurements are within the normal range.
- The participant should be referred to their primary care doctor for further lipid management.

If the repeat CK is greater than 5x ULN but less than 10xULN, the following should occur:

- CK levels should be monitored at least weekly until at least 2 consecutive levels are less than 5X ULN.
- Once two consecutive CK levels are less than 5x ULN, the clinical site may rechallenge the participant with ACCORD Lipid Medications. The order of rechallenge is masked study medication followed by simvastatin 1 month later. CK levels must be monitored and sent to the Central Lab after each lipid study drug addition.

If the repeat CK is less than or equal to 5x ULN, the participant may be rechallenged with ACCORD Lipid Medications. The medications should be added one at a time with the masked study medication added first, then simvastatin 1 month later. A CK level should be checked after each addition.

If a CPK value > 5x ULN but less than 10x ULN (**see Figure 10**) is encountered during routine laboratory follow-up, the Clinic Site will receive an automated email from the Coordinating Center. A repeat CPK should be drawn in one week and sent to the Central Lab. The participant may continue their ACCORD Lipid Medications.

If the repeat CK is greater than 5x ULN, the following will occur:

- The clinic site will receive an automated email from the Coordinating Center.
- The Clinic Site should have the participant temporarily discontinue their ACCORD lipid medications.
- CK levels should be monitored at least weekly until at least 2 consecutive levels are less than 5X ULN.
- Once two consecutive CK levels are less than 5x ULN, the clinical site may rechallenge the participant with ACCORD Lipid Medications. The order of rechallenge is masked study medication followed by simvastatin 1 month later. CK levels must be monitored and sent to the Central Lab after each lipid study drug addition.

If the repeat blood draw is less than or equal to 5X ULN, the following should occur:

- The participant may continue their ACCORD lipid medications.
- The clinic staff should assess the participant for the use of other medications that may interact with the lipid medications and determine if the participants has other underlying causes of the elevation.
- At the next clinic visit, the participant should be assessed for muscle symptoms.
- Consider checking a prn CK level in 2-4 weeks.

6.3.9 What to do if the Participant Complains of Hepatitis-like Symptoms or Has an Elevated ALT

Participants will be advised to report unexplained nausea, anorexia, vomiting, dark urine, or jaundice. Participants reporting such should be instructed to temporarily discontinue study lipid medication (statin and fibrate/placebo) as well as any study glitazone and metformin, and an ALT (Central Lab) should be obtained within one week. The study coordinator should also determine and, if possible, address other factors known to be associated with elevated transaminases i.e. alcohol use, excessive NSAID or acetominophen use. Use of other agents known to elevate transaminases should also be determined i.e. glitazones, estrogen, androgen, anticonvulsants. If the ALT is >3X ULN, the study lipid medication (as well as any study glitazone and metformin) should not be resumed and the participant should be followed for resolution of elevated ALT. If the ALT resolves, the staff may decide to rechallenge the subject with study medications. If the ALT does not resolve quickly after discontinuation of study medications, the participant should also be referred to their primary physician for clinical evaluation of other causes of hepatitis. The Coordinating Center should be provided with a summary of the evaluation, pertinent lab values, and liver biopsy results if performed.

Participants in whom asymptomatic ALT > 3X ULN are encountered in routine laboratory monitoring the following should occur (**see Figure 11**):

- An automated email is sent to the Clinical Site by the Coordinating Center. A repeat ALT should be drawn within 2 weeks and sent to the Central Lab.
- Participants may continue their study medications during this time.
- Participants in whom ALT is >3X ULN on repeat determination should have study medications discontinued in the following order: simvastatin, TZD, masked study medication. ALT should be checked after each discontinuation.
- Once ALT $\leq$ 3x ULN on 2 occasions, the clinical site may rechallenge the participant with one month between medications. Suggested order: masked medication, simvastatin, TZD. After restarting each medication, an ALT should be drawn.
- If participant is off all meds for 8 weeks, but ALT still >3x ULN, clinic should refer participant to private physician

6.3.10 What to do if Participant Cannot Tolerate Simvastatin

If intolerance to study simvastatin is confirmed following discontinuation OR the treating physician feels that additional LDL lowering would be in the best interest of the participant, masked fenofibrate/placebo may be continued, provided the treating physician administers a non-study lipid lowering agent at allowed doses. Specifically: the masked study fenofibrate/placebo cannot be administered if the participant is on any of the following lipid medications:

a) > 40 mg/day of simvastatin (Zocor®)
b) > 20 mg/day of atorvastatin (Lipitor®)
c) > 40 mg/day of lovastatin (Mevacor®)
d) > 80 mg/day of pravastatin (Pravachol®)

e) > 40 mg/day of fluvastatin (Lescol®)
f) > 10 mg/day of rosuvastatin (Crestor®)
g) > 10/40 mg/day of ezetimibe/simvastatin (Vytorin ®)
h) > 10 mg ezetimibe (Zetia ®)
i) any fibrate
j) any niacin
k) any resin

Stated differently, the masked study fenofibrate/placebo can be administered if the participant is on the following lipid medications:

a) ≤ 40 mg/day of simvastatin (Zocor®)
b) ≤ 20 mg/day of atorvastatin (Lipitor®)
c) ≤ 40 mg/day of lovastatin (Mevacor®)
d) ≤ 80 mg/day of pravastatin (Pravachol®)
e) ≤ 40 mg/day of fluvastatin (Lescol®)
f) ≤ 10 mg/day of rosuvastatin (Crestor®)
g) ≤ 10/40 mg/day ezetimibe/simvastatin (Vytorin®)
h) ≤10 mg ezetimibe (Zetia®)
i) or on no lipid medication other than masked study medication

Note: ACCORD would prefer that a participant stay on the masked study medication. If possible, clinic staff should work with the private physician to see if the participant could be placed on an agent/dose that could be administered in combination with the masked medication.

What to do if the participant cannot tolerate masked study medication
If intolerance to fenofibrate is suspected: study fenofibrate/placebo may be temporarily discontinued and the impact on symptoms assessed after an appropriate period of time. Re-challenge with study fenofibrate/placebo may be undertaken at the investigator's discretion. If intolerance to study fenofibrate/placebo is confirmed, it may be discontinued and study simvastatin may be continued.

Table 6.3.10 Allowed Doses of Non-Study Statin in ACCORD

%LDL reduction	Simvastatin (Zocor)	Lovastatin (Mevcor)	Fluvastatin (Lescol)	Pravastatin (Pravach)	Atorvastatin (Lipitor)	Rosuvastatin (Crestor)	Ezetimibe/ Simvastatin (Vytorin)
28%	10 mg	20 mg	40 mg	20 mg			
34%	20 mg	40 mg		40 mg	10 mg		
40 %	40 mg			80 mg	20 mg	5 mg	
46%						10 mg	10/10 mg
52%							10/20 mg
58%							10/40 mg

Fig 1: What to do if Participant is on 20 mg Simvastatin, but LDL-C is Reported by ACCORD Central Lab as > 100 mg/dl (2.59 mmol/l)

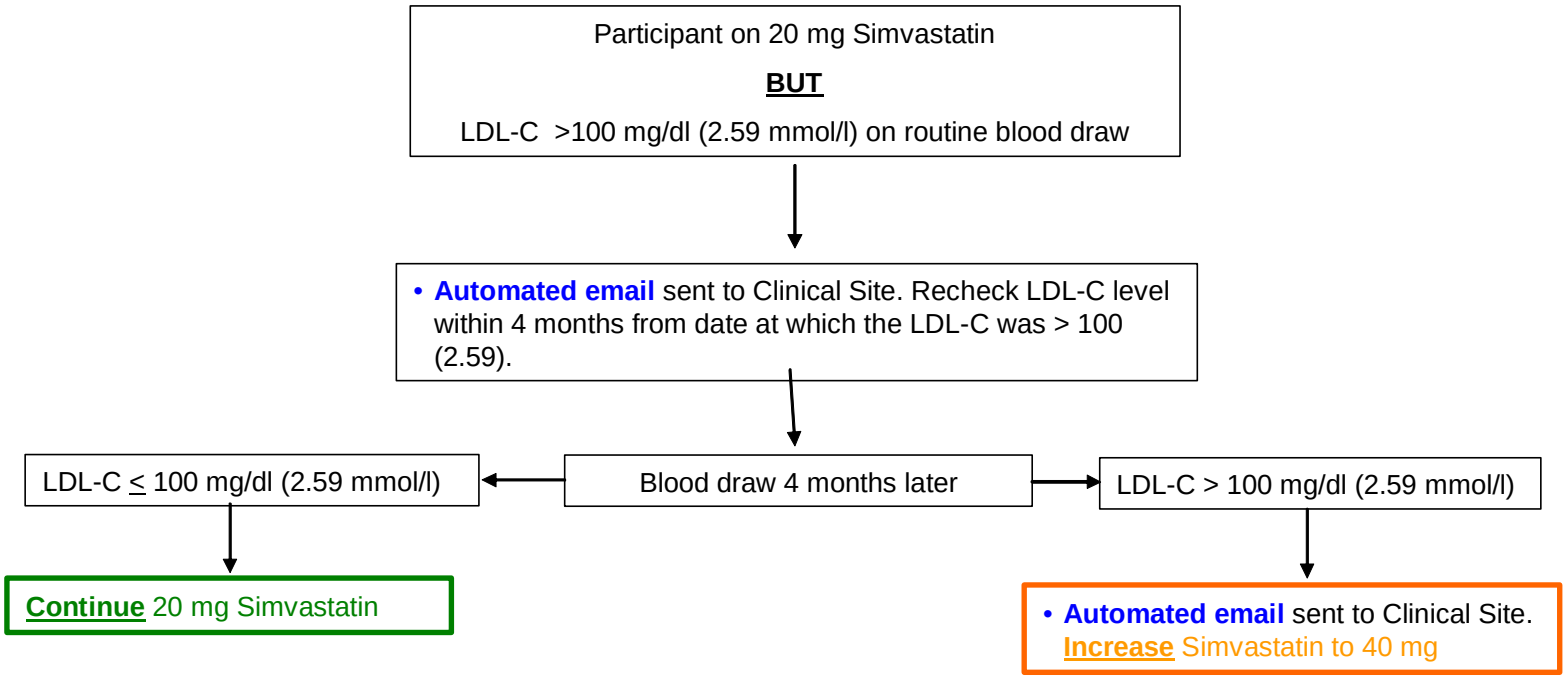
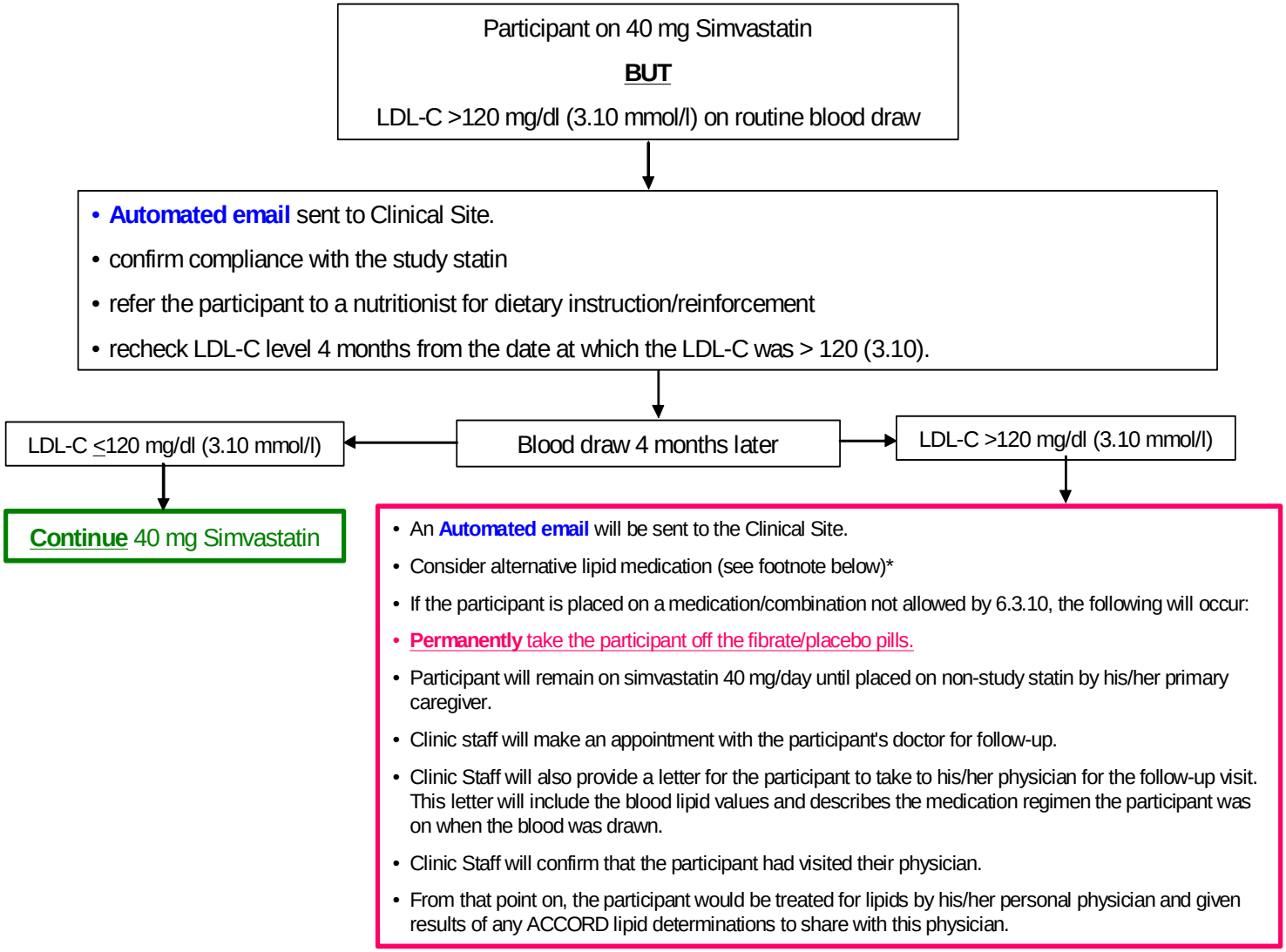


Fig 2: What to do if Participant is on 40 mg Simvastatin, but LDL-C is Reported by ACCORD Central Lab as > 120 mg/dl (3.10 mmol/l)



*See Section 6.3.10 for allowed medications. If other lipid medications are used in conjunction with the masked medication, ALT, CPK and fasting lipid level should be drawn at the next regular 4 month visit after the start of the new medication and sent to the central lab

Fig 3: What to do if Participant is on 40 mg Simvastatin, but LDL-C is Reported by ACCORD Central Lab as < 40 mg/dl (1.03 mmol/l)

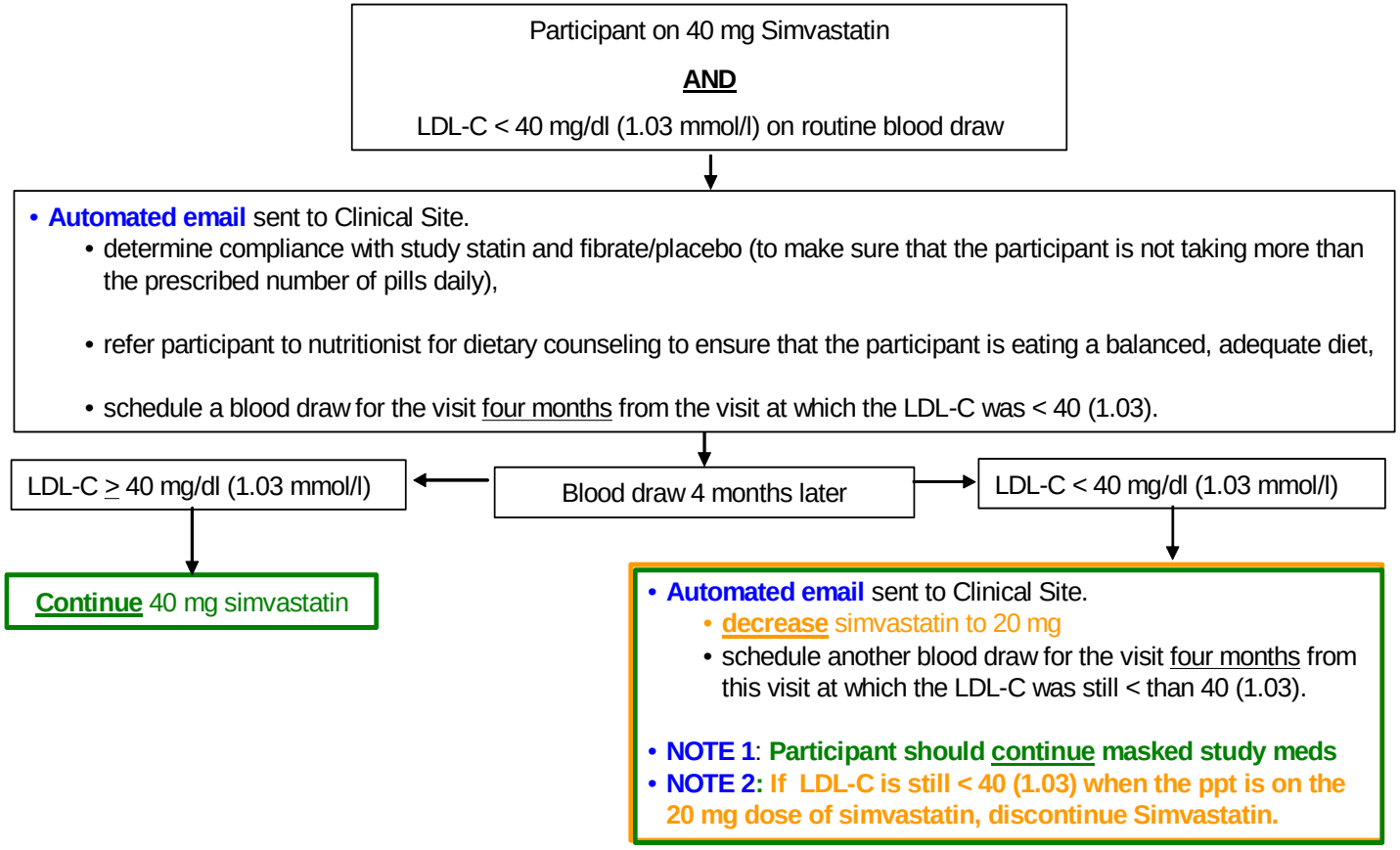


Fig 4: What to do if Participant is on 20 mg Simvastatin, but LDL-C is Reported by ACCORD Central Lab as < 40 mg/dl (1.03 mmol/l)

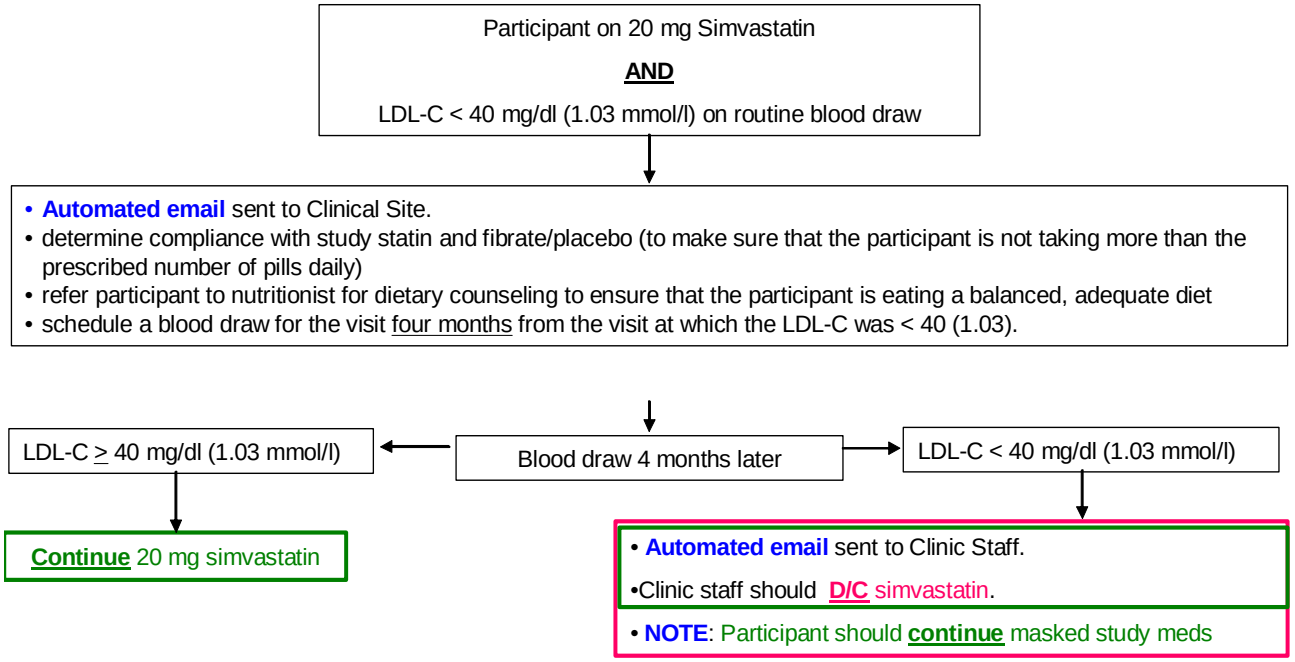


Fig 5: What to do if Participant is on Full Dose of Masked Medication and the GFR (as Reported to Clinic by Coordinating Center) Decreases below 50 ml/min/1.73m²

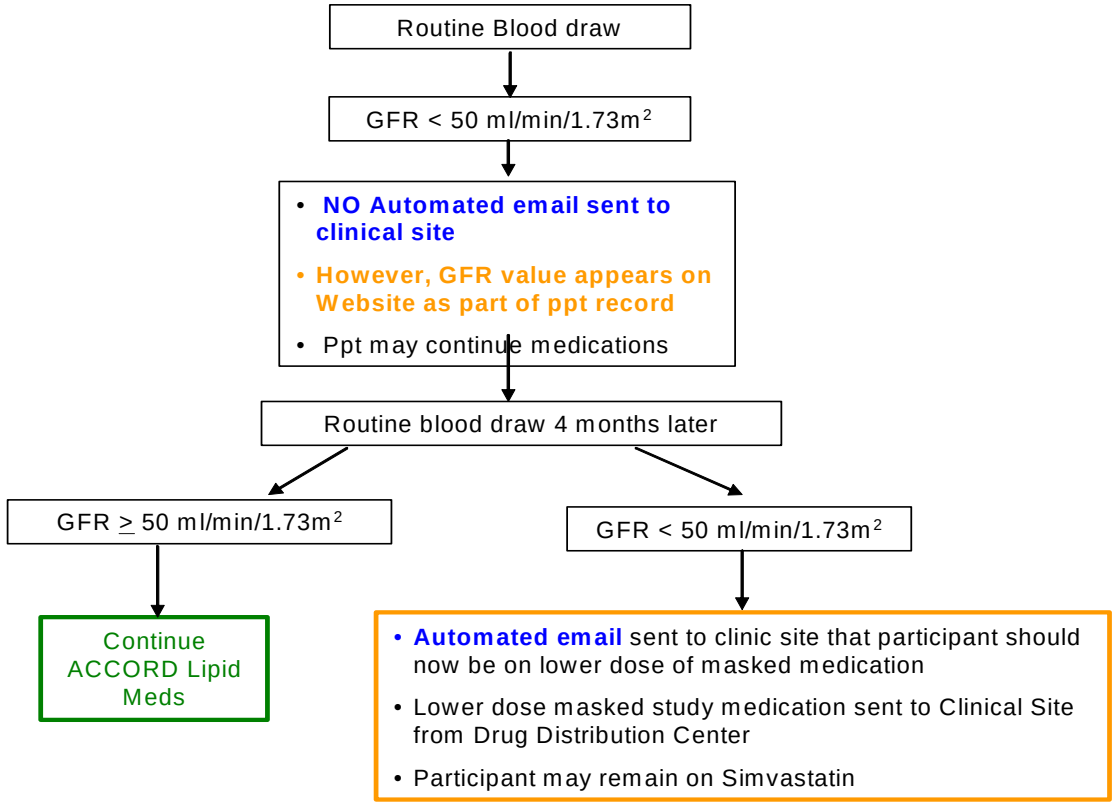


Fig 6: What to do if the GFR (as Reported to Clinic by Coordinating Center) decreases below 30 ml/min/1.73m^2

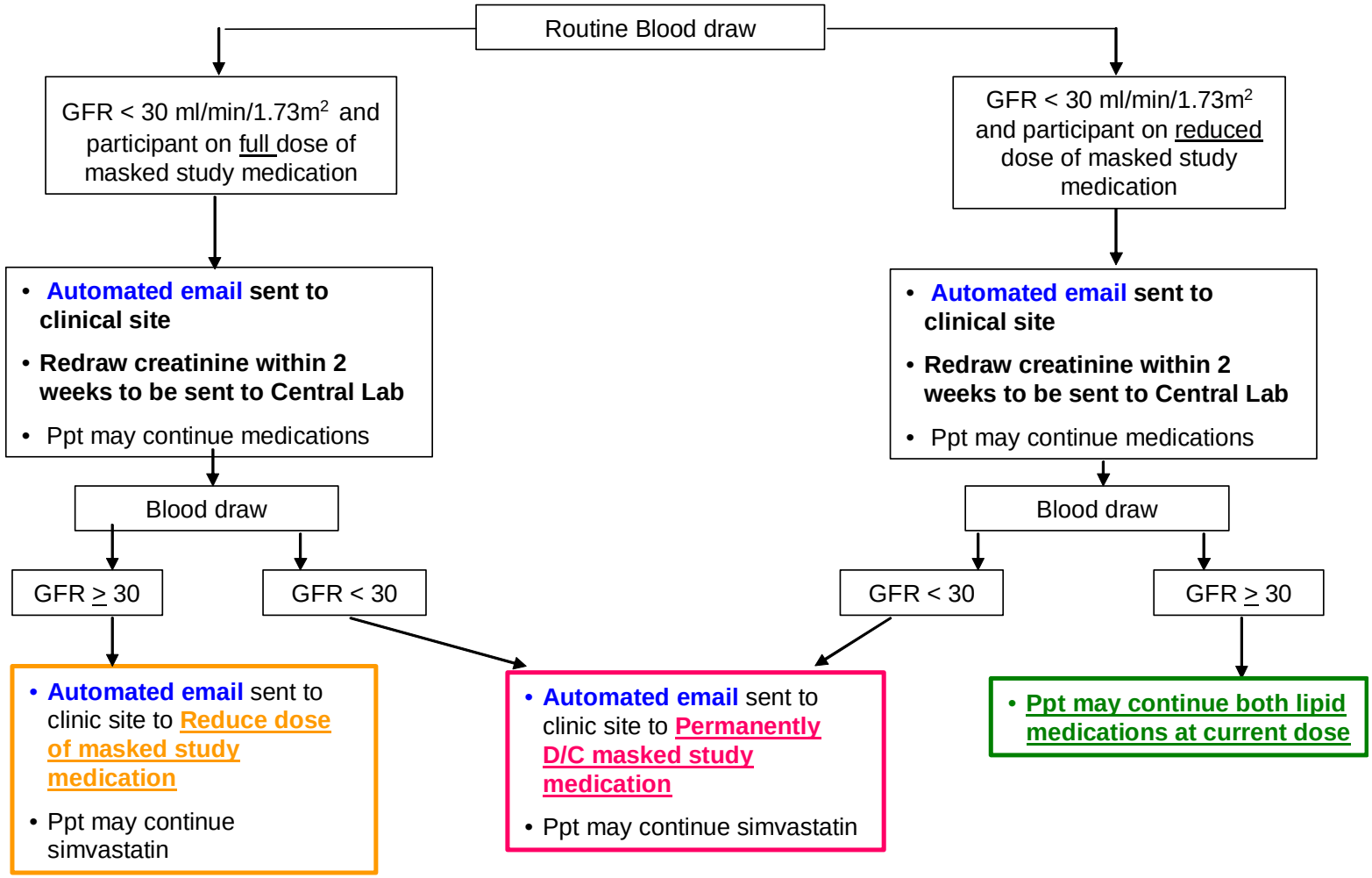
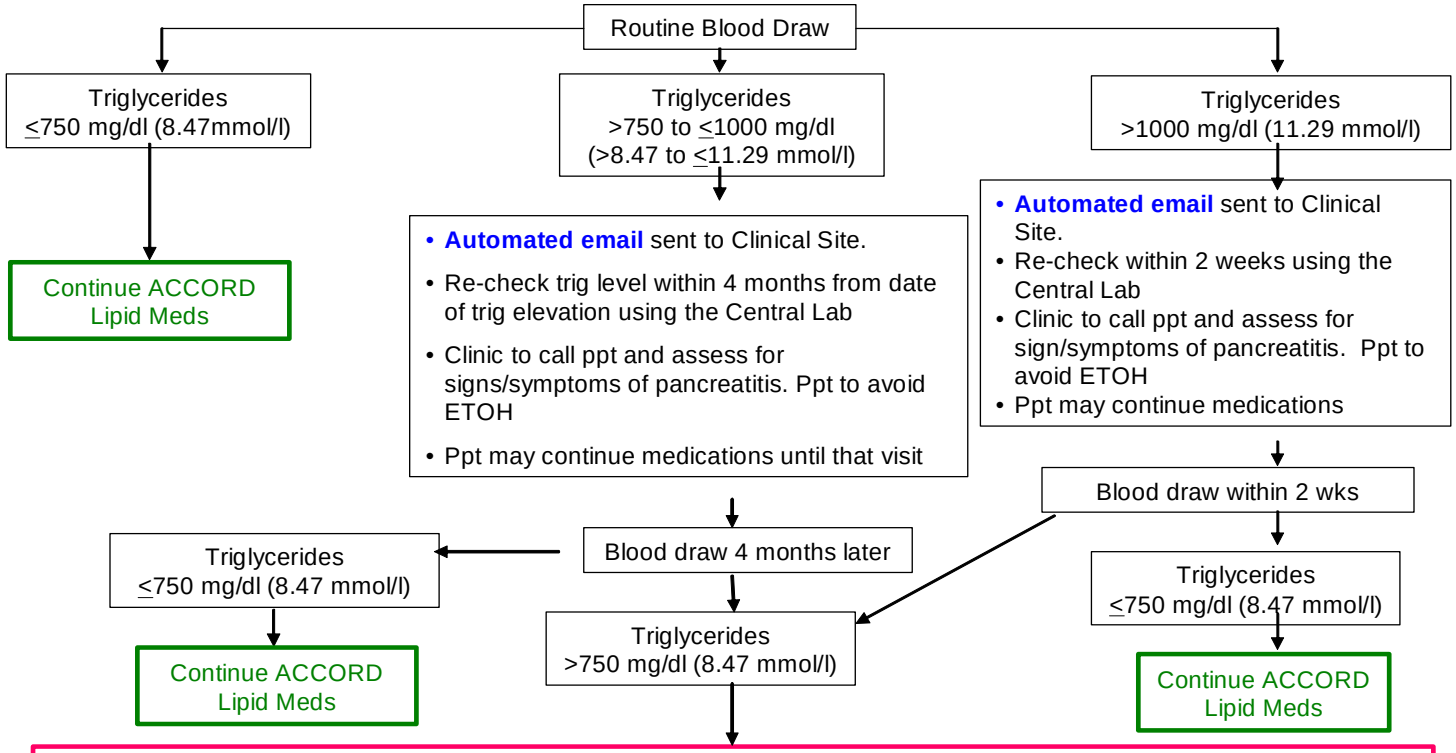


Fig 7: What to do if Triglycerides are Reported by ACCORD Central Lab to be Elevated



- An **Automated email** will be sent to the Clinical Site.
- **Permanently** take participant off **both** simvastatin and the masked fibrate/placebo medication.
- Ppt will be dispensed 160 mg/day tablet of fenofibrate or 600 mg BID of gemfibrozil until placed on nonstudy fibrate by his/her primary caregiver.
- Clinic Staff will make the appointment for follow-up by the participant's physician and will confirm that the appointment was kept.
- Clinic Staff will also provide a letter for the participant to take to their physician for the follow-up visit. This letter will include the blood lipid values and describes the medication regimen the participant was on when the blood was drawn.
- From that point on, the participant will be treated for their lipids by his/her personal physician and given results of any ACCORD lipid determinations to share with this physician.

Fig 8: What to do if the participant reports muscle symptoms on ACCORD Study Forms

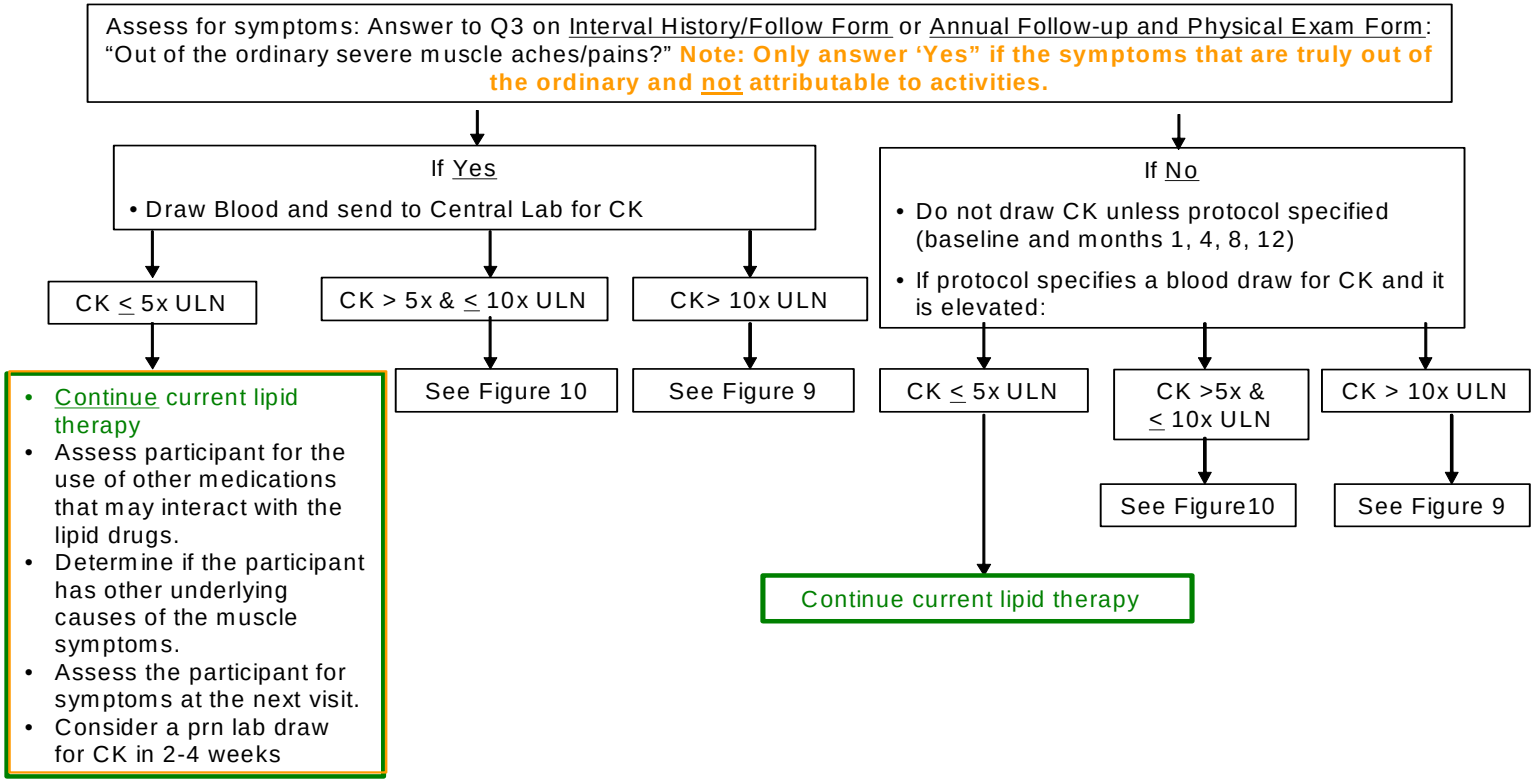
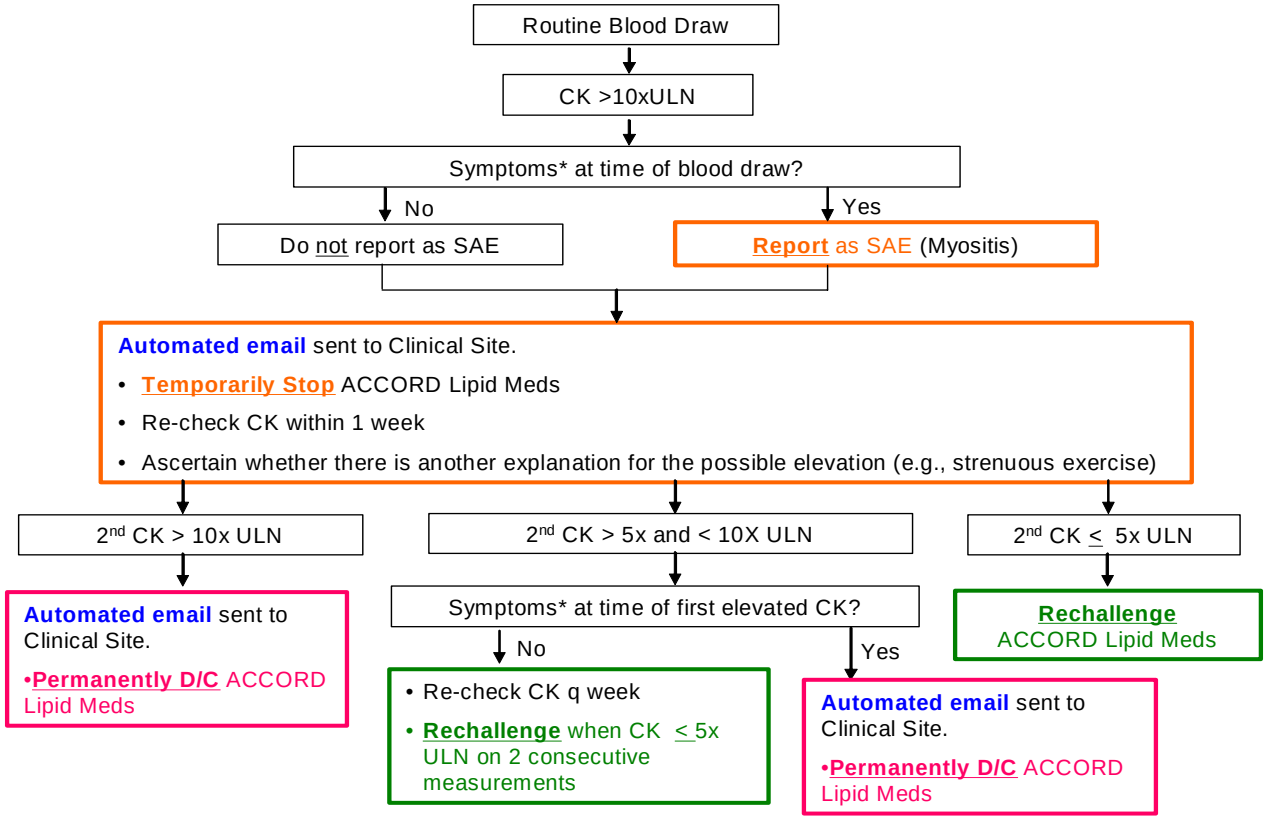
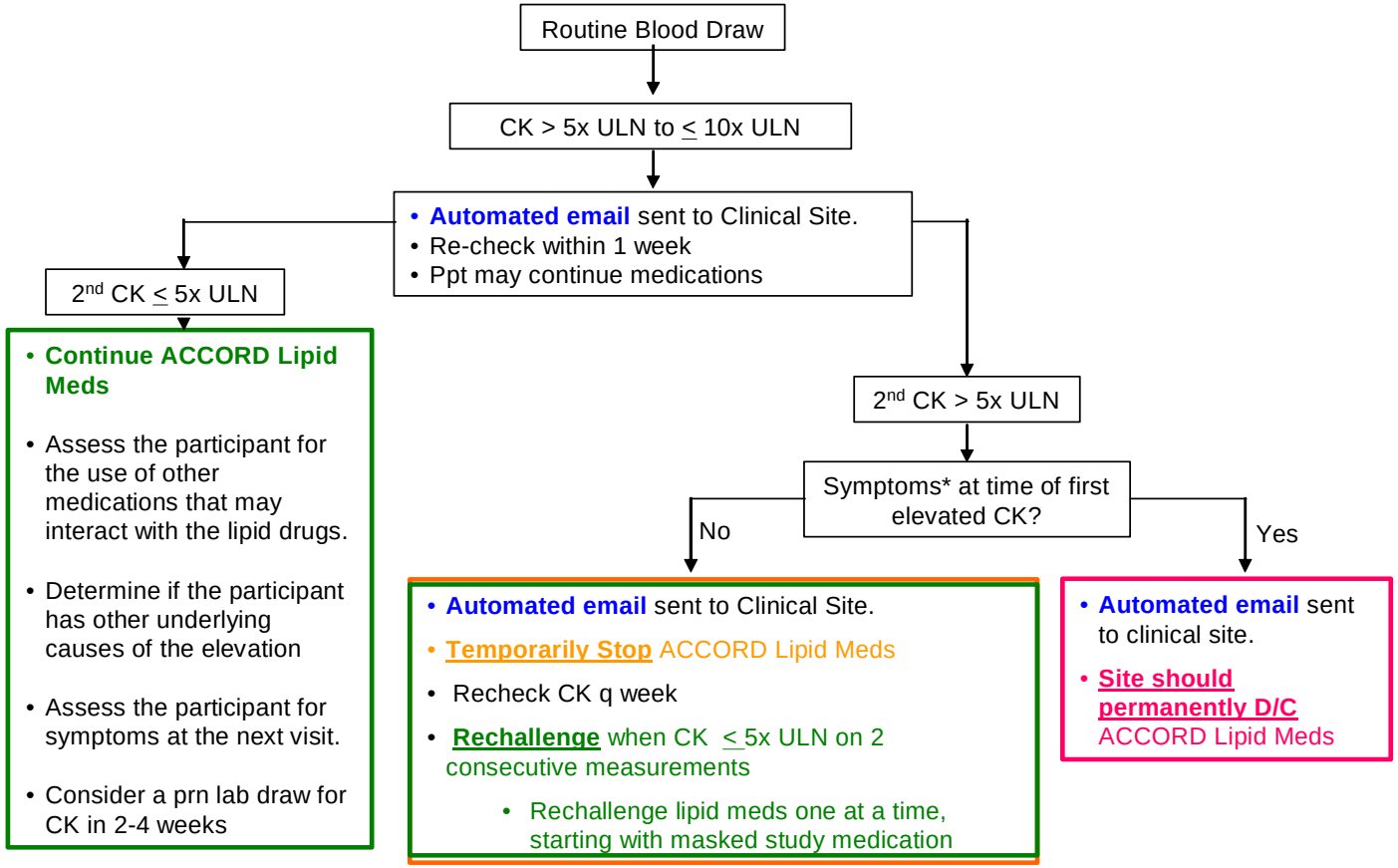


Fig 9: What to do if the CK is Reported by ACCORD Central Lab to be > 10x Upper Limit of Normal (ULN)



*Symptoms: Answer to Q3 on Lab date-matched Interval History/Follow Form or Annual Follow-up and Physical Exam Form ("Out of the ordinary severe muscle aches/pains?") **Note: Only answer 'Yes" if the symptoms that are truly out of the ordinary and not attributable to activities.**

Fig 10: What to do if the CK is Reported by ACCORD Central Lab to be > 5 but </= 10x Upper Limit of Normal (ULN)



*Symptoms: Answer to Q3 on Lab date-matched Interval History/Follow Form or Annual Follow-up and Physical Exam Form ("Out of the ordinary severe muscle aches/pains?") **Note: Only answer 'Yes" if the symptoms that are truly out of the ordinary and not attributable to activities.**

Fig 11: What to do if ALT is Reported by ACCORD Central Lab to be > 3x Upper Limit of Normal (ULN)

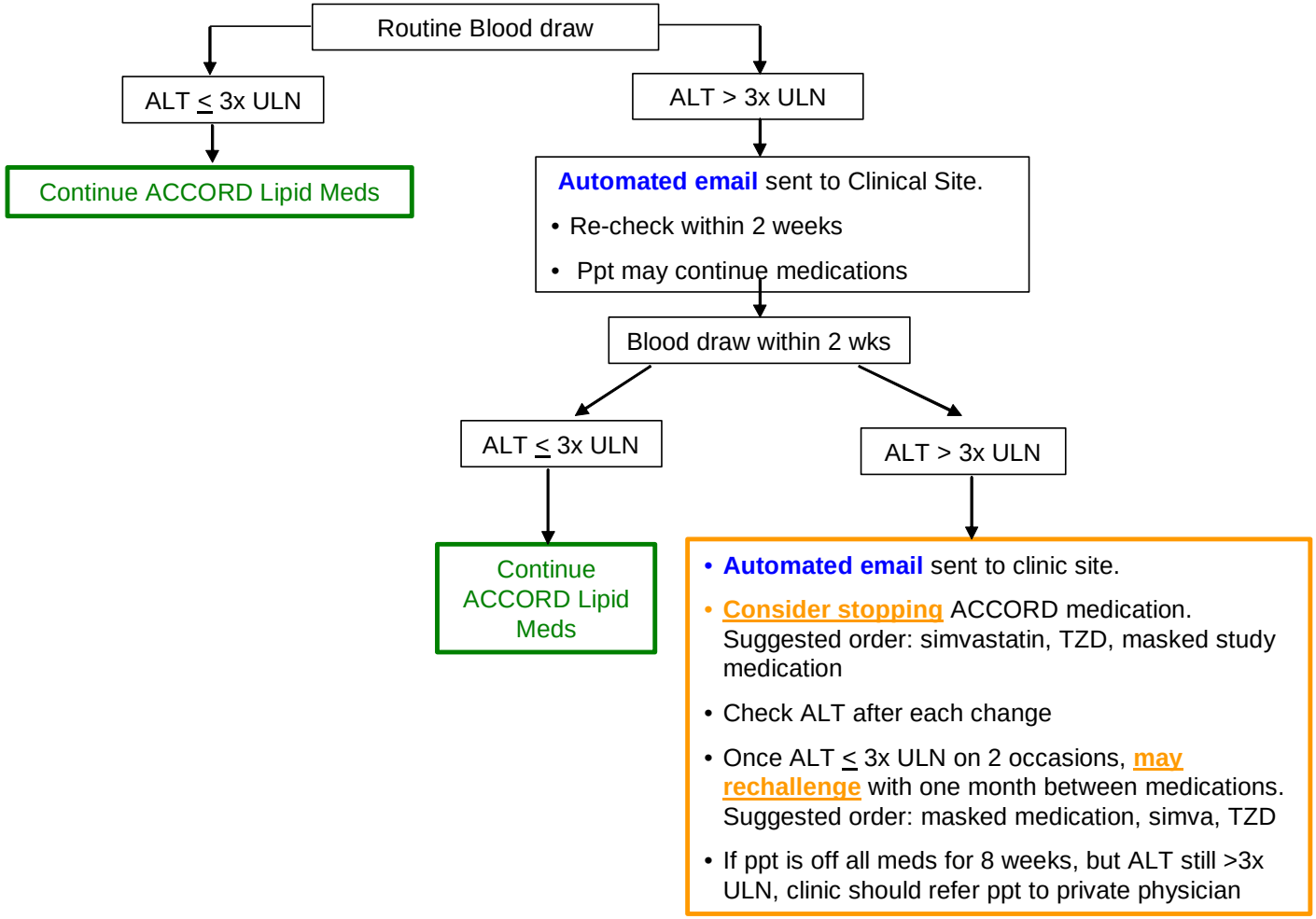
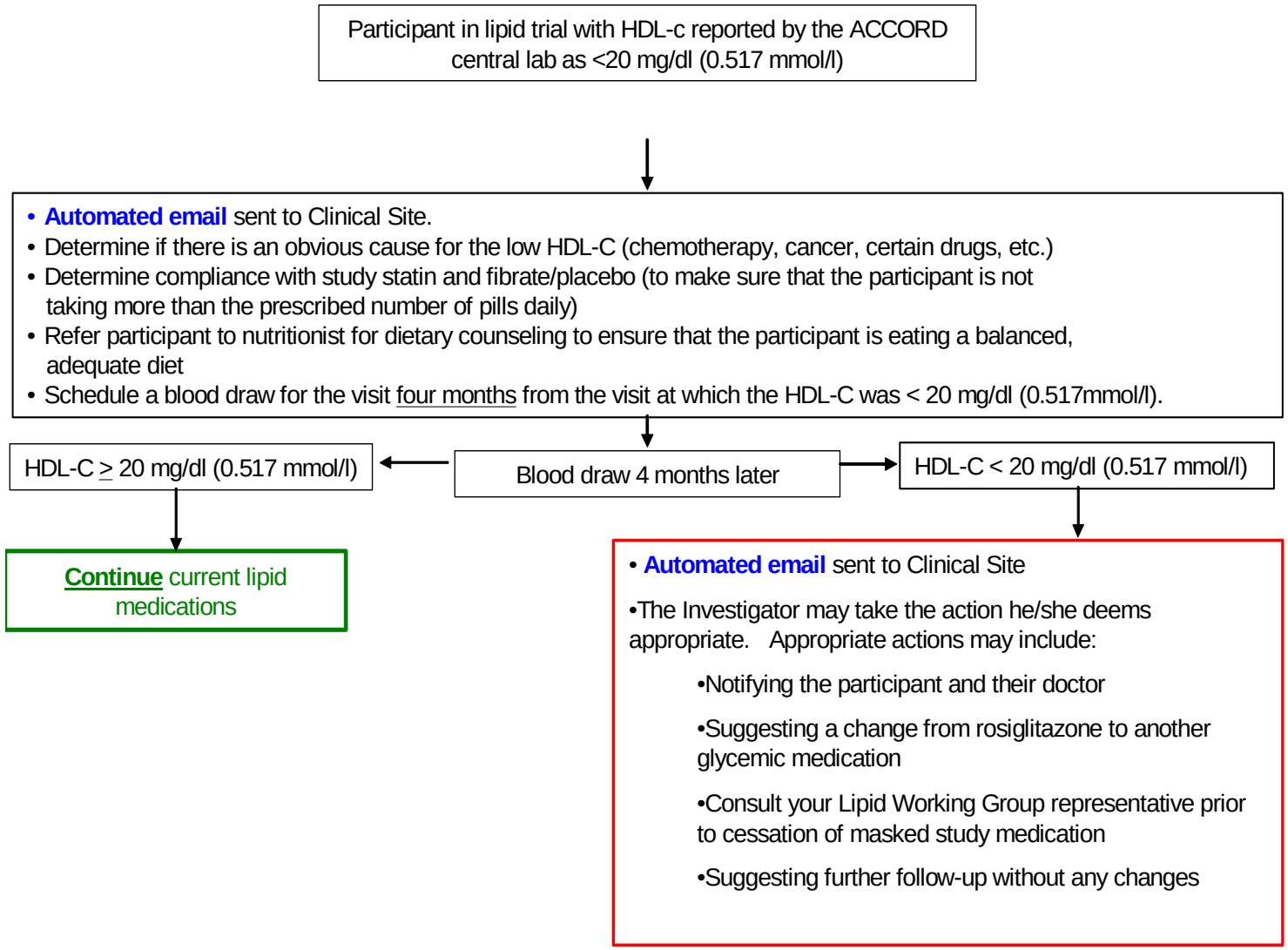


Fig 12: What to do if HDL-C is Reported by ACCORD Central Lab as < 20 mg/dl (0.517 mmol/l)



6.4 Special Renal Study

Last spring, after it was observed that a small number (213) Lipid Trial participants had increases in serum creatinine, a series of steps were initiated in which participants with increases in serum creatinine of greater than 30% and either an estimated glomerular filtration rate (GFR) of less than 60 ml/min/1.73 meter^2 or a creatinine clearance of 50 ml/min had additional blood tests and were taken off their masked medication. One month later, those same participants had repeat blood tests. Note that some of these participants were on placebo and some were on active fenofibrate.

The results of the "Special Renal Study" indicated that there was no permanent reduction in renal function in the subjects taking fenofibrate. The exact results remain blinded, but the conclusion, which is consistent with most of the prior literature, is that even when serum creatinine rises during fenofibrate treatment, that level will fall toward the levels present prior to treatment once fenofibrate is stopped.

6.4.1 Re-challenging Participants

Participants being re-challenged with either simvastatin or blinded fenofibrate/placebo should start taking the medication at their next scheduled visit. All lab tests and forms must be completed as usual. If participants are off both simvastatin and blinded medication and are cleared to re-challenge, they may start both medications at the same time. If the clinical site feels that this is too much for the participants, start the simvastatin first and the blinded medication one month later.

Because "Special Renal Study" participants were removed from masked medication in order to conduct additional measures, these participants should not restart masked medications until they are informed about what has transpired. Sites will need to obtain IRB approval to inform them about the changes. The Coordinating Center has developed a sample letter describing the "Special Renal Study" the sites can provide to their IRBs, and a sample letter to the participants. These letters can be found at the end of this section. After sites have received IRB approval they should:

- Notify the Coordinating Center
- Re-challenge all Special Renal Participants, at each participant's next regularly scheduled visit.

The participants in the "Special Renal Study" will then be treated as all other ACCORD Lipid Trial participants and will receive the masked medication at doses consistent with the GFR guidelines.

Example letter to IRB's explaining the plan to restart Special Renal Visits

Date: *Today's Date*
To: *your IRB*
From: *your PI*
Re: Rationale for restarting ACCORD Special Renal participants

---

In April 2004, IRB's were notified by ACCORD investigators that a rise in serum creatinine had been seen among a small number of ACCORD Lipid Trial participants and that this increase may be caused by the blinded study medication (fenofibrate or placebo). An internal investigation and a literature review was undertaken to better understand the changes seen. The internal investigation consisted of selection of renal criteria for temporary discontinuation of blinded study medication and additional laboratory measures. After consideration, criteria for temporary discontinuation of blinded medication were established to be participants with a 30% increase in creatinine from baseline and either a calculated creatinine clearance less than 50 ml/min (from the Cockroft-Gault equation) or a GFR less than 60 mL/min/1.73m^2 (from the MDRD equation). Both equations have been used in research and clinical practice and were used here to be conservative in order to identify the highest number of participants with potential problems. Participants meeting those criteria were requested to undergo a series of blood tests (serum creatinine, BUN, cystatin C, CPK and urine microalbumin), to stop their blinded medication, and one month later to repeat the laboratory tests. WFUSM IRB and all clinical IRB's were notified of this action at the time (see attached copy of original letter).

The literature review found that the elevating effect of fibrates (except gemfibrozil) on serum creatinine level is known and has been reported. The average increase in serum creatinine reported is 15-20%. It usually occurs within the first few weeks of treatment. The potential mechanism remains largely unknown although several have been postulated including an increase in creatinine production and alteration of renal hemodynamics. Renal impairment appears to be uniformly reversible after fibrate discontinuation if no severe chronic renal failure is present at baseline.

The laboratory investigations undertaken in the ACCORD participants whose blinded medication was discontinued confirm the findings in the literature. Approximately 15% of participants enrolled in ACCORD as of April 2004 met the Special Renal Criteria established, similar to that previously reported in the literature. The increase in serum creatinine was generally seen by month 4 of study participation and was stable over time. Once fenofibrate was discontinued, serum creatinine decreased toward baseline with the decrease paralleled by cystatin C and BUN.

Given the finding's described above, study investigators are confident that the rise in serum creatinine seen with some ACCORD Lipid Trial Participants is reversible and that, as long as dose adjustment is made for participants with renal impairment and renal

function is monitored, it would be medically appropriate to administer fenofibrate to these participants.

During the investigation described above, 213 Lipid Trial participants (out of a total of 2,898 enrolled in the Lipid Trial) had their blinded study medication discontinued. We propose restarting those Lipid Trial participants back on their blinded study medication under the guidelines of the recent protocol amendments, which would mandate that their study medication be adjusted as per protocol amendment #30 (adjustment of fenofibrate dosage based on GFR) and their renal function monitored every 4 months, with subsequent dosage adjustments as described in the revised protocol.

Please note that all actions taken to date have retained the double-blind, with neither investigators nor study participants aware of which participants were receiving active or placebo medications. This approach would be continued by having a lower dose fibrate and matching placebo available in the study.

SAMPLE Letter to participants previously involved in the Special Renal Cohort

November 10, 2004

Letter to participants in the Special Renal Study

Dear…..

You are a participant in the ACCORD Lipid trial. Last spring we stopped your "blinded medication" because of an increase seen in your creatinine level. Creatinine is a substance in blood that is used to see how well your kidneys are working. An increase in creatinine may suggest some worsening of how well your kidneys are working. The medication you received could have been the drug fenofibrate (Tricor or Lipidil) or the placebo. Because this is a blinded trial we do not know which you medication you were on.

At the time we stopped the medication, we took extra blood samples. After one month, we collected more blood samples. The results of those blood tests showed us that the increase in blood creatinine that we had seen was no longer present. When the medication was stopped, the blood creatinine level went down. This suggests that the change in kidney function we had seen in some patients was not permanent.

Because there was no evidence of a long-term effect, we want to start your blinded medication again with some new precautions. We will monitor your kidney function more closely. If, at any time during the rest of the ACCORD Lipid Trial, your blood creatinine rises above a certain level, we will reduce the dose of the blinded medication or even stop it. If, at any time during the rest of the ACCORD Lipid Trial, you are not comfortable being on blinded medication, you may choose to stop.

The safety of our participants is of the utmost concern to us, the investigators and staff of ACCORD study. Your continued participation in this study is vital to the success of ACCORD. We appreciate your help!

Sincerely

If you have any questions regarding the lipid protocol or about how to handle a particular patient, contact your CCN Lipid Working Group Representative. They are:

Canada:
Western:
Minn/Iowa:
Ohio/ Mich:
Northeastern:
Southeastern:
VA:

6.5 Prohibited Lipid Regulating Medications

Except where noted, the following lipid regulating medications should not to be taken at any time during participation in the lipid trial (unless as part of the ACCORD Protocol):

HMG-CoA Reductase Inhibitors (Statins):
- Atorvastatin (Lipitor®)
- Cerivastatin (Baychol ®)
- Fluvastatin (Lescol®)
- Lovastatin (Mevacor®)
- Pravastatin (Pravachol®)
- Simvastatin (Zocor®).

Fibric Acid Derivatives (Fibrates):
- Fenofibrate (Tricor®)
- Clofibrate (atromid®)
- Gemfibrozil (Lopid®)

Nicotinic Acid:
- all OTC Niacin preparations (Nicotinex Elixir®),
- prescription niacin (Niacor®), (Nicobid®), (Niaspan®), (Slo-Niacin®).

NOTE: Small amounts of niacin (< 100 mg) are allowed as part of a multivitamin complex.

Bile Acid Sequestrants:
- Colestipol (Colestid®) tablets or powder, (LoCholest®) powder
- Cholestryramine (Questran®) powder
- Colesevelam (WellChol®)

Cholesterol absorption inhibitors:
- Ezetimibe (Zetia®)

b. Except where noted, the following agents are also prohibited for those ACCORD participants who are on the trial statin, simvastatin. **NOTE**: If a participant needs to be temporarily placed on one of these agents, the use of simvastatin may be temporarily stopped and restarted when the participant no longer requires the agent.

Immunosuppressive agents: Cyclosporin (Neoral®), (Sandimmune®).

Antibiotics known to inhibit the cytochrome p450 CYP3A4 system:

Erythromycin
Erythrocin®
Ery-Tab®
Eryc Delayed Release Capsules®
Ilosone®
Eryzole Oral Suspension®
E.E.S liquid, granules, filmtab®.
Clarithromycin (Biaxin®)
* any oral or intravenous macrolide antibiotic with the exception of Azithromycin (Zithromax®)

NOTE: Azithromycin (Zithromax®), use is permitted. Also, there is little systemic absorption of topical erythromycin, so that is permissible.

Antifungal Agents (systemic use):

Systemic (oral or IV) administration of azole antifungal agents:
Ketoconazole (Nizoral®)
Itraconazole (Sporanox®)
Fluconazole (Diflucan®)

NOTE: The following antifungal agents are allowed: Terbinafine (Lamisil®), Griseofulvin (Fulvicin® Grifulvin®), Amphoteracin (Abelcet® Ambisome® Amphotec®), Flucytosine (Ancobon®), topical antifungals i.e. miconozole, ketokonozole may be used with careful observation for muscle complaints.

Specific Antidepressants

Nefazodone

6.6 Special Note Regarding the Concomitant Use of Fenofibrate and Warfarin (Coumadin)

The use of a fibrate generally necessitates a reduction in the dose of Coumadin to avoid excessive bleeding.

For persons who are on Coumadin at the start of the trial, the participant's physician should be informed both by phone and in writing of the possibility that the participant may be on a fibrate. Until the physician or someone who will manage the

Coumadin dose is reached by phone or in person, the participant should not be randomized.

During the trial, you will ask about the possibility of Coumadin use at each visit and if you find that the participant is now on Coumadin, record its use in your source notes. If Coumadin has been started, the clinician prescribing it should be notified that the participant may be on a fibrate. Remember, in some cases the clinician prescribing the Coumadin may not be the clinician notified at the start of the trial of the participant's participation in the trial and randomization to fibrate or placebo.

6.7 Unmasking A Participant's Fibrate/Placebo Assignment

The fibrate/placebo arms of ACCORD are the only masked portion of the trial. Even the statin component of the lipid portion of ACCORD is unmasked, although the centrally measured lipid levels are masked. If the masked fibrate/placebo study medication is stopped for any reason, neither the participant nor the clinic staff need to be unmasked regarding the study medication's true identity, unless there are other circumstances dictating unmasking.

Before unmasking a participant's treatment group assignment, and assuming that this is not an emergency situation, the Clinical Site Principal Investigator is encouraged to discuss the situation with the Clinical Center Network Principal Investigator. Rather than unmasking, there may be other options available, such as temporarily stopping the study medication (and resuming after the situation has resolved).

6.7.1 Unmasking Procedure

The treatment code will only be broken (unmasked) if that knowledge (i.e. knowing exactly which study drug the patient is taking) is essential to the medical management of a person who has taken the medication. Code breaks are discouraged; however the participant's safety must always be paramount. In those situations where the investigator feels it is essential to break the code, he/she is instructed to contact the ACCORD Drug Distribution Center (DDC) at (505)- 248-3203, which provides 24 hours/day, 7-days/week coverage. Be prepared to provide the following information:

1. Study Name
2. Site Name
3. Name of person calling and their telephone number
4. Patient Identification Number
5. Reason Code Break is necessary
6. Name of Physician requesting code break

6.7.2 Documenting the Unmasking Episode

A full written report will be required by the Clinical Site PI documenting the entire episode, including why the unmasking was felt to be necessary what

options to unmasking were considered, and why these options were not selected. This report should be co-signed by the CCN PI and sent to the ACCORD Executive Committee (in care of the ACCORD Coordinating Center) for review and filing.

7. Visit Schedule of Study Activities by Randomization Cell

A. Intensive Glycemia and Intensive Blood Pressure

A.1 Overview

One of the key aims of the ACCORD study is to determine if targeting a HbA1c of < 6.0% (the upper limit of the nondiabetic range) reduces the rate of cardiovascular disease (CVD) events to a greater extent than targeting a HbA1c of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%, which is 25% above the upper limit of the nondiabetic range) in high risk middle-aged or older people with type 2 diabetes. The approaches used to implement these targets, suggested algorithms for the use of pharmacologic agents and follow-up schedules are described in MOP Chapters 5 and 6.

The ACCORD blood pressure (BP) trial component is designed to test whether a therapeutic strategy that targets a systolic blood pressure (SBP) of < 120 mmHg reduces the rate of cardiovascular events in a middle-aged or older type 2 diabetic population at high risk for cardiovascular events compared to a strategy that targets a SBP of < 140 mmHg in the context of good glycemic control. Details regarding the implementation of the protocol for the intensive glycemia and intensive blood pressure control groups are described below.

A.1.1 Algorithms for Intensive Glycemic and Intensive Blood Pressure Control; Choice of Agents

Figures A.3 and A.5 at the end of this chapter are suggested algorithms to guide changes in glycemic therapy for the intensive group. The exact changes to be made whenever glycemic therapy needs to be intensified on the basis of the HbA1c or the SMBG results will be determined by the individual site using the figures as guides.

The algorithm for the intensive BP group calls for an assessment of the participants' antihypertensive medication regimen at baseline to determine the starting point on the decision tree for future monitoring and medication adjustments needed to achieve their assigned SBP goal (< 120 mmHg) (Refer to Figure A.6 at the end of this chapter).

A.1.2 Targets and Action Required Levels

A.1.2.a) Intensive Glycemic Control

Table A.1.2 outlines the glycemic target for the intensive group, which is identical to that described in Table 3.1 in the protocol.

Table A.1.2: Intensive Glycemic Target and Threshold for Action for ACCORD			
		"Action Required" Threshold	
	HbA1c Targets	HbA1c	> 50% of SMBG Results/4Days
Intensive Therapy	< 6.0%	≥ 6.0%*	Fasting/ac > 100 mg/dl (5.6 mmol/l) Or 2 hrs pc > 140 mg/dl (7.8 mmol/l)

pc: postcibal (after meals); ac: antecibal (before meals); SMBG: self monitoring of blood glucose; * antihyperglycemic therapy will be advanced if either the HbA1c or the SMBG "action required " criteria are met at any particular encounter

A.1.2.b) Intensive Blood Pressure Control

Participants randomized to the intensive blood pressure control will have a SBP goal of < 120 mmHg. The BP intervention will begin at the randomization visit. The investigator may choose from among the available ACCORD agents or select another as determined appropriate. It is recommended that the regimen include a drug class associated with reduced cardiovascular events in diabetes (ACE-inhibitor, beta-blocker, calcium channel blocker or diuretic). For participants in the intensive BP group, a combination of a diuretic and either an ACE inhibitor or a beta-blocker, a calcium channel blocker or an angiotensin II receptor blocker (ARB) is strongly encouraged for initial therapy at randomization. (Refer to Drug Availability List – MOP Chapter 5)

A.1.3.a) Adjusting Glycemic Therapy

As noted in the following table (A.1.3), a range of approaches will be used to target the HbA1c levels shown in Table A.1.2.

A.1.3 Achieving Glycemic Goals	Intensive Group
Visits (1st 4 months)	Monthly
Visits (> 4 months)	Q 2 mo
Phone contact	Research staff initiated (≥1 inter-visit)
Supplemental contact	Severe hypoglycemia OR HbA1c = action req'd OR SMBG = action req'd (based on review of logbooks)
Point of Care HbA1c	Mandatory
Routine use of postprandial SMBG values to guide therapy	Yes
SMBG freq.[a] (not on insulin)	≥ 2/day and 4/day if glucose is > target (2 ac/day and 2 pc/day)
SMBG freq.[a] (insulin)	4-8/d (at least 2 ac/day and 2

	pc/day; occasional 3 am test prn)
Self titration principles	Avoid severe hypoglycemia[b] AND Adjust therapy every 4 days AND Use CHO/patterns (if on insulin)
Initial Minimum Rx	Diet/lifestyle AND 2 oral agents
Insulin Use (when needed)	Flexible

[a]less frequent if goals are achieved; [b] including avoiding SMBG levels < 70 mg/dl (3.9 mmol/l) on > 1/4 of the readings

It is expected that patients in the intensive group will experience mild, self-treated hypoglycemic episodes approximately 2-3 times/week. Moreover, initially, people may report such episodes more frequently, until they become accustomed to physiologic glycemic control.

A.1.3.b) Glycemia Safety Issues/ Adjusting Therapy for Hypoglycemia

Hypoglycemic events may occur in individuals in either the intensive or standard group. Severe hypoglycemia is unusual in people with type 2 diabetes (even when normoglycemia is targeted). Mild episodes of hypoglycemia are, however, likely to occur.

All participants will be instructed to check their glucose levels regularly as described in the protocol. They will also be taught how to recognize and self-treat hypoglycemia and will be instructed to keep glucose available at all times (as tablets). Moreover, any participant who has had an episode of severe hypoglycemia will be provided with glucagon and they and any cohabiting partner will be taught how to administer it.

Severe hypoglycemia is defined as any episode of loss of consciousness/seizure or documented hypoglycemia (glucose < 50 mg/dl or 2.8 mmol/l) that also requires hospitalization or treatment by emergency personnel. If this occurs:

- Complete **Severe Hypoglycemia Action Form.** (See MOP Chapter 8, Section 8.4.4 for more details).
- For participants in either group who have an episode of severe hypoglycemia, adjust glycemic targets to achieve a fasting and 2 hour glucose (postprandial) of 100 – 140 mg/dl (5.5 – 7.8 mmol/l) and < 180 mg/dl (10 mmol/l) respectively, and a HbA1c of 7.0% - 7.9% for at least 4 weeks.
- Ensure that a complete medical assessment by the health care provider is completed to identify other potential causes (e.g. pituitary or adrenal insufficiency)
- Ensure that the health care provider reassesses the glycemic goals at subsequent visits.
- Ensure that the participant has received glucagons and that the participant and cohabitant know how to administer it.
- Have telephone contact with the participant before the next visit to assess blood glucose records and freedom from hypoglycemia.

Minor hypoglycemia is defined as self-reported transient symptoms such as lightheadedness, tremor, shaking, sweating, tingling, blurry vision, trouble concentrating etc., that are self-treated by ingestion of carbohydrates and resolve on their own. (See MOP Chapter 6, Section 6.1.6). All participants will be asked to note such episodes in their glucose logbooks and to confirm them with a blood glucose reading whenever possible. The estimated frequency (of confirmed and suspected minor hypoglycemia) will be recorded at every visit.

A.1.3.c) Self Treatment of Hypoglycemia

1. If the glucose value is < 50-70 mg/dl (3.9 mmol/l), it should be treated by ingestion of 15 grams of CHO (e.g. 3-4 glucose tablets, 5 Lifesavers, 4-6 oz. of a regular – (nondiet) – soft drink, or 8 oz. low fat milk);
2. If the glucose value is < 50 mg/dl (2.8 mmol/l), it should be treated by ingestion of 20-30 grams of CHO (e.g. 6-8 glucose tablets);
3. Blood glucose should be self-tested 15-20 minutes after therapy and therapy repeated if the level is still low (as above);
4. If no meal will be eaten within 1-2 hours, a mixed nutrient snack, including CHO, protein, and fat should be ingested right after the initial therapy to prevent another episode.
5. If the glucose value is low or there is significant cognitive or motor impairment, individuals should treat and re-test glucose value. The glucose value should be > 70 mg/dl (3.9 mmol/l) before driving a car or operating heavy machinery.

A.1.3.d) Education and Minimization of Hypoglycemia in Participants

Hypoglycemia is an inherent risk in the treatment of diabetes. It is important to inform participants of the signs and symptoms of hypoglycemia, techniques to minimize the risk and appropriate methods of treatment. Several tools are available for use in educating participants:

1. Hypoglycemia Cartoon
2. Participant Wallet Card
3. Primer on Hypoglycemia
4. Participant Newsletters

All participants must be provided with the written material listed above at the beginning of the study. Study staff should review verbally the signs and symptoms with the participant and family members. Participants and their families should be encouraged to review the hypoglycemic video either in the clinic or at home. Both participants and family members should be educated on the appropriate treatment for symptoms, and provided with glucose tablets. Those participants suffering one severe hypoglycemic event should be provided with a glucagon kit and both the participant and the family member taught how to use it. This material must be reviewed annually with all participants and after every reported hypoglycemic event.

A.1.3.e) Safety Issues for Thiazolidinedione (TZD) Drugs

For participants on TZD (e.g. Avandia or Rosiglitazone), check for the presence of edema at every visit and obtain a Central Lab ALT every 2 months for the first year of treatment and annually thereafter.

As TZDs are contraindicated in people with stage 3 or 4 heart failure, if a participant who is taking a TZD does develop heart failure, the TZD should be stopped and the heart failure treated and investigated. Depending on the results of these investigations the investigator may reconsider cautiously reinstituting TZD if the heart failure resolves, and was judged to have not been directly caused by TZD alone.

A handout to give to the participants at the discretion of the site concerning TZD use is available and can be found on page 29 at the end of this chapter.

A.1.3.f) Adjusting Antihypertensive Therapy

Participant's BP should be monitored at every visit. For the intensive BP group, initiation of study therapy is dependent upon the participant's medication status at baseline. If on 0 - 1 antihypertensive medication at baseline, the participant should begin a study drug combination (an ACE-I, a beta-blocker, a calcium channel blocker, or an angiotensin II receptor blocker (ARB) combined with the diuretic) and be monitored as indicated by the protocol. If the participant is on 2 or 3 medications at baseline, they may continue their present therapy if at goal (< 120 mm Hg). It is strongly encouraged that a diuretic be included as part of the study antihypertensive regimen. If the participant is not at goal ($\geq$ 120 mm Hg) therapy should be adjusted (e.g. dosage titration, addition of another agent, or change to an alternate combination) to move toward the study goal. The SBP goal for the intensive group is < 120 mm Hg. Action must occur at each visit and is required at each **Milepost** visit (4 month intervals through the 24-month visit and annually thereafter based on date of randomization), throughout the duration of the study for those participants who remain above goal (SBP $\geq$ 120 mm Hg). If the SBP remains $\geq$ 120 mm Hg upward dose titration or an additional drug (not already in use) must be added and the participant should be seen at monthly intervals until at goal. If at a **Milepost** visit the SBP is not < 120 mm Hg, an antihypertensive medication from a different class not already in use MUST be added. If the SBP has reached the desired goal and remains < 120 mm Hg, therapy and monitoring will continue as per protocol.

A.2 Intensive Glycemic and Intensive Blood Pressure Control Visit Procedures

A.2.1 Baseline – Randomization Visit

The participants will be instructed to attend the clinic following an overnight fast (since ~10 pm the previous evening). They should not take their glycemia or lipid (if applicable) medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support

person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. All data collected during the screening process will be reviewed.
2. Verify eligibility status for the Glycemia, Blood Pressure and Lipid Trials (including occurrence of events that may prohibit patient from participating).
   a) Review current medications including OTC, herbal remedies and vitamins.
   b) Review, evaluate and calculate the percentage of participant's compliance with at least 2 weeks of SMBG monitoring as part of the run-in procedures.
   c) Assure that the qualifying HbA1c value was obtained within the last 3 months prior to the randomization date.
3. If ineligible, the participant will be thanked for their time and dismissed from the clinic.
4. If eligible, proceed with randomization process:
   a) Verify that a full-scale consent form has been obtained and signed and HIPAA authorization obtained.
   b) Obtain and perform baseline history and physical exam, including demographics, medical history, concomitant medications, weight, height, waist circumference, visual acuity, and foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
   c) Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completed all items before end of visit.
   d) Verify that all information on the **Inclusion/Exclusion Summary Form, the Blood Pressure Trial Screening Form,** and **the Lipid Trial Screening Form** is complete and correct both on the forms and in the computer.
   e) Click "Randomize pt" on data entry screen. A pop-up screen will appear to remind staff to provide the participant with Eye Sub-study and MIND Sub-study (Canada, Western, Minnesota/Iowa, Ohio/Michigan, Northeast, and Southeast CCNs) introductory materials.
   f) Input the percent of participant's report of compliance for SMBG.
   g) Verify that the **Baseline History and Physical Exam Form** has been completed.
5. The participant will be assigned a treatment regimen. The randomization screen will display this information and list target dates for the follow-up visits. It is recommended that the participant's treatment assignment and visit schedule be printed out and filed in their research record.
6. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, ALT, Creatinine, Lipid Profile, CPK, and for storage of additional aliquots (where approved).
7. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Laboratory.
8. An ECG will be obtained and transmitted to the ACCORD ECG Reading Center. Retain a copy for participant's research records.
9. Collect all glycemic related information:
   a) Measure and record POC HbA1c. Currently there are only 3 acceptable means of attaining a HbA1c value:

- The Central Lab
- A Bayer DCA 2000, and
- An approved local lab

Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times. Remember POC values should be adjusted for any systematic differences from Central Lab HbA1c values.

b) Review screening blood glucose diary, download SMBG meter values to laptop and assess blood glucose values for implementation of the glycemia intervention.
c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia in the source documents. Review symptoms and therapy of hypoglycemia (See Section A.1.3.b, A.1.3.c and MOP Chapter 8, Section 8.4.4).
d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document. Record current glycemic medications on the **Baseline History and Physical Exam Form** only by class of medication.
e) Record name and dose of all **current** (at visit entry) oral glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.
f) Conduct nutrition assessment and plan.
g) Instruct participants on their diet, foot care, an exercise program and the relationship of medications with nutrition and exercise.
h) Reinforce proper SMBG technique and instruct participant to test per instructions on MOP Table A.1.3 (4/day if diet/oral therapy (2 ac/day, 2 pc/day) and 4 -8 times/day (at least 2 ac/day and 2 pc/day; occasional 3 am test) if on insulin.
i) Provide SMBG logbooks and instructions for their completion.
j) Check Central Lab HbA1c at the time the results are available if drawn and make any additional changes to achieve target (See Section A.2.2).
k) Dispense glucose meter if necessary (**Canadian Sites only**).
l) Provide sufficient strips through the next visit to the participant. (**Canadian Sites only**).
m) Fill out the **Unified Form** to ensure a smooth and steady flow of diabetic testing supplies being shipped by NetGroup Diabetic Services (**US sites only**).
n) Adjust and convert all glucose lowering medications to study provided medications as needed to improve glycemic control based on POC result and screening blood glucose diary (See Figure A.3 at the end of this chapter). Participant should be on at least 2 oral agents at visit exit.
o) Recommend medical ID if participant is being started on insulin.

10. Collect all blood pressure related information:
    a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
    b) Record current BP medications on the **Baseline History and Physical Exam Form** only by class of medication.

c) Using appropriate technique with the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
d) If on 0 - 1 antihypertensive medication at baseline, the participant should begin a study drug combination (an ACE-I, a beta-blocker, a calcium channel blocker, or an angiotensin II receptor blocker (ARB) combined with the diuretic) and be monitored as indicated by the protocol. If the participant is on 2 or 3 medications at baseline, they may continue their present therapy if at goal (< 120 mm Hg) and the regimen includes a diuretic. If the regimen does not include a diuretic it is recommended that the current regimen be adjusted and include a diuretic. If the participant is not at goal (≥ 120 mm Hg) therapy should be adjusted (e.g. dosage titration, addition of another agent, or change to an alternate combination) to move toward the study goal.
e) Initiate or convert all blood pressure-lowering medications to study drugs (if necessary); record name of drug and dose on the **Blood Pressure Medications Log**.
f) Instruct participants on actions to limit symptomatic orthostasis.

11. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
12. Participants assigned in substudies (Health Related Quality of Life (HRQL), Physical Activity, Diet) will complete the appropriate questionnaires. Verify that the participant completes all items before end of visit.
13. If you have not acted upon a Central Lab HbA1c > 6%, refer to Section A.2.2. Schedule follow-up phone/fax/email/mail contact within 2 weeks and a clinic appointment in 1 month.
14. Remind participants to bring all their medications, glucose meters and SMBG records to each visit.
15. Remind participants to take blood pressure medications the morning of next visit.
16. Collect all related Lifestyle and Background information:
    a) Assess smoking status. Follow guidelines (if necessary) in MOP Chapter 4, Section 4.3.1 for smoking cessation activities.
    b) Assess aspirin use. Recommend aspirin therapy (if appropriate) in accordance with guidelines in MOP Chapter 4, Section 4.3.2.
17. Contact primary care provider as necessary.
18. Obtain a release of information form in case of need for subsequent events.
19. Complete the following forms and enter data as required:
    a) **Inclusion/Exclusion Summary Form**
    b) **Blood Pressure Trial Screening Form**
    c) **Lipid Trial Screening Form**
    d) **Participant Contact Information Form (if not previously completed)**
    e) **Visual Acuity Worksheet**
    f) **Ophthalmology Exam Form (as necessary)**
    g) **Baseline History and Physical Exam Form**
    h) **Intensive Glycemia Management Form**
    i) **Glycemia Medications Log**
    j) **Intensive Blood Pressure Management Form**

k) **Blood Pressure Medications Log**
l) **Encounter and Disposition Form**
m) **Health Utilities Index Form**
n) **The Unified Form (US sites only)**
o) **Assigned Substudy Questionnaires (as necessary)**
p) **Drug Dispensing Form (as necessary)**
q) **Event Forms (as necessary)**

A.2.2 Upon Receipt of Central Lab HbA1c Values Drawn

1. If the Central HbA1c result measured at that visit returns > 6.0%, and no change in therapy was made at the time of the visit (when the Central Lab HbA1c was obtained), and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   a. Contact the participant, and intensify the therapy per protocol
      - Increase dose of current agent (if on submaximal dose) or add another agent (see Figure A.3).
   b. Complete appropriate glycemia forms regarding the changes in therapy made to achieve or maintain target levels.

A.2.3 Phone/FAX/email/mail Contact at 0.5, 1.5, 2.5 and 3.5 Months

These contacts are for participants assigned to the intensive glycemic treatment group and should occur within a +/- 1-week window. The participants will be contacted by one of the means listed above and the following procedures will be conducted:

1. Record the participant's report of their SMBG results for the previous 2 weeks if you have not already received them by phone, fax, email or mail. Encourage participants to comply with advance requests for SMBG results.
2. Complete **Intensive Glycemia Management Form**. Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section A.1.3.b, A.1.3.c and MOP Chapter 8, Section 8.4.4).
3. Record current glycemic medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record appropriate information on the **Intensive Glycemia Management Form**.
4. Adjust or maintain therapy according to the following:
   a) If < 50% of fasting levels over 4 days are > 100 mg/dl (5.6 mmol/l) **AND** < 50% over 4 days of the 2 hr levels are > 140 mg/dl (7.8 mmol/l);
      - Remain at the same dose of current medications.
   b) If ≥ 50% of fasting levels over 4 days are > 100 mg/dl (5.6 mmol/l); **AND/OR** ≥ 50% of the 2 hr levels over 4 days are > 140 mg/dl (7.8 mmol/l); **AND** no contraindication (See MOP Chapter 6) to intensify therapy:
      - Increase dose of current agent (if currently on submaximal dose) or add another drug (See A.3 or A.5) and reinforce diet and exercise.
5. Reinforce appropriate SMBG frequency according to Table A.1.3:

- Diet/oral therapy ($\geq$ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.

6. Instruct participants on when and how to self-titrate therapy. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.
7. Remind participant of next clinic visit.
8. Remind participant to take blood pressure medications the morning of next visit.
9. Complete the following form and enter data as required:
   a) **Intensive Glycemia Management Form**
   b) **Glycemia Medications Log**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   d) **Study Status Form (as necessary)**

A.2.4 One, 2, 3, and 6 month Visits

These visits should occur within a +/- 1-week window. The participants will report to the clinic and the following procedures will be conducted:

1. Obtain weight, and record in source documentation.
2. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See Mop Chapter 9, Section 9.2.3).
3. Collect all glycemia related information:
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

   Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustment in the glycemia intervention.
   c) Complete **Intensive Glycemia Management Form**. Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section A.1.3.b, A.1.3.c and MOP Chapter 8, Section 8.4.4).
   d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
   e) Adjust or maintain therapy according to the following:
      1. If POC HbA1c < 6% **AND** < 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
         - Maintain current therapy.
      3. If POC HbA1c < 6% **BUT** $\geq$ 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** $\geq$ 50% of the 2 hour postprandial levels over 4

days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:

- Increase dose of current agent (if on submaximal dose) or add another agent (See A.3 or A.5).

4. If POC HbA1c is ≥ 6.0% and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   - Increase dose of current agent (if on submaximal dose) or add another agent (See A.3 or A.5).

f) **If participant was started on a TZD, check for edema at every visit**. Obtain an ALT every 2 months for the first year of treatment, annually thereafter. Provide participant information on TZDs as necessary.

g) Reinforce appropriate SMBG frequency according to Table A.1.3:
   - Diet/oral therapy (≥ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.

h) Assess comprehension/understanding of dietary counseling.
   - Reinforce diet and exercise. Repeat at subsequent visits as necessary.

i) Instruct participants on when and how to self-titrate. If on insulin, instruct participants on when and how to self-titrate every 4 days (if applicable).

j) Record name and dose of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on **Intensive Glycemia Management Form**.

k) Provide SMBG logbooks and instructions in their completion.

5. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self-report of adherence in source documents.
   c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
   d) If the SBP is at the desired goal of < 120 mm Hg, maintain current therapy
   e) If the SBP ≥ 120 mm Hg, an upward dose titration or an additional drug (not already in use) should be added. Participants should be seen at monthly intervals until at goal.
   f) Record name, dose, and adherence of **all** blood pressure medications on the **Blood Pressure Medications Log.**

5. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
6. At the month 1, 2, and 3 visits, schedule follow-up phone/fax/email/mail contact in 2 weeks and a clinic appointment in 1 month. At the 6 month visit, schedule phone/fax/email/mail contact in 1 month and a clinic appointment in 2 months

7. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
8. Remind participant to take blood pressure medications the morning of next visit.
9. Complete the following forms and enter data as required:
   a) **Intensive Glycemia Management Form**
   b) **Glycemia Medication Log**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   d) **Intensive Blood Pressure Management Form**
   e) **Blood Pressure Medications Log**
   f) **Encounter and Disposition Form**
   g) **Drug Dispensing Form (as necessary)**
   h) **Study Status Form (as necessary)**

A.2.5 Four & 8 Month Visit

The 4-month visit should occur within a +/- 1-week visit window. The 8-month visit should occur within a +/- 2-week window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia or lipid (if applicable) medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter the **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the physical exam, including weight. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, Creatinine and ALT.
4. Collect all glycemia related information.
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC

values should be adjusted for any systematic differences from Central HbA1c values.

b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustments in the glycemia intervention.

c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section A.1.3.b, A.1.3.c and MOP Chapter 8, Section 8.4.4).

d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.

e) Adjust and maintain therapy according to the following:

1. If POC HbA1c < 6% **AND** < 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
   - Maintain current therapy.
2. If POC HbA1c < 6% **BUT** ≥ 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** ≥ 50% of the 2 hour levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   - Increase dose of current agent (if on submaximal dose) or add another agent (See Figure A.3 or A.5).
3. If POC HbA1c is ≥ 6.0% and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   - Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).

f) **If participant was started on a TZD, check for edema at every visi**t. Obtain an ALT every 2 months for the first year of treatment, annually thereafter. Provide participant information sheet on TZD as necessary.

g) Reinforce appropriate SMBG frequency according to Table A.1.3:
Diet/oral therapy (> 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.

h) Assess comprehension/understanding of dietary counseling.
   - Reinforce diet and exercise. Repeat at subsequent visits as necessary.

i) Instruct participants on when and how to self-titrate. If on insulin, instruct the participant on when and how to self-titrate every 4 days (if applicable).

j) Record name, dose, and adherence of all glycemia medications on the **Glycemia Medications Log.** If on insulin, record name and dose on the **Intensive Glycemia Management Form**.

k) Provide SMBG logbooks and instructions for their completion.

l) Check Central Lab HbA1c at the time the results are available if drawn and make any additional changes to achieve target (See Section A.2.2).

5. **This is a Milepost Visit.** Collect all blood pressure related information:

a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not

taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.

b) Record current medications, dose and self- report of adherence in source document.
c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
d) If the SBP is at the desired goal of < 120 mm Hg, maintain current or equivalent therapy.
e) If the SBP ≥ 120 mm Hg, **you must add an additional drug class** (not already in use) as this is considered a milepost visit for evaluation of BP goals. If in the investigator's clinical judgement, an adjustment in the medication regimen is not possible, you must complete a **Milepost Blood Pressure Drug Exception Form** explaining the reason. Participants should be seen at monthly intervals until at goal.
f) Instruct participants on actions to limit symptomatic orthostasis.
g) Record name, and dose of all blood pressure medications dispensed on the **Blood Pressure Medications Log.**

6. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
7. Complete **Cost Substudy Form** for participants in the Cost Substudy.
8. Schedule follow-up phone/fax/email/mail contact in 1 month +/- 2 weeks and a clinic appointment in 2 months or any other required supplemental visits (See MOP Chapter 6).
9. Remind participants to bring all their medications, glucose meter and SMBG records to next visit.
10. Remind participant to take blood pressure medications the morning of next clinic visit.
11. Complete the following forms and enter data as required:
    a) **Interval History and Follow-up Form**
    b) **Intensive Glycemia Management Form**
    d) **Glycemia Medication Log**
    e) **Severe Hypoglycemia Action Form (as necessary)**
    d) **Intensive Blood Pressure Management Form**
    e) **Blood Pressure Medications Log**
    f) **Encounter and Disposition Form**
    g) **Preliminary Event Notification Form (as necessary)**
    h) **Event Forms (as necessary)**
    i) **Milepost Blood Pressure Drug Exception Form (as necessary)**
    j) **Drug Dispensing Form (as necessary)**
    k) **Cost Substudy Form (as necessary)**
    l) **Study Status Form (as necessary)**

A.2.6 Bi-Monthly Phone/FAX/email/ mail Contacts From Month 5 visit Through End Of Study

These contacts are for participants assigned to the intensive glycemic treatment group and should occur within a +/- 2-week window. The participants will be contacted by one of the means listed above and the following procedures will be conducted:

1. Record the participant's report of their SMBG results for the previous 2 weeks if you have not already received them by phone, fax, email or mail. Encourage participants to comply with advance requests for SMBG results.
2. Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section A.1.3.b, A.1.3.c and MOP Chapter 8, Section 8.4.4).
3. Record current glycemic medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record appropriate information on the **Intensive Glycemia Management Form**.
4. Adjust or maintain therapy according to the following:
   a) If < 50% of fasting levels over 4 days are > 100 mg/dl (5.6 mmol/l) **AND** < 50% over 4 days of the 2 hr levels are > 140 mg/dl (7.8 mmol/l);
      - Remain at the same dose of current medications.
   b) If ≥ 50% of fasting levels over 4 days are > 100 mg/dl (5.6 mmol/l); **AND/OR** ≥ 50% of the 2 hr levels over 4 days are > 140 mg/dl (7.8 mmol/l); **AND** no contraindication (See MOP Chapter 6) to intensify therapy:
      - Increase dose of current agent (if on submaximal dose) or add another drug (See Figure A.3 or A.5) and reinforce diet and exercise.
5. Reinforce appropriate SMBG frequency according to Table A.1.3:
   - Diet/oral therapy (≥ 2 times/day if at target or 4 times/day (2 ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.
6. Instruct participants on when and how to self-titrate therapy. If on insulin, instruct the participant on when and how to self-titrate every 4 days (if applicable).
7. Remind participant of next 2-month clinic appointment.
8. Remind participant to take blood pressure medications the morning of next visit.
9. Complete the following form and enter data as required:
   a) **Intensive Glycemia Management Form**
   b) **Glycemia Medications Log**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   d) **Study Status Form (as necessary)**

A.2.7 Visits at Follow-up Months 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74,78, 82, 86, 90, and 94

These visits should occur within a +/- 2-week window. The participants will report to the clinic and the following procedures will be conducted:

1. Obtain weight, and record in source documentation.

2. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, section 9.2.3).
3. Collect all glycemia related information:
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustment in the glycemia intervention.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section A.1.3.b, A.1.3.c and MOP Chapter 8, Section 8.4.4).
   d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
   e) Adjust or maintain therapy according to the following:
      1. If POC HbA1c $< 6\%$ **AND** $< 50\%$ of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** $< 50\%$ of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
         - Maintain current therapy.
      2. If POC HbA1c $< 6\%$ **BUT** $\geq 50\%$ of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** $\geq 50\%$ of the 2 hour levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
         - Increase dose of current agent (if on submaximal dose) or add another agent (See Figure A.3 or A.5).
      3. If POC HbA1c is $\geq 6.0\%$ and there is no contraindication (See MOP Chapter 6) to intensify therapy:
         - Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).
   f) **If participant was started on a TZD, check for edema at every visit**. Obtain an ALT every 2 months for the first year of treatment, annually thereafter. Provide participant information sheet on TZDs as necessary.
   g) Reinforce appropriate SMBG frequency according to Table A.1.3:
      - Diet/oral therapy (≥ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.
   h) Assess comprehension/understanding of dietary counseling.
      - Reinforce diet and exercise. Repeat at subsequent visits as necessary.

i) Instruct participants on when and how to self-titrate. If on insulin, instruct the participant on when and how to self-titrate every 4 days (if applicable).
j) Record name and dose of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.
k) Provide SMBG logbooks and instructions in their completion.

4. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self-report of adherence.
   c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
   d) If the SBP is at the desired goal of < 120 mm Hg, maintain current therapy
   e) If the SBP $\geq$ 120 mm Hg, an upward dose titration or an additional drug (not already in use) should be added. Participants should be seen at monthly intervals until at goal.
   f) Record name, dose, and adherence of **all** blood pressure medications on the **Blood Pressure Medications Log.**
5. Remove labels from study medications and place on drug dispensing form then dispense blood pressure-lowering study medication. Scan label bar codes into the computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
6. Schedule follow-up phone/fax/email/mail contact in 1 month and a clinic appointment in 2 months.
7. Remind participants to bring all their medications, glucose meter and SMBG records to each visit.
8. Remind participant to take blood pressure medications the morning of next visit.
9. Complete the following forms and enter data as required:
   a) **Intensive Glycemia Management Form**
   b) **Glycemia Medication Log**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   d) **Intensive Blood Pressure Management Form**
   e) **Blood Pressure Medications Log**
   f) **Encounter and Disposition Form**
   g) **Drug Dispensing Form (as necessary)**
   h) **Study Status Form (as necessary)**

A.2.8 Annual Visits (12, 24, 36, 48, 60, 72, 84, and 96 Months)

This visit should occur within a +/- 2-week visit window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia or lipid (if applicable) medications on the morning of this clinic visit but should be instructed to bring their medications, glucose

meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Review and update Contact Information.
2. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter the **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
3. Perform the annual physical exam, including weight, height, weight circumference, visual acuity, and foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
4. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, Creatinine, Lipid Profile and ALT. **(Blood samples for storage of additional aliquots, where approved, should occur at the 24-month, 48-month 72-month and 96-month visits)**.
5. Review the Concomitant Medications list located in the **Annual Follow-up and Physical Exam Form** with participant to document all non-study medications currently taking.
6. Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completes all items before end of visit. **(12-month, 36-month, and 48 month visits)**.
7. **A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Lab for the 24-month, 48-month, 72-month and 96-month visits.**
8. **An ECG will be obtained and transmitted to the ACCORD ECG Reading Center for the 24-month, 48-month, 72-month and 96-month visits**. Retain a copy for participant's research records.
9. Collect all glycemia related information.
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.

b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustments in the glycemia intervention.
c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section A.1.3.b, A.1.3.c and MOP Chapter 8, Section 8.4.4).
d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
e) Adjust and maintain therapy according to the following:
   1. If POC HbA1c < 6% **AND** < 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
      - Maintain current therapy.
   2. If POC HbA1c < 6% **BUT** ≥ 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** ≥ 50% of the 2 hour levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
      - Increase dose of current agent (if on submaximal dose) or add another agent (See Figure A.3 or A.5).
   3. If POC HbA1c is ≥ 6.0% and there is no contraindication (See MOP Chapter 6) to intensify therapy:
      - Increase dose of current agent (if on submaximal dose) or add another agent (See Figure A.3 or A.5).
f) **If participant was started on a TZD, check for edema at every visit**. Obtain an ALT every 2 months for the first year of treatment, annually thereafter. Provide participant information sheet on TZDs as necessary.
g) Reinforce appropriate SMBG frequency according to Table A.1.3:
   Diet/oral therapy (≥ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.
h) Assess comprehension/understanding of dietary counseling.
   - Reinforce diet and exercise. Repeat at subsequent visits as necessary.
i) Instruct participants on when and how to self-titrate. If on insulin, instruct the participant on when and how to self-titrate every 4 days (if applicable).
j) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.
k) Provide SMBG logbooks and instructions for their completion.
l) Check Central Lab HbA1c at the time the results are available if drawn and make any additional changes to achieve target (See Section A.2.2).
m) Review and update the **Unified Form** to ensure a smooth and steady flow of diabetic testing supplies being shipped by the NetGroup Diabetic Services **(US sites only)**.

10. **This is a Milepost Visit.** Collect all blood pressure related information:

a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
b) Record current medications, dose and self- report of adherence.
c) Using the appropriate technique for the Omron device (See MOP Chapter 9, Section 9.2.3) obtain and evaluate blood pressure values.
d) If the SBP is at the desired goal of < 120 mm Hg, maintain current or equivalent therapy.
e) If the SBP $\geq$ 120 mmHg, **you must add an additional drug class** (not already in use) as this is considered a milepost visit for evaluation of BP goals. If in the investigator's clinical judgement, an adjustment in the medication regimen is not possible, you must complete a **Milepost Blood Pressure Drug Exception Form** explaining the reason. Participants should be seen at monthly intervals until at goal.
f) Instruct participants on actions to limit symptomatic orthostasis.
g) Record name, and dose of **all** blood pressure medications dispensed on the **Blood Pressure Medications Log.**

11. Remove labels from study medications and place on **Drug Dispensing Form** then dispense blood pressure lowering study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
12. Participants assigned in the substudies (Health Related Quality of Life (HRQL), Physical Activity, Diet) will complete the appropriate questionnaires. **(12-month, 36-month, and 48-month visits)**. Verify that the participant completes all items before end of visit. Complete **Cost Substudy Form** for participants in the Cost Substudy.
13. Schedule follow-up phone/fax/email/mail contact in 1 month +/- 2 weeks and a clinic appointment in 2 months or any other required supplemental visits (See MOP Chapter 6).
14. Remind participants to bring all their medications, glucose meter and SMBG records to next visit.
15. Complete the following forms and enter data as required:
    a) **Participant Contact Information Form (as necessary)**
    b) **Annual Follow-up and Physical Exam Form**
    c) **Intensive Glycemia Management Form**
    d) **Glycemia Medications Log**
    e) **Severe Hypoglycemia Action Form (as necessary)**
    f) **Intensive Blood Pressure Management Form**
    g) **Blood Pressure Medications Log**
    h) **Encounter and Disposition Form**
    i) **Health Utilities Index Form (12-month, 36-month)**
    j) **Visual Acuity Worksheet (24- month, 48-month, 72- month, and exit visits)**
    k) **The Unified Form (US sites only)**
    l) **Ophthalmology Exam Form (as necessary)**
    m) **Preliminary Event Notification Form (as necessary)**

n) **Event Forms (as necessary)**
o) **Milepost Blood Pressure Drug Exception Form (as necessary)**
p) **Assigned Substudy Questionnaires (as necessary at 12-month, 36-month, and 48-month visits)**
q) **Cost Substudy Form (as necessary)**
r) **Drug Dispensing Form (as necessary)**
s) **Severe Hypoglycemia Action Form (as necessary)**
t) **Study Status Form (as necessary)**

A.2.9 Visits at Follow-up Months 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, and 92

These visits are for participants assigned to the intensive glycemia/intensive BP treatment intervention and should occur within a +/- 2- week window. **These visits are Milepost visits for the intensive blood pressure participants for the 16-month and 20-month visit**. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter the **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Obtain weight.
3. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
4. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c.
5. Collect all glycemia related information.
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustments in the glycemia intervention.

c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section A.1.3.b, A.1.3.c and MOP Chapter 8, Section 8.4.4).

d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.

e) Adjust and maintain therapy according to the following:

1. If POC HbA1c < 6% **AND** < 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
   - Maintain current therapy.
2. If POC HbA1c < 6% **BUT** ≥ 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** ≥ 50% of the 2 hour levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   - Increase dose of current agent (if on submaximal dose) or add another agent (See Figure A.3 or A.5).
3. If POC HbA1c is ≥ 6.0% and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   - Increase dose of current agent (if on submaximal dose) or add another agent (See Figure A.3 or A.5).

f) Reinforce appropriate SMBG frequency according to Table A.1.3:
Diet/oral therapy (≥ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.

g) Assess comprehension/understanding of dietary counseling.
   - Reinforce diet and exercise. Repeat at subsequent visits as necessary.

h) Instruct participants on when and how to self-titrate. If on insulin, instruct the participant on when and how to self-titrate every 4 days (if applicable).

i) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log**.

j) Provide SMBG logbooks and instructions for their completion.

k) Check Central Lab HbA1c at the time the results are available if drawn and make any additional changes to achieve target (See Section A.2.2).

6. **This is a Milepost Visit for the 16-month and the 20-month visit.** Collect all blood pressure related information:

a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.

b) Record current medications, dose and self- report of adherence.

c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).

d) If the SBP is at the desired goal of < 120 mm Hg, maintain current or equivalent therapy.

e) If the SBP $\geq$ 120 mm Hg, **you must add an additional drug class** (not already in use) as this is considered a milepost visit for evaluation of BP goals for the 16-month and the 20-month visit. If in the investigator's clinical judgement, an adjustment in the medication regimen is not possible, you must complete a **Milepost Blood Pressure Drug Exception Form** explaining the reason.
f) If the SBP $\geq$ 120 mm Hg for all the other visits, an upward dose titration or an additional drug (not already in use) should be added. Participants should be seen at monthly intervals until at goal.
g) Instruct participants on actions to limit symptomatic orthostasis.
h) Record name, and dose of all blood pressure medications dispensed on the **Blood Pressure Medications Log.**

7. Remove labels from study medications and place on **Drug Dispensing Form** then dispense blood pressure lowering study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
8. Complete **Cost Substudy Form** for participants in the Cost Substudy.
9. Schedule follow-up phone/fax/email/mail contact in 1 month +/- 2 weeks and a clinic appointment in 2 months or any other required supplemental visits (See MOP Chapter 6).
10. Remind participants to bring all their medications, glucose meter and SMBG records to next visit.
11. Remind participant to take blood pressure medications the morning of next clinic visit.
12. Complete the following forms and enter data as required:
    a) **Interval History and Follow-up**
    b) **Intensive Glycemia Management Form**
    c) **Glycemia Medication Log**
    d) **Severe Hypoglycemia Action Form (as necessary)**
    e) **Intensive Blood Pressure Management Form**
    f) **Blood Pressure Medications Log**
    g) **Encounter and Disposition Form**
    h) **Preliminary Event Notification Form (as necessary)**
    i) **Event Forms (as necessary)**
    j) **Milepost Blood Pressure Drug Exception Form (as necessary for 16-month and 20-month visit)**
    k) **Drug Dispensing Form (as necessary)**
    l) **Cost Substudy Form (as necessary)**
    m) **Study Status Form (as necessary)**

A.2.10 Exit Visit

This visit should occur within a +/- 2-week visit window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia or lipid (if applicable) medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should,

however, take their blood pressure medication (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter the **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the annual physical exam, including weight, height, weight circumference, visual acuity, and foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, Creatinine, Lipid Profile, ALT and CPK and for storage of additional aliquots (where approved).
4. Review the Concomitant Medications list located in the **Annual Follow-up and Physical Exam Form** with participant to document all non-study medications currently taking.
5. Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completes all items before end of visit.
6. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Lab.
7. An ECG will be obtained and transmitted to the ACCORD ECG Reading Center. Retain a copy for participant's research records.
8. Collect all glycemia related information.
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section A.1.3.b, A.1.3.c and MOP Chapter 8, Section 8.4.4).
   d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.

e) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on **Intensive Glycemia Management Form**.

9. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self- report of adherence.
   c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
   d) Record name, and dose of **all** blood pressure medications dispensed on the **Blood Pressure Medications Log.**
10. Participants will be prescribed appropriate non-study antihyperglycemia and antihypertensive therapy based on their current status and post-trial follow-up care will be arranged.
11. Complete the following forms and enter data as required:
    a) **Participant Contact Information Form (as necessary)**
    b) **Annual Follow-up and Physical Exam Form**
    c) **Intensive Glycemia Management Form**
    d) **Glycemia Medications Log**
    e) **Severe Hypoglycemia Action Form (as necessary)**
    f) **Intensive Blood Pressure Management Form**
    g) **Blood Pressure Medications Log**
    h) **Encounter and Disposition Form**
    i) **Health Utilities Index Form**
    j) **Visual Acuity Worksheet**
    k) **Ophthalmology Exam Form (as necessary)**
    l) **Preliminary Event Notification Form (as necessary)**
    m) **Event Forms (as necessary)**
    n) **Study Status Form (as necessary)**

Figure A.3
Treatment Algorithm for Intensive Glycemic Therapy Group (Goal: HbA1c<6%)

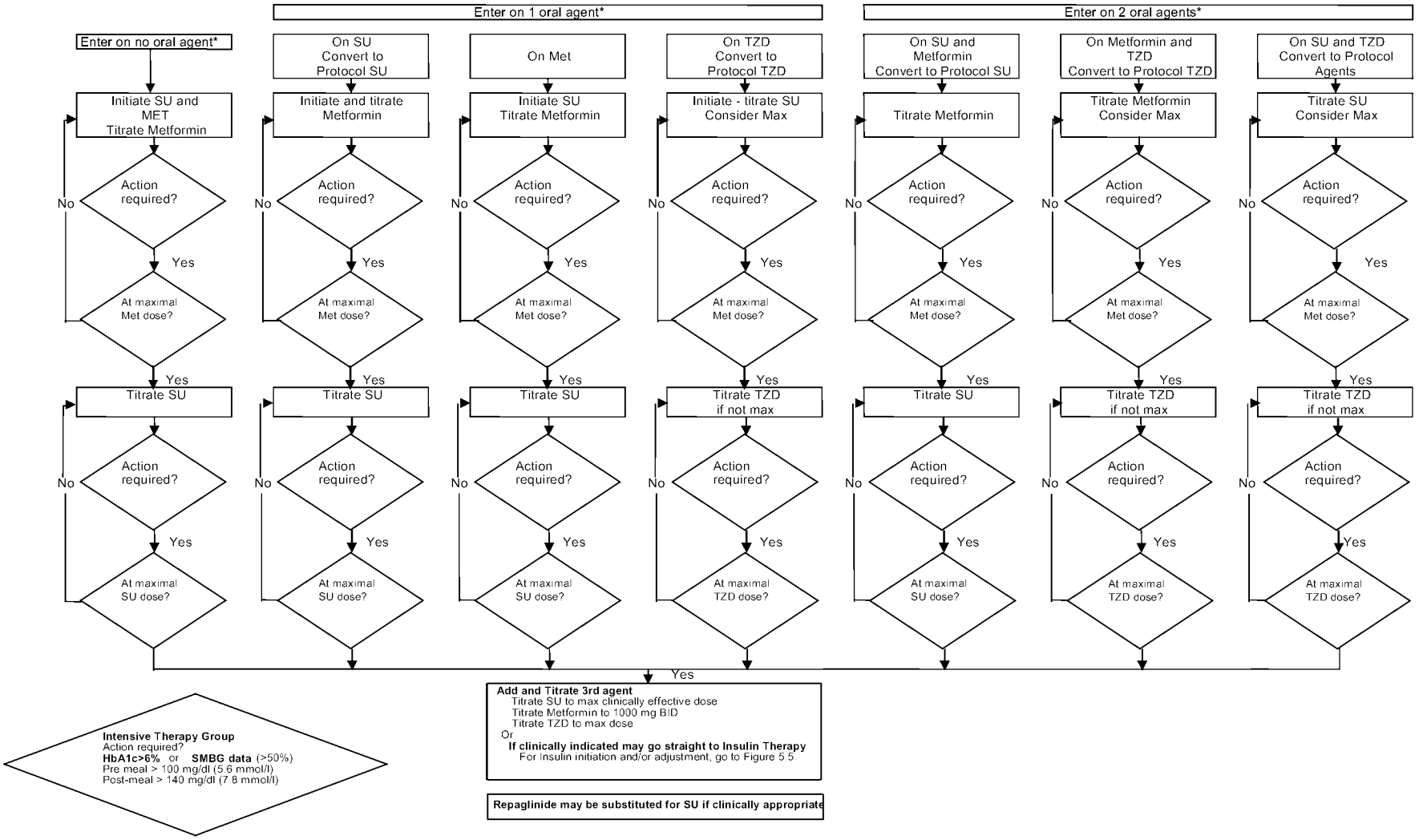
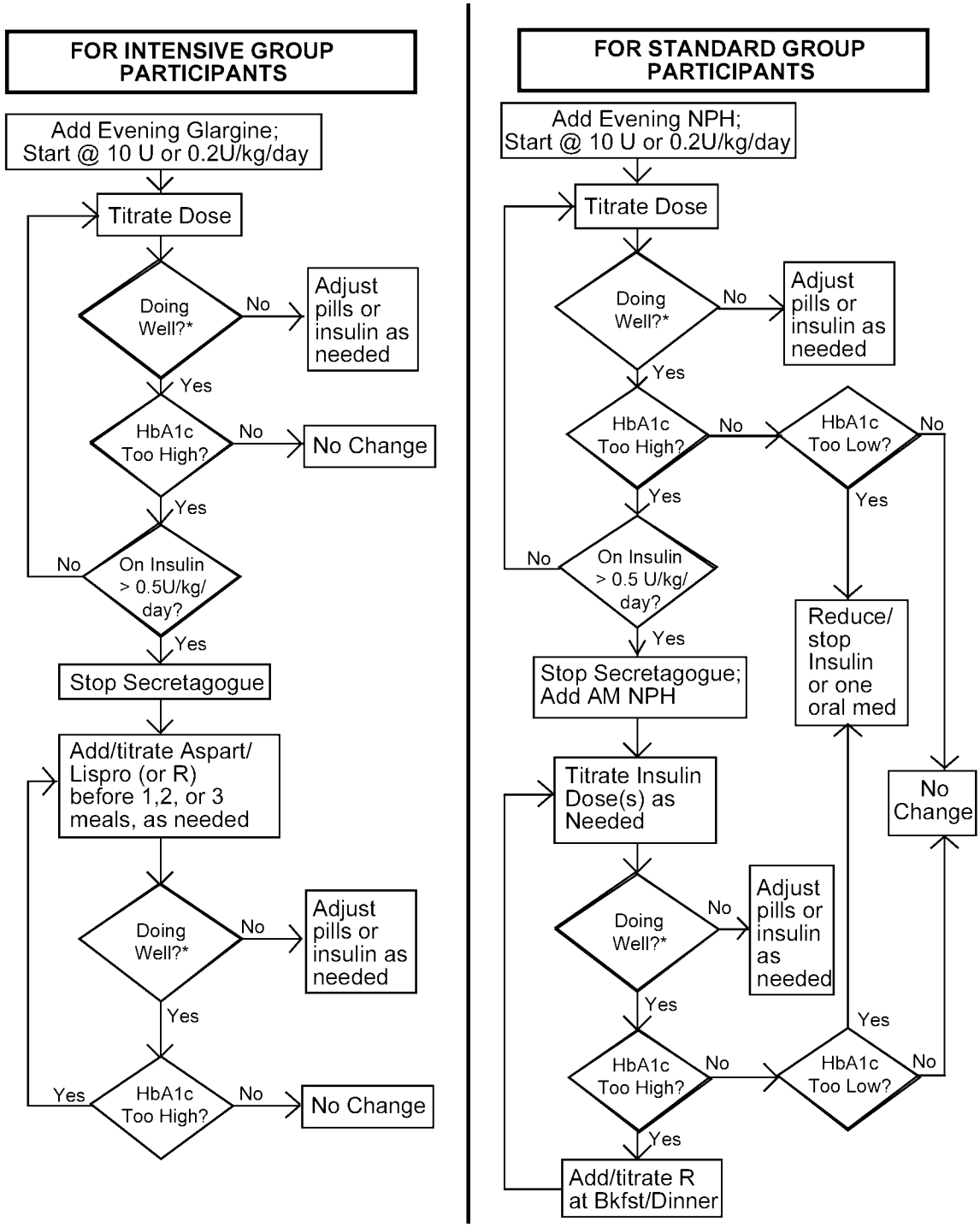
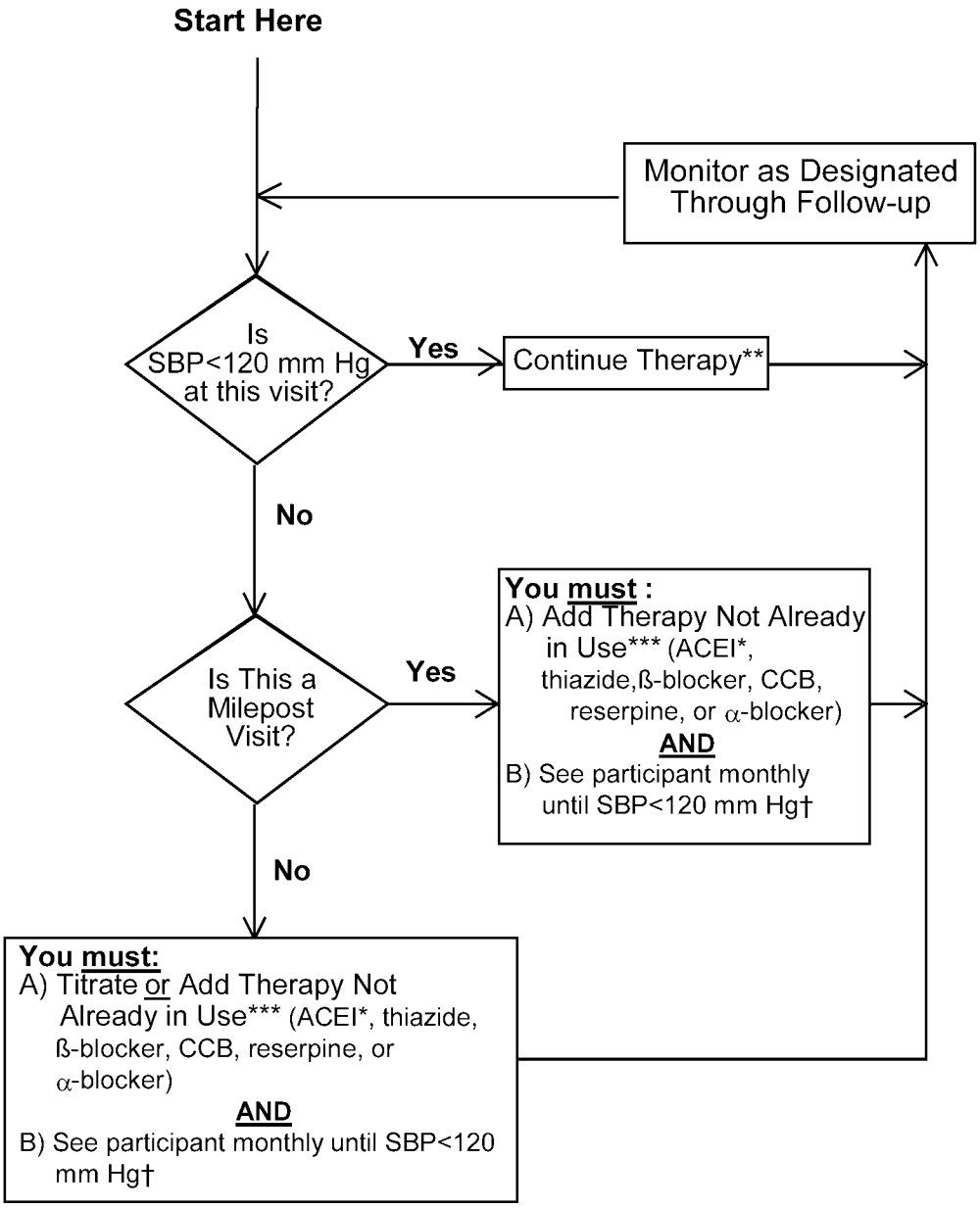


Figure 3.3:
Use of Insulin for Participants On Maximal Oral Therapy



*Doing well: no severe hypoglycemic or adverse event or no reason to reduce therapy (as described in Figure 3.2)

Figure A.6: Treatment Algorithm for Intensive Blood Pressure Group (Goal: SBP < 120 mm Hg)



* ARB can be considered as a substitute for participants who do not tolerate ACEI therapy
** Unless side effects warrant change in therapy
*** Consult with the Clinical Center Network before adding a fifth antihypertensive medication
† or until a clinical decision is made that therapy should not be increased further

Thiazolidinedione Drugs (e.g. Avandia or Rosiglitazone)

ACTIONS of THIAZOLIDINEDIONES

The drug Avandia (rosiglitazone) belongs to a group of medications called thiazolidinediones (or glitazones or TZD's), and may be supplied as part of the ACCORD trial. Actos (pioglitazone) is another drug that belongs in this group. These drugs lower the blood glucose by reducing the body's resistance to the action of insulin (i.e. making your own insulin work more effectively). They can be used alone or can be combined with other diabetes pills or insulin.

COMMON SIDE EFFECTS

1. Hypoglycemia (low blood sugar)

These drugs can lead to hypoglycemia. When taken alone, the risk of hypoglycemia is low. When taken with insulin or other pills, the risk of hypoglycemia is higher.

If you do experience symptoms of a low blood sugar (such as lightheadedness, sweating, nervousness, hunger, a sensation of a racing heart, headache, or sudden fatigueat unusual times), check your blood sugar. If the level is less than 70 mg/dl (3.9 mmol/l) you may be suffering from hypoglycemia. If so, drink 4 ounces of juice or regular soda or eight ounces of milk or have three glucose tablets or five Life Savers (i.e. 15 grams of carbohydrate). Recheck your blood sugar in 15 minutes to make sure it has risen to at least 90 mg/dl (5.0 mmol/L). If low blood sugar reactions are frequent, severe or unexpected, call your doctor.

2. Weight Gain

These drugs may lead to weight gain. Weight gain is due to the lowering of blood sugar by insulin and drugs that act like insulin. This reduces the amount of sugar lost in the urine and helps the body store extra energy in fat cells. Sometimes, weight gain may be due to some fluid retention. Regardless of the cause, the amount of weight gained or lost depends on the level of physical activity and diet, or can be due to other drugs that are being taken. For example, some people gain more weight if insulin is also being taken. To minimize weight gain or to cause weight loss, exercise regularly, eat low fat foods, avoid extra snacks and large portions.

3. Fluid Retention

These drugs may lead to fluid retention. Fluid retention is generally mild with some swelling in the ankle or leg or bloating; it may be more pronounced when these drugs are used together with insulin, and rarely, the fluid retention can be severe or even life threatening. If you develop major leg swelling or especially shortness of breath either with activity or at rest, see your doctor as soon as possible. Reducing the dose, adding diuretics (water pills) or adjusting other medications (such as blood pressure pills, calcium channel blockers, non-steroidal anti-inflammatory drugs or arthritis pills) can also be used to manage this problem. ***You and your doctor should pay close attention to fluid retention if you take insulin or have heart failure or other heart problems.***

POTENTIAL SIDE EFFECTS

Because of rare cases of severe liver disease with a related medicine that is no longer available (Rezulin or troglitazone), you must have your blood drawn for liver enzyme tests (ALT) when treated with these drugs every 2 months for the first year of treatment and intermittently thereafter. If you develop persistent nausea, vomiting, belly pain, fatigue, loss of appetite, dark urine, yellowing of the eyes or skin while treated with this drug, stop the medication and see your doctor for a blood draw within a few days.

DOSING

Avandia (rosiglitazone) can be taken once a day, but may work a bit better if taken twice daily. Actos (pioglitazone) can be taken any time of the day. Both drugs can be taken either with or without food. It may take 12 weeks to see the full effect of a dose.

7. Visit Schedule of Study Activities by Randomization Cell

B. Intensive Glycemia and Standard Blood Pressure

B.1 Overview

One of the key aims of the ACCORD study is to determine if targeting a HbA1c of < 6.0% (the upper limit of the nondiabetic range) reduces the rate of cardiovascular disease (CVD) events to a greater extent than targeting a HbA1c of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%, which is 25% above the upper limit of the nondiabetic range) in high risk middle-aged or older people with type 2 diabetes. The approaches used to implement these targets, suggested algorithms for the use of pharmacologic agents and follow-up schedules are described in MOP Chapters 5 and 6.

The ACCORD blood pressure (BP) trial component is designed to test whether a therapeutic strategy that targets a systolic blood pressure (SBP) of < 120 mm Hg reduces the rate of cardiovascular events in a middle-aged or older type 2 diabetic population at high risk for cardiovascular events compared to a strategy that targets a SBP of < 140 mm Hg in the context of good glycemic control. Details regarding the implementation of the protocol for the intensive glycemia and standard blood pressure control groups are described below.

B.1.1 Algorithms for Intensive Glycemic and Standard Blood Pressure Control; Choice of Agents

Figures B.3 and B.5 at the end of this chapter are suggested algorithms to guide changes in glycemic therapy for the intensive group. The exact changes to be made whenever glycemic therapy needs to be intensified on the basis of the HbA1c or the SMBG results will be determined by the individual site using the figures as guides.

The algorithm for the standard BP group calls for an assessment of the participants' antihypertensive medication regimen at baseline to determine the starting point on the decision tree for future monitoring and medication adjustments needed to achieve their assigned SBP goal (< 140 mmHg) (Refer to Figure B.7 at the end of this chapter).

B.1.2 Targets and Action Required Levels

B.1.2.a) Intensive Glycemic Control

Table B.1.2 outlines the glycemic target for the intensive group, which is identical to that described in Table 3.1 in the protocol.

Table B.1.2: Intensive Glycemic Target and Threshold for Action for ACCORD			
		"Action Required" Threshold	
	HbA1c Targets	HbA1c	> 50% of SMBG Results/4Days
Intensive Therapy	< 6.0%	≥ 6.0%*	Fasting/ac > 100 mg/dl (5.6 mmol/l) Or 2 hrs pc > 140 mg/dl (7.8 mmol/l)

pc: postcibal (after meals); ac: antecibal (before meals); SMBG: self monitoring of blood glucose; * antihyperglycemic therapy will be advanced if either the HbA1c or the SMBG "action required " criteria are met at any particular encounter

B.1.2.b) Standard Blood Pressure Control

Participants randomized to the standard blood pressure control will have a SBP goal of < 140 mm Hg. The BP intervention will begin at the randomization visit. The investigator may choose from among the available ACCORD agents or select another as determined appropriate. It is recommended that the regimen include a drug class associated with reduced cardiovascular events in diabetes (ACE-inhibitor, beta-blocker, calcium channel blocker or diuretic). (Refer to Drug Availability List – MOP Chapter 5)

B.1.3.a) Adjusting Glycemic Therapy

As noted in the following table (B.1.3), a range of approaches will be used to target the HbA1c levels shown in Table B.1.2.

B.1.3 Achieving Glycemic Goals	Intensive Group
Visits (1st 4 months)	Monthly
Visits (> 4 months)	Q 2 mo
Phone contact	Research staff initiated (≥1 inter-visit)
Supplemental contact	Severe hypoglycemia OR HbA1c = action req'd OR SMBG = action req'd (based on review of logbooks)
Point of Care HbA1c	Mandatory
Routine use of postprandial SMBG values to guide therapy	Yes
SMBG freq.[a] (not on insulin)	≥ 2/day and 4/day if glucose is > target (2 ac/day and 2 pc/day)
SMBG freq.[a] (insulin)	4-8/d (at least 2 ac/day and 2 pc/day; occasional 3 am test prn)
Self titration principles	Avoid severe hypoglycemia[b] AND Adjust therapy every 4 days AND

	Use CHO/patterns (if on insulin)
Initial Minimum Rx	Diet/lifestyle AND 2 oral agents
Insulin Use (when needed)	Flexible

[a]less frequent if goals are achieved; [b] including avoiding SMBG levels < 70 mg/dl (3.9 mmol/l) on > 1/4 of the readings

It is expected that patients in the intensive group will experience mild, self-treated hypoglycemic episodes approximately 2-3 times/week. Moreover, initially, people may report such episodes more frequently, until they become accustomed to physiologic glycemic control.

B.1.3.b) Glycemia Safety Issues/ Adjusting Therapy for Hypoglycemia

Hypoglycemic events may occur in individuals in either the intensive or standard group. Severe hypoglycemia is unusual in people with type 2 diabetes (even when normoglycemia is targeted). Mild episodes of hypoglycemia are, however, likely to occur.

All participants will be instructed to check their glucose levels regularly as described in the protocol. They will also be taught how to recognize and self-treat hypoglycemia and will be instructed to keep glucose available at all times (as tablets). Moreover, any participant who has had an episode of severe hypoglycemia will be provided with glucagon and they and any cohabiting partner will be taught how to administer it.

Severe hypoglycemia is defined as any episode of loss of consciousness/seizure or documented hypoglycemia (glucose < 50 mg/dl or 2.8 mmol/l) that also requires hospitalization or treatment by emergency personnel. If this occurs:

- Complete **Severe Hypoglycemia Action Form.** (See MOP Chapter 8, Section 8.4.4).
- For participants in either group who have an episode of severe hypoglycemia, adjust glycemic targets to achieve a fasting and 2 hour glucose (postprandial) of 100 – 140 mg/dl (5.5 – 7.8 mmol/l) and < 180 mg/dl (10 mmol/l) respectively, and a HbA1c of 7.0% - 7.9% for at least 4 weeks.
- Ensure that a complete medical assessment by the health care provider is completed to identify other potential causes (e.g. pituitary or adrenal insufficiency)
- Ensure that the health care provider reassesses the glycemic goals at subsequent visits.
- Ensure that participant has received glucagon and that the participant and cohabitant know how to administer it.
- Have telephone contact with the participant before the next visit to assess blood glucose records and freedom from hypoglycemia.

Minor hypoglycemia is defined as self-reported transient symptoms such as lightheadedness, tremor, shaking, sweating, tingling, blurry vision, trouble concentrating etc., that are self-treated by ingestion of carbohydrates and resolve on their own. (See

MOP Chapter 6, Section 6.1.6). All participants will be asked to note such episodes in their glucose logbooks and to confirm them with a blood glucose reading whenever possible. The estimated frequency (of confirmed and suspected minor hypoglycemia) will be recorded at every visit.

B.1.3.c) Self Treatment of Hypoglycemia

1. If the glucose value is < 50 - 70 mg/dl (3.9 mmol/l), it should be treated by ingestion of 15 grams of CHO (e.g. 3-4 glucose tablets, 5 Lifesavers, 4-6 oz. of a regular – (nondiet) – soft drink, or 8 oz. low fat milk);
2. If the glucose value is < 50 mg/dl (2.8 mmol/l), it should be treated by ingestion of 20-30 grams of CHO (e.g. 6-8 glucose tablets);
3. Blood glucose should be self-tested 15-20 minutes after therapy and therapy repeated if the level is still low (as above);
4. If no meal will be eaten within 1-2 hours, a mixed nutrient snack, including CHO, protein, and fat should be ingested right after the initial therapy to prevent another episode.
5. If the glucose value is low or there is significant cognitive or motor impairment, individuals should treat and re-test glucose value. The glucose value should be > 70 mg/dl (3.9 mmol/l) before driving a car or operating heavy machinery.

B.1.3.d) Education and Minimization of Hypoglycemia in Participants

Hypoglycemia is an inherent risk in the treatment of diabetes. It is important to inform participants of the signs and symptoms of hypoglycemia, techniques to minimize the risk and appropriate methods of treatment. Several tools are available for use in educating participants:

1. Hypoglycemia Cartoon
2. Participant Wallet Card
3. Primer on Hypoglycemia
4. Participant Newsletters

All participants must be provided with the written material listed above at the beginning of the study. Study staff should review verbally the signs and symptoms with the participant and family members. Participants and their families should be encouraged to review the hypoglycemic video either in the clinic or at home. Both participants and family members should be educated on the appropriate treatment for symptoms, and provided with glucose tablets. Those participants suffering one severe hypoglycemic event should be provided with a glucagon kit and both the participant and the family member taught how to use it. This material must be reviewed annually with all participants and after every reported hypoglycemic event.

B.1.3.e) Safety Issues for Thiazolidinedione (TZD) Drugs

For participants on TZD (e.g. Avandia or Rosiglitazone), check for the presence of edema at every visit and obtain a Central Lab Alt every 2 months for the first year of treatment and annually thereafter.

As TZDs are contraindicated in people with stage 3 or 4 heart failure, if a participant who is taking a TZD does develop heart failure, the TZD should be stopped and the heart failure treated and investigated. Depending on the results of these investigations the investigator may reconsider cautiously reinstituting TZD therapy if the heart failure resolves, and was judged to have not been directly caused by TZD alone.

A handout to give to the participants at the discretion of the site concerning TZD use is available and can be found on page 28 at the end of this chapter.

B.1.3.f) Adjusting Antihypertensive Therapy

The participants' BP should be monitored at each protocol-scheduled visit. It is strongly encouraged that a diuretic be the drug of choice for initial therapy or be a component of any multi-drug antihypertensive regimen. The standard participants' blood pressure will be measured and assessed for progress toward the goal (SBP < 140 mm Hg). Should the SBP fall under 130 mm Hg at a single visit, or under 135 mm Hg on two consecutive visits, step-down therapy (a reduction of dose or number of antihypertensive drugs) is indicated at the discretion of the ACCORD therapist, after consultation with the participant. However, if the SBP ≥ 160 mm Hg at a single visit or ≥ 140 mm Hg on two consecutive visits, upward dose titration or an additional drug (not already in use) must be added. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg. If the SBP is 130-139 mm Hg at a single visit or 135 –139 mm Hg for 2 consecutive visits, one should continue therapy and monitor as prescribed by the protocol.

B.2 Intensive Glycemic and Standard Blood Pressure Control Visit Procedures

B.2.1 Baseline – Randomization Visit

The participants will be instructed to attend the clinic following an overnight fast (since ~10 pm the previous evening). They should not take their glycemia or lipid (if applicable) medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. All data collected during the screening process will be reviewed.
2. Verify eligibility status for the Glycemia, Blood Pressure and Lipid Trials (including occurrence of events that may prohibit patient from participating).

a) Review current medications including OTC, herbal remedies and vitamins.
b) Review, evaluate and calculate the percentage of participant's compliance with at least 2 weeks of SMBG monitoring as part of the run-in procedures.
c) Assure that the qualifying HbA1c value was obtained within the last 3 months prior to the randomization date.

3. If ineligible, the participant will be thanked for their time and dismissed from the clinic. Hard copies of screening forms are to be sent to the Coordinating Center.
4. If eligible, proceed with randomization process:
   a) Verify that a full-scale consent form has been obtained and signed and HIPAA authorization obtained.
   b) Obtain and perform baseline history and physical exam, including demographics, medical history, concomitant medications, weight, height, waist circumference, visual acuity, and foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
   c) Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completes all items before end of visit.
   d) Verify that all information on the **Inclusion/Exclusion Summary Form, the Blood Pressure Screening Form,** and **the Lipid Trial Screening Form** is complete and correct both on the forms and in the computer.
   e) Click "Randomize pt" on data entry screen. A pop-up screen will appear to remind staff to provide the participant with Eye Sub-study and MIND Sub-study (Canada, Western, Minnesota/Iowa, Ohio/Michigan, Northeast and Southeast CCNs) introductory materials.
   f) Input the percent of participant's report of compliance for SMBG.
   g) Verify that the **Baseline History and Physical Exam Form** has been completed.
5. The participant will be assigned a treatment regimen. The randomization screen will display this information and list target dates for the follow-up visits. It is recommended that the participant's treatment assignment and visit schedule be printed out and filed in their research record.
6. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, ALT, Creatinine, Lipid Profile, CPK and for storage of additional aliquots (where approved).
7. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Laboratory.
8. An ECG will be obtained and transmitted to the ACCORD ECG Reading Center. Retain a copy for participant's research records.
9. Collect all glycemic related information:
   a) Measure and record POC HbA1c. Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times. Remember POC values should be adjusted for any systematic differences from Central Lab HbA1c values.

b) Review screening blood glucose diary, download SMBG meter values to laptop and assess blood glucose values for implementation of the glycemia intervention.
c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia in the source documents. Review symptoms and therapy for hypoglycemia (See Section B.1.3.b, B.1.3.c and MOP Chapter 8, Section 8.4.4).
d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document. Record current glycemic medications on the **Baseline History and Physical Exam Form** only by class of medication.
e) Record name and dose of all **current** (at visit entry) oral glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.
f) Conduct nutrition assessment and plan.
g) Instruct participants on their diet, foot care and an exercise program and the relationship of medications with nutrition and exercise.
h) Reinforce proper SMBG technique and instruct participant to test per instructions on MOP Table B.1.3 (4/day if diet/oral therapy (2 ac/day, 2 pc/day) and 4 -8 times/day (at least 2 ac/day and 2pc/day; occasional 3 am test) if on insulin.
i) Provide SMBG logbooks and instructions for their completion.
j) Dispense glucose meter if necessary **(Canadian Sites only).**
k) Provide sufficient strips through the next visit to the participant **(Canadian Sites only)**.
l) Check Central Lab HbA1c at the time the results are available if drawn and make any additional changes to achieve target (See Section A.2.2).
m) Fill out the **Unified Form** to ensure a smooth and steady flow of diabetic testing supplies being shipped by NetGroup Diabetic Services (**US Sites only**).
n) Adjust and convert all glucose lowering medications to study provided medications as needed to improve glycemic control based on POC result and screening blood glucose diary. See Figure B.3 at the end of this chapter).
o) Recommend medical ID if participant is being started on insulin.

10. Collect all blood pressure related information:
a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
b) Record current BP medications on the **Baseline History and Physical Exam Form** only by class of medication.
c) Using appropriate technique with the Omron device, obtain and evaluate blood pressure values (See Mop Chapter 9, Section 9.2.3).
d) If the SBP is 131- 160 mm Hg, maintain current or equivalent therapy.
e) If SBP $\geq$ 160 mm Hg at this visit titrate or add therapy not already in use. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg.
f) If SBP < 130 mm Hg at this visit, consider stepping down BP therapy.

g) Complete **Standard Blood Pressure Management Form**. Initiate or convert all blood pressure lowering medications to study drugs (if necessary). A diuretic should be considered part of the regimen.
h) Record name and dose of all blood pressure medications on the **Blood Pressure Medications Log**.
i) Instruct participants on actions to limit symptomatic orthostasis.

11. Remove labels from study medications and place on drug dispensing form then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
12. Participants assigned in substudies (Health Related Quality of Life (HRQL), Physical Activity, Diet) will complete the appropriate questionnaires. Verify that the participant completes all items before end of visit.
13. If you have not acted upon a Central Lab HbA1c > 6%, refer to Section B.2.2. Schedule follow-up phone/fax/email/mail contact within 2 weeks and a clinic appointment in 1 month.
14. Remind participants to bring all their medications, glucose meters and SMBG records at each visit.
15. Remind participants to take blood pressure medications the morning of next visit.
16. Collect all related Lifestyle and Background information:
    a) Assess smoking status. Follow guidelines (if necessary) in chapter 4 of the MOP, section 4.3.1 for smoking cessation activities.
    b) Assess aspirin use. Recommend aspirin therapy (if appropriate) in accordance with guidelines in chapter 4 of the MOP, section 4.3.2.
17. Contact primary care provider as necessary.
18. Obtain a release of information form in case of need for subsequent events.
19. Complete the following forms and enter data as required:
    a) **Inclusion/Exclusion Summary Form**
    b) **Blood Pressure Trial Screening Form**
    c) **Lipid Trial Screening Form**
    d) **Participant Contact Information Form (if not previously completed)**
    e) **Visual Acuity Worksheet**
    f) **Ophthalmology Exam Form (as necessary)**
    g) **Baseline History and Physical Exam Form**
    h) **Intensive Glycemia Management Form**
    i) **Glycemia Medications Log**
    j) **Severe Hypoglycemia Action Form (as necessary)**
    k) **Standard Blood Pressure Management Form**
    l) **Blood Pressure Medications Log**
    m) **Encounter and Disposition Form**
    n) **Health Utilities Index Form**
    o) **The Unified Form (US sites only)**
    p) **Assigned Substudy Questionnaires (as necessary)**
    q) **Drug Dispensing Form (as necessary)**
    r) **Event Forms (as necessary)**

B.2.2 Upon Receipt of Central Lab HbA1c Values Drawn

1. If the Central HbA1c result measured at that visit returns > 6.0%, and no change in therapy was made at the time of the visit (when the Central Lab HbA1c was obtained), and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   a. Contact the participant, and intensify the therapy per protocol
      - Increase dose of current agent (if on submaximal dose) or add another agent (see Figure A.3).
   b. Complete appropriate glycemia forms regarding the changes in therapy made to achieve or maintain target levels.

B.2.3 Phone/FAX/email/mail Contact at 0.5, 1.5, 2.5 and 3.5 Months

These contacts are for participants assigned to the intensive glycemic treatment group and should occur within a +/- 1-week window. The participants will be contacted by one of the means listed above and the following procedures will be conducted:

1. Record the participant's report of their SMBG results for the previous 2 weeks if you have not already received them by phone, fax, email or mail. Encourage participants to comply with advance requests for SMBG results.
2. Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section B.1.3.b, B.1.3.c and MOP Chapter 8, Section 8.4.4).
3. Record current glycemic medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record appropriate information on the **Intensive Glycemia Management Form**.
4. Adjust or maintain therapy according to the following:
   a) If < 50% of fasting levels over 4 days are > 100 mg/dl (5.6 mmol/l) **AND** < 50% over 4 days of the 2 hr levels are > 140 mg/dl (7.8 mmol/l);
      - Remain at the same dose of current medications.
   b) If ≥ 50% of fasting levels over 4 days are > 100 mg/dl (5.6 mmol/l); **AND/OR** ≥ 50% of the 2 hr levels over 4 days are > 140 mg/dl (7.8 mmol/l); **AND** no contraindication (See Chapter 6 of MOP) to intensify therapy:
      - Increase dose of current agent (if currently on submaximal dose) or add another drug (See Figure B.3 or B.5).
5. Reinforce appropriate SMBG frequency according to Table A.1.3:
   - Diet/oral therapy (≥ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.
6. Instruct participants on when and how to self-titrate therapy. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.
7. Remind participant of next clinic appointment.
8. Remind participant to take blood pressure meds the morning of next visit.
9. Complete the following form and enter data as required:

a) **Intensive Glycemia Management Form**
b) **Glycemia Medications Log**
c) **Severe Hypoglycemia Action Form (as necessary)**
d) **Study Status Form (as necessary)**

B.2.4 One, 2, 3, and 6 month Visits

These visits should occur within a +/- 1-week window. The participants will report to the clinic and the following procedures will be conducted:

1. Obtain weight, and record in source documentation.
2. Using the appropriate technique for the Omron device, **obtain blood pressure and pulse for the 1 month visit only** (See MOP Chapter 9, Section 9.2.3).
3. Collect all glycemia related information:
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustment in the glycemia intervention.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section B.1.3.b, B.1.3.c and MOP Chapter 8, Section 8.4.4).
   d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
   e) Adjust or maintain therapy according to the following:
      1. If POC HbA1c < 6% **AND** < 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
         - Maintain current therapy.
      2. If POC HbA1c < 6% **BUT** $\geq$ 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** $\geq$ 50% of the 2 hour postprandial levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
         - Increase dose of current agent (if on submaximal dose) or add another agent (See Figure B.3 or B.5).
      3. If POC HbA1c is $\geq$ 6.0% and there is no contraindication (See MOP Chapter 6) to intensify therapy:

- Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).

f) **If participant was started on a TZD, check for edema at every visit**. Obtain an ALT every 2 months for the first year of treatment, annually thereafter. Provide participant information on TZDs as necessary.

g) Reinforce appropriate SMBG frequency according to Table A.1.3:
   - Diet/oral therapy ($\geq$ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.

h) Assess comprehension/understanding of dietary counseling.
   - Reinforce diet and exercise. Repeat at subsequent visits as necessary.

i) Instruct participants on when and how to self-titrate. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.

j) Record name and dose of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.

k) Provide SMBG logbooks and instructions in their completion.

4. Collect all blood pressure related information: (**For 1 month visit only**)
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self-report of adherence.
   c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
   d) If the SBP is 130 –139 mm Hg at this visit and was > 135 mm Hg at previous visit, maintain current therapy.
   e) If the SBP < 130 mm Hg at this visit or < 135 mm Hg on 2 consecutive visits, step down therapy is indicated.
   f) If SBP is $\geq$ 160 mm Hg at this visit or $\geq$140 mm Hg on 2 consecutive visits, an upward dose titration or an additional drug (not already in use) must be added. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg.
   g) Complete **Standard Blood Pressure Management Form**
   h) Record name, dose, and adherence of **all** blood pressure medications on the **Blood Pressure Medications Log.**
   i) Instruct participants on actions to limit symptomatic orthostasis.
5. Remove labels from study medications and place on **Drug Dispensing Form** then dispense blood pressure-lowering study medication. Scan label bar codes into the computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
6. At the month 1, 2, and 3 visits, schedule follow-up phone/fax/email/mail contact in 2 weeks and a clinic appointment in 1 month. At the 6-month visit, schedule phone/fax/email/mail contact in 1 month and a clinic appointment in 2 months

7. Remind participants to bring all their medications, glucose meter and SMBG records to each visit.
8. Remind participant to take blood pressure medications the morning of next visit.
9. Complete the following forms and enter data as required:
   a) **Intensive Glycemia Management Form**
   b) **Glycemia Medication Log**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   d) **Standard Blood Pressure Management Form (for the 1 month visit only)**
   e) **Blood Pressure Medication Log (for the 1 month visit only)**
   f) **Encounter and Disposition Form**
   g) **Drug Dispensing Form (as necessary)**
   h) **Study Status Form (as necessary)**

B.2.5 Four & 8 Month Visit

The 4-month visit should occur within a +/- 1-week visit window. The 8-month visit should occur within a +/- 2-week window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia or lipid (if applicable) medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the physical exam, including weight. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, Creatinine and ALT.
4. Collect all glycemia related information.
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC

values should be adjusted for any systematic differences from Central HbA1c values.

b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustments in the glycemia intervention.

c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section B.1.3.b, B.1.3.c and MOP Chapter 8, Section 8.4.4).

d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.

e) Adjust and maintain therapy according to the following:

1. If POC HbA1c < 6% **AND** < 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);

- Maintain current therapy.

2. If POC HbA1c < 6% **BUT** ≥ 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** ≥ 50% of the 2 hour levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:

- Increase dose of current agent (if on submaximal dose) or add another agent (See Figure B.3 or B.5).

3. If POC HbA1c is ≥ 6.0% and there is no contraindication (See MOP Chapter 6) to intensify therapy:

- Increase dose of current agent (if on submaximal dose) or add another agent (according to Figure B.3 or B.5).

f) **If participant was started on a TZD, check for edema at every visit.** Obtain an ALT every 2 months for the first year of treatment, annually thereafter. Provide participant information sheet on TZDs if necessary.

g) Reinforce appropriate SMBG frequency according to Table A.1.3:
Diet/oral therapy (≥ 2 times/day if at target or 4 times/day (2ac/day,2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.

h) Assess comprehension/understanding of dietary counseling.
1) Reinforce diet and exercise. Repeat at subsequent visits as necessary.

i) Instruct participants on when and how to self-titrate. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.

j) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.

k) Provide SMBG logbooks and instructions for their completion.

l) Check Central Lab HbA1c at the time the results are available if drawn and make any additional changes to achieve target (See Section B.2.2).

5. Collect all blood pressure related information:

a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not

taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.

b) Record current medications, dose and self- report of adherence.
c) Using the appropriate technique for the Omron device (See MOP Chapter 9, Section 9.2.3) obtain and evaluate blood pressure values.
e) If SBP is 130 – 139 mm Hg at this visit and was > 135 mm Hg at previous visit, maintain current therapy.
e) If SBP is 140 – 159 mm Hg at this visit and < 140 mm Hg at previous visit, maintain current therapy.
f) If SBP is < 130 mm Hg at this visit or < 135 mm Hg on 2 consecutive visits, step down therapy is indicated..
g) If SBP is ≥ 160 mm Hg at this visit or ≥ 140 mm Hg on 2 consecutive visits, an upward dose titration or an additional drug (not already in use) must be added. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg.
h) Instruct participants on actions to limit symptomatic orthostasis.
i) Complete **Standard Blood Pressure Management Form**.
j) Record name, and dose of **all** blood pressure medications dispensed on the **Blood Pressure Medications Log.**

6. Remove labels from study medications and place on drug dispensing form then dispense blood pressure lowering study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
7. Complete **Cost Substudy Form** for participants in the Cost Substudy.
8. Schedule follow-up phone/fax/email/mail contact in 1 month +/- 2 weeks and a clinic appointment in 2 months or any other required supplemental visits (See Chapter 6).
9. Remind participants to bring all their medications, glucose meter and SMBG records to next visit.
10. Remind participant to take blood pressure medications the morning of next clinic visit.
11. Complete the following forms and enter data as required:
    a) **Interval History and Follow-up**
    b) **Glycemia Medication Log**
    c) **Severe Hypoglycemia Action Form (as necessary)**
    d) **Intensive Glycemia Management Form**
    e) **Blood Pressure Medication Log**
    f) **Standard Blood Pressure Management Form**
    g) **Encounter and Disposition Form**
    h) **Preliminary Event Notification Form (as necessary)**
    i) **Event Forms (as necessary)**
    j) **Drug Dispensing Form (as necessary)**
    k) **Cost Substudy Form (as necessary)**
    l) **Study Status Form (as necessary)**

B.2.6 Bi-Monthly Phone/FAX/email/ mail Contacts From Month 5 visit through End of Study

These contacts are for participants assigned to the intensive glycemic treatment group and should occur at 2-weeks +/- 1 week. The participants will be contacted by one of the means listed above and the following procedures will be conducted:

1. Record the participant's report of their SMBG results for the previous 2 weeks if you have not already received them by phone, fax, email or mail. Encourage participants to comply with advance requests for SMBG results.
2. Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section B.1.3.b, B.1.3.c and MOP Chapter 8, Section 8.4.4).
3. Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
4. Adjust or maintain therapy according to the following:
   If < 50% of fasting levels over 4 days are > 100 mg/dl (5.6 mmol/l) **AND** < 50% over 4 days of the 2 hr levels are > 140 mg/dl (7.8 mmol/l);
   - Remain at the same dose of current medications.

   If ≥ 50% of fasting levels over 4 days are > 100 mg/dl (5.6 mmol/l); **AND/OR** ≥ 50% of the 2 hr levels over 4 days are > 140 mg/dl (7.8 mmol/l); **AND** no contraindication (Chapter 6 of MOP) to intensify therapy:
   - Increase dose of current agent (if on submaximal dose) or add another drug (according to Figure B.3 or B.5) and reinforce diet and exercise.
5. Reinforce appropriate SMBG frequency according to Table A.1.3:
   - Diet/oral therapy (≥ 2 times/day if at target or 4 times/day (2ac/day,2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.
6. Instruct participants on when and how to self-titrate therapy. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.
7. Remind participant of next 2-month clinic appointment. At 3.5-month contact, remind participant to fast prior to the 4-month clinic visit and not to take their glycemic medications the morning of the visit.
8. Remind participant to take blood pressure medications the morning of next visit.
9. Complete the following form and enter data as required:
   a) **Intensive Glycemia Management Form**
   b) **Glycemia Medications Log**
   c) **Study Status Form (as necessary)**

B.2.7 Visits at Follow-up Months 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, and 94

These visits should occur within a +/- 2-week window. The participants will report to the clinic and the following procedures will be conducted:

1. Obtain weight, and record in source documentation.
2. Collect all glycemia related information:
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustment in the glycemia intervention.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section B.1.3.b, B.1.3.c and MOP Chapter 8, Section 8.4.4).
   d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
   e) Adjust or maintain therapy according to the following:

      1. If POC HbA1c < 6% **AND** < 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
         - Maintain current therapy.

      2. If POC HbA1c < 6% **BUT** $\geq$ 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** $\geq$ 50% of the 2 hour levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
         - Increase dose of current agent (if on submaximal dose) or add another agent (according to Figure B.3 or B.5 in Chapter 5 of the MOP).

      3. If POC HbA1c is $\geq$ 6.0% and there is no contraindication (See MOP Chapter 6) to intensify therapy:
         - Increase dose of current agent (if on submaximal dose) or add another agent (according to Figure B.3 or B.5).
   f) **If participant was started on a TZD, check for edema at every visit** Obtain an ALT every 2 months for the first year of treatment, annually thereafter. Provide participant information on TZDs if necessary.
   g) Reinforce appropriate SMBG frequency according to Table A.1.3:
      - Diet/oral therapy ($\geq$ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.
   h) Assess comprehension/understanding of dietary counseling.
      1) Reinforce diet and exercise. Repeat at subsequent visits as necessary.
   i) Instruct participants on when and how to self-titrate. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.

j) Record name and dose of all glycemia medications on the **Glycemia Medications Log** as needed. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.
k) Provide SMBG logbooks and instructions in their completion.

3. Remove labels from study medications and place on drug dispensing form then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
4. Schedule follow-up phone/fax/email/mail contact in 1 month and a clinic appointment in 2 months.
5. Remind participants to bring all their medications, glucose meter and SMBG records to each visit.
6. Remind participant to take blood pressure medications the morning of next visit.
7. Complete the following forms and enter data as required:
   a) **Intensive Glycemia Management Form**
   b) **Glycemia Medications Log**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   c) **Encounter and Disposition Form**
   d) **Drug Dispensing Form (as necessary)**
   e) **Study Status Form (as necessary)**

B.2.8 Annual Visits (12, 24, 36, 48, 60, 72, 84 Months)

These visits should occur within a +/- 2-week visit window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia medications or lipid (if applicable) medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Review and update Contact information.
2. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
3. Perform the annual physical exam, including weight, height, weight circumference, visual acuity, foot exam. Using the appropriate technique for the Omron device, obtain Blood pressure and pulse (See Chapter 9, Section 9.2.3.).
4. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium Creatinine, Lipid

Profile and ALT. **(Blood samples for storage of additional aliquots, where approved, should occur at the 24-month, 48-month, and 72-month visits).**

5. Review the Concomitant Medications list located in the **Annual Follow-up and Physical Exam Form** with participant to document all non-study medications currently taking.
6. Participants will be given the **Health Utilities Index Form** and instructed on how to complete it **(12-month, 36-month, 48-month visits)**. Verify that the participant completes all items before end of visit.
7. **A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Lab for the 24-month, 48-month, and 72 month visits.**
8. **An ECG will be obtained and transmitted to the ACCORD ECG Reading Center for the 24-month, 48-month, and 72 month visits**. Retain a copy for participant's research records.
7. Collect all glycemia related information.
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustments in the glycemia intervention.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section B.1.3.b, B.1.3.c and MOP Chapter 8, Section 8.4.4).
   d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
   e) Adjust and maintain therapy according to the following:
      1. If POC HbA1c $< 6\%$ **AND** $< 50\%$ of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** $< 50\%$ of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
      - Maintain current therapy.
      2. If POC HbA1c $< 6\%$ **BUT** $\geq 50\%$ of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** $\geq 50\%$ of the 2 hour levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
      - Increase dose of current agent (if on submaximal dose) or add another agent (according to Figure B.3 or B.5).
      3. If POC HbA1c is $\geq 6.0\%$ and there is no contraindication (See MOP Chapter 6) to intensify therapy:

- Increase dose of current agent (if on submaximal dose) or add another agent (according to Figure 5.3 or 5.5 in Chapter 5 of the MOP).

f) **If participant was started on a TZD, check for edema at every visit**. Obtain an ALT every 2 months for the first year of treatment, annually thereafter. Provide participant information sheet on TZDs if necessary.

g) Reinforce appropriate SMBG frequency according to Table A.1.3:
Diet/oral therapy ($\geq$ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.

h) Assess comprehension/understanding of dietary counseling.
1) Reinforce diet and exercise. Repeat at subsequent visits as necessary.

i) Instruct participants on when and how to self-titrate. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.

j) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.

k) Provide SMBG logbooks and instructions for their completion.

l) Check Central Lab HbA1c at the time the results are available if drawn and make any additional changes to achieve target (See Section A.2.2).

m) Review and update the **Unified Form** to ensure a smooth and steady flow of diabetic testing supplies being shipped by the NetGroup Diabetic Services **(US sites only)**.

8. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self- report of adherence.
   c) Using the appropriate technique for the Omron device (See MOP Chapter 9, Section 9.2.3) obtain and evaluate blood pressure values.
   d) If SBP is 130 –139 mm Hg at this visit and was > 135 mm Hg at previous visit, maintain current therapy.
   e) If the SBP is 140 – 159 mm Hg at this visit and SBP < 140 at previous visit, maintain current therapy.
   f) If the SBP is < 130 mm Hg at this visit or < 135 mm Hg on 2 consecutive visits, step down therapy is indicated..
   g) If SBP is $\geq$ 160 mm Hg at this visit or $\geq$ 140 mm Hg on 2 consecutive visits, an upward dose titration or an additional drug (not already in use) must be added. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg.
   h) Instruct participants on actions to limit symptomatic orthostasis.
   i) Complete **Standard Blood Pressure Management Form**.
   j) Record name, and dose of **all** blood pressure medications dispensed on the **Blood Pressure Medications Log.**

9. Remove labels from study medications and place on drug dispensing form then dispense blood pressure lowering study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
10. Participants assigned in the substudies (Health Related Quality of Life (HRQL), Physical Activity, Diet) will complete the appropriate questionnaires **(12-month, 36-month, and 48-month visits)**. Verify that the participant completes all items before end of visit. Complete **Cost Substudy Form** for participants in the Cost Substudy.
11. Schedule follow-up phone/fax/email/mail contact in 1 month +/- 2 weeks and a clinic appointment in 2 months or any other required supplemental visits (See Chapter 6).
12. Remind participants to bring all their medications, glucose meter and SMBG records to next visit.
13. Complete the following forms and enter data as required:
    a) **Participant Contact Information Form (as necessary)**
    b) **Annual Follow-up and Physical Exam Form**
    c) **Intensive Glycemia Management Form**
    d) **Glycemia Medications Log**
    e) **Severe Hypoglycemia Action Form (as necessary)**
    f) **Standard Blood Pressure Management Form**
    g) **Blood Pressure Medications Log**
    h) **Encounter and Disposition Form**
    i) **Health Utilities Index Form (12-month, 36-month, and exit visits)**
    j) **Visual Acuity Worksheet (24-month, 48-month, and 72-month visits)**
    k) **The Unified Form (US sites only)**
    l) **Ophthalmology Exam Form (as necessary)**
    m) **Preliminary Event Notification Form (as necessary)**
    n) **Event Forms (as necessary)**
    o) **Assigned Substudy Questionnaires (as necessary)**
    p) **Drug Dispensing Form (as necessary)**
    q) **Cost Substudy Form 9as necessary)**
    r) **Study Status Form (as necessary)**

B.2.9 Visits at Follow-up Months 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88 and 92

These visits are for participants assigned to the intensive glycemia/standard BP treatment intervention and should occur within a +/- 2- week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome**

Report Form. Upon completion these forms and supporting documentation are mailed to the Coordinating Center.

2. Obtain weight.
3. Using the appropriate technique for the Omron device (See MOP Chapter 9, Section 9.2.3), obtain blood pressure and pulse.
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c.
4. Collect all glycemia related information.
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustments in the glycemia intervention.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section B.1.3.b, B.1.3.c and MOP Chapter 8, Section 8.4.4).
   d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
   e) Adjust and maintain therapy according to the following:

      1. If POC HbA1c < 6% **AND** < 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
         - Maintain current therapy.

      2. If POC HbA1c < 6% **BUT** ≥ 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** ≥ 50% of the 2 hour levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
         - Increase dose of current agent (if on submaximal dose) or add another agent (according to Figure B.3 or B.5 in Chapter 5 of the MOP).

      3. If POC HbA1c is ≥ 6.0% and there is no contraindication (See MOP Chapter 6) to intensify therapy:
         - Increase dose of current agent (if on submaximal dose) or add another agent (according to Figure B.3 or B.5).
   f) Reinforce appropriate SMBG frequency according to Table A.1.3:
      Diet/oral therapy (≥ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.
   g) Assess comprehension/understanding of dietary counseling.

- Reinforce diet and exercise. Repeat at subsequent visits as necessary.

h) Instruct participants on when and how to self-titrate. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.

i) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.

j) Provide SMBG logbooks and instructions for their completion.

k) Check Central Lab HbA1c at the time the results are available if drawn and make any additional changes to achieve target (See Section A.2.2).

5. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self- report of adherence.
   c) Using the appropriate technique for the Omron device (See MOP Chapter 9, Section 9.2.3) obtain and evaluate blood pressure values.
   d) If SBP is 130 –139 mm Hg at this visit and was > 135 mm Hg at previous visit, maintain current therapy.
   e) If SBP is 140 – 159 mm Hg at this visit and SBP < 140 mm Hg at previous visit, maintain current therapy.
   f) If SBP is < 130 mm Hg at this visit or < 135 mm Hg on 2 consecutive visits, step down therapy is indicated..
   g) If SBP is $\geq$ 160 mm Hg at this visit or $\geq$ 140 mm Hg on 2 consecutive visits, an upward dose titration or an additional drug (not already in use) must be added. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg.
   h) Instruct participants on actions to limit symptomatic orthostasis.
   i) Complete **Standard Blood Pressure Management Form**.
   j) Record name, and dose of all blood pressure medications dispensed on the **Blood Pressure Medications Log.**
6. Remove labels from study medications and place on drug dispensing form then dispense blood pressure lowering study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
7. Complete **Cost Substudy Form** for participants in the Cost Substudy.
8. Schedule follow-up phone/fax/email/mail contact in 1 month +/- 2 weeks and a clinic appointment in 2 months or any other required supplemental visits (See Chapter 6).
9. Remind participants to bring all their medications, glucose meter and SMBG records at next visit.
10. Remind participant to take blood pressure medications the morning of next clinic visit.
11. Complete the following forms and enter data as required:
    a) **Interval History and Follow-up**
    b) **Intensive Glycemia Management Form**

c) **Glycemia Medications Log**
d) **Severe Hypoglycemia Action Form (as necessary)**
e) **Standard Blood Pressure Management Form**
f) **Blood Pressure Medications Log**
g) **Encounter and Disposition Form**
h) **Preliminary Event Notification Form (as necessary)**
i) **Event Forms (as necessary)**
j) **Assigned Substudy Questionnaires (as necessary)**
k) **Drug Dispensing Form (as necessary)**
l) **Cost Substudy Form (as necessary)**
m) **Study Status Form (as necessary)**

B.2.10 Exit Visit

This visit should occur within a +/- 2-week visit window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia or lipid (if applicable) medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the annual physical exam, including weight, height, weight circumference, visual acuity, foot exam, Omron blood pressure using the appropriate technique (See MOP Chapter 9, Section 9.2.3), and pulse.
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium Creatinine, Lipid Profile, ALT and CPK and storage for additional aliquots (where approved).
4. Review the Concomitant Medications list located in the **Annual Follow-up and Physical Exam Form** with participant to document all non-study medications currently taking.
5. Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completes all items before end of visit.
6. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Lab.
7. An ECG will be obtained and transmitted to the ACCORD ECG Reading Center. Retain a copy for the participant's research file

8. Collect all glycemia related information.
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustments in the glycemia intervention.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section B.1.3.b, B.1.3.c and MOP Chapter 8, Section 8.4.4).
   d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
   e) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.
9. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self- report of adherence.
   c) Obtain, review and evaluate blood pressure values using the appropriate technique for the Omron device (See MOP Chapter 9, Section 9.2.3).
   d) Complete **Standard Blood Pressure Management Form**.
   e) Record name, and dose of **all** blood pressure medications dispensed on the **Blood Pressure Medications Log.**
10. Participants will be prescribed appropriate non-study antihyperglycemia and antihypertensive therapy based on their current status and post-trial follow-up care will be arranged.
11. Complete the following forms and enter data as required:
    a) **Participant Contact Information Form (as necessary)**
    b) **Annual Follow-up and Physical Exam Form**
    c) **Intensive Glycemia Management Form**
    d) **Glycemia Medications Log**
    e) **Severe Hypoglycemia Action Form (as necessary)**
    f) **Standard Blood Pressure Management Form**
    g) **Blood Pressure Medications Log**
    h) **Encounter and Disposition Form**

i) **Health Utilities Index Form**
j) **Visual Acuity Worksheet**
k) **Ophthalmology Exam Form (as necessary)**
l) **Preliminary Event Notification Form (as necessary)**
m) **Event Forms (as necessary)**
n) **Study Status Form (as necessary)**

Figure B.3
Treatment Algorithm for Intensive Glycemic Therapy Group (Goal: HbA1c<6%)

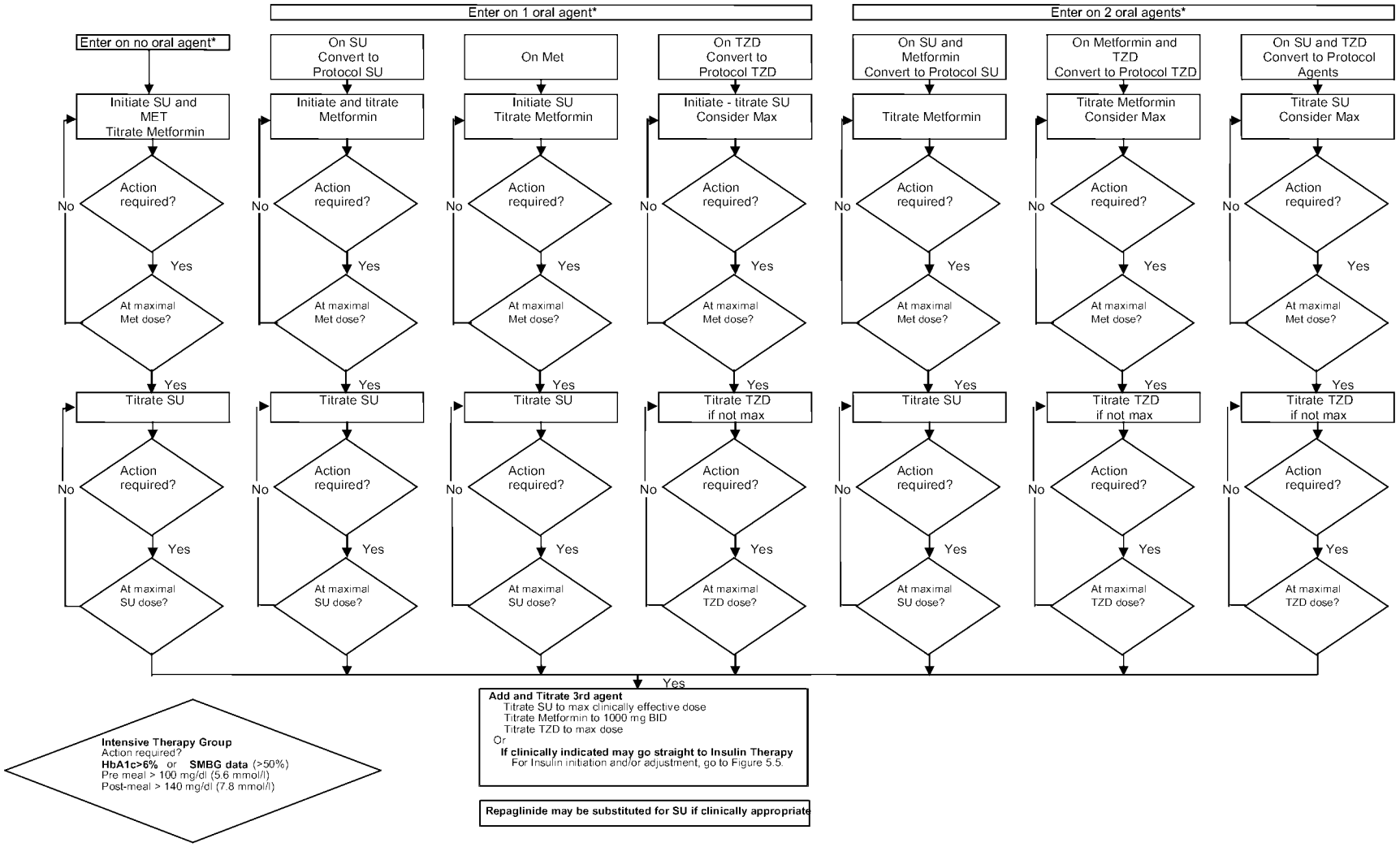
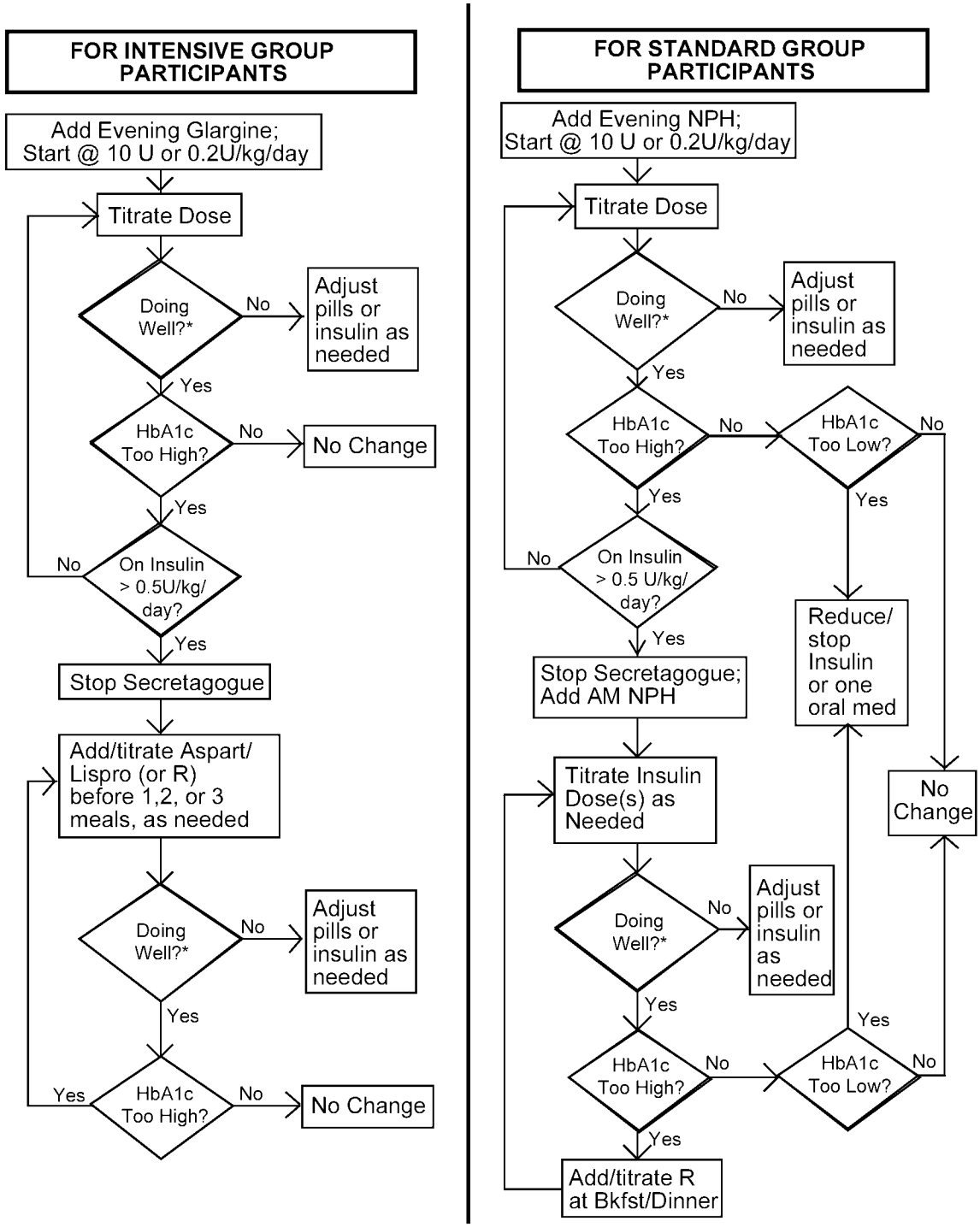
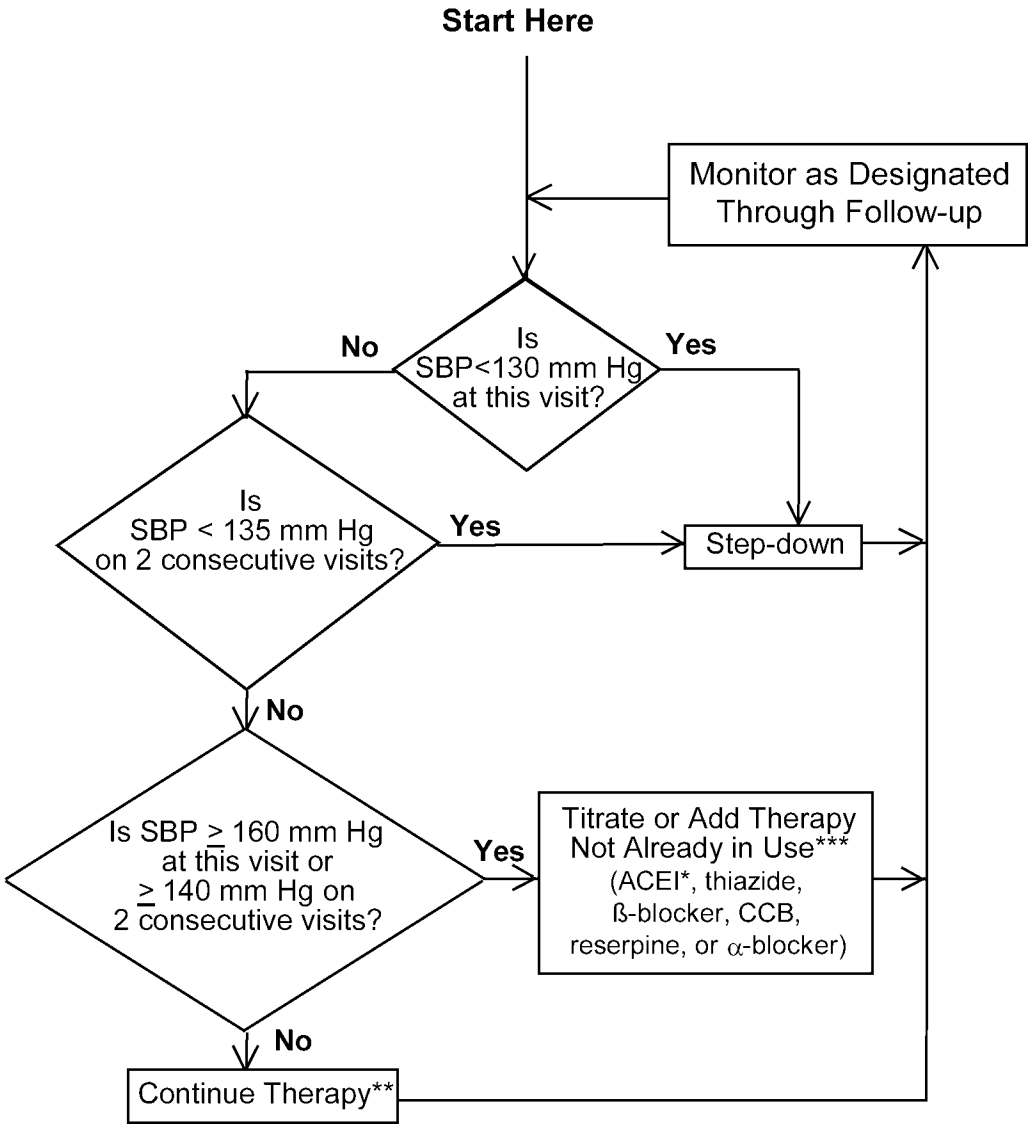


Figure 3.3:
Use of Insulin for Participants On Maximal Oral Therapy



*Doing well: no severe hypoglycemic or adverse event or no reason to reduce therapy (as described in Figure 3.2)

Figure B.7: Treatment Algorithm for Standard Blood Pressure (Goal: SBP < 140 mm Hg)



* ARB can be considered as a substitute for participants who do not tolerate ACEI therapy
** Unless side effects warrant change in therapy
*** Consult with the Clinical Center Network before adding a fifth antihypertensive medication

Thiazolidinedione Drugs (e.g. Avandia or Rosiglitazone)

ACTIONS of THIAZOLIDINEDIONES

The drug Avandia (rosiglitazone) belongs to a group of medications called thiazolidinediones (or glitazones or TZD's), and may be supplied as part of the ACCORD trial. Actos (pioglitazone) is another drug that belongs in this group. These drugs lower the blood glucose by reducing the body's resistance to the action of insulin (i.e. making your own insulin work more effectively). They can be used alone or can be combined with other diabetes pills or insulin.

COMMON SIDE EFFECTS

1. Hypoglycemia (low blood sugar)

These drugs can lead to hypoglycemia. When taken alone, the risk of hypoglycemia is low. When taken with insulin or other pills, the risk of hypoglycemia is higher.

If you do experience symptoms of a low blood sugar (such as lightheadedness, sweating, nervousness, hunger, a sensation of a racing heart, headache, or sudden fatigueat unusual times), check your blood sugar. If the level is less than 70 mg/dl (3.9 mmol/l) you may be suffering from hypoglycemia. If so, drink 4 ounces of juice or regular soda or eight ounces of milk or have three glucose tablets or five Life Savers (i.e. 15 grams of carbohydrate). Recheck your blood sugar in 15 minutes to make sure it has risen to at least 90 mg/dl (5.0 mmol/L). If low blood sugar reactions are frequent, severe or unexpected, call your doctor.

2. Weight Gain

These drugs may lead to weight gain. Weight gain is due to the lowering of blood sugar by insulin and drugs that act like insulin. This reduces the amount of sugar lost in the urine and helps the body store extra energy in fat cells. Sometimes, weight gain may be due to some fluid retention. Regardless of the cause, the amount of weight gained or lost depends on the level of physical activity and diet, or can be due to other drugs that are being taken. For example, some people gain more weight if insulin is also being taken. To minimize weight gain or to cause weight loss, exercise regularly, eat low fat foods, avoid extra snacks and large portions.

3. Fluid Retention

These drugs may lead to fluid retention. Fluid retention is generally mild with some swelling in the ankle or leg or bloating; it may be more pronounced when these drugs are used together with insulin, and rarely, the fluid retention can be severe or even life threatening. If you develop major leg swelling or especially shortness of breath either with activity or at rest, see your doctor as soon as possible. Reducing the dose, adding diuretics (water pills) or adjusting other medications (such as blood pressure pills, calcium channel blockers, non-steroidal anti-inflammatory drugs or arthritis pills) can also be used to manage this problem. ***You and your doctor should pay close attention to fluid retention if you take insulin or have heart failure or other heart problems.***

POTENTIAL SIDE EFFECTS

Because of rare cases of severe liver disease with a related medicine that is no longer available (Rezulin or troglitazone), you must have your blood drawn for liver enzyme tests (ALT) when treated with these drugs every 2 months for the first year of treatment and intermittently thereafter. If you develop persistent nausea, vomiting, belly pain, fatigue, loss of appetite, dark urine, yellowing of the eyes or skin while treated with this drug, stop the medication and see your doctor for a blood draw within a few days.

DOSING

Avandia (rosiglitazone) can be taken once a day, but may work a bit better if taken twice daily. Actos (pioglitazone) can be taken any time of the day. Both drugs can be taken either with or without food. It may take 12 weeks to see the full effect of a dose.

7. Visit Schedule of Study Activities by Randomization Cell

C. Intensive Glycemia and Lipid Trial

C.1 Overview

One of the key aims of the ACCORD study is to determine if targeting a HbA1c of < 6.0% (the upper limit of the nondiabetic range) reduces the rate of cardiovascular disease (CVD) events to a greater extent than targeting a HbA1c of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%, which is 25% above the upper limit of the nondiabetic range) in high risk middle-aged or older people with type 2 diabetes. The approaches used to implement these targets, suggested algorithms for the use of pharmacologic agents and follow-up schedules are described in MOP Chapters 5 and 6.

The ACCORD lipid component is designed to test whether lowering plasma triglyceride and increasing plasma HDL cholesterol levels with a fibrate in addition to lowering LDL cholesterol levels with an HMG CoA reductase inhibitor (hereafter referred to as "statin") will reduce the rate of CVD events more than statin alone. The specific fibrate to be used in ACCORD is fenofibrate and the specific statin is simvastatin.

C.1.1 Algorithms for Intensive Glycemic and Lipid Trial; Choice of Agents

Figures C.3 and C.5 at the end of this chapter are suggested algorithms to guide changes in glycemic therapy for the intensive group. The exact changes to be made whenever glycemic therapy needs to be intensified on the basis of the HbA1c or the SMBG results will be determined by the individual site using the figures as guides.

Eligible participants in the lipid trial will be randomized to micronized fenofibrate or placebo. All participants will be treated with simvastatin.

C.1.2 Targets and Action Required Levels

C.1.2.a) Intensive Glycemic Control

Table C.1.2 outlines the glycemic targets for the intensive group, which is identical to Table 3.1 in the protocol.

Table C.1.2: Intensive Glycemic Target and Threshold for Action for ACCORD			
		"Action Required" Threshold	
	HbA1c Targets	HbA1c	> 50% of SMBG Results/4 days
Intensive Therapy	< 6.0%	≥ 6.0%*	Fasting/ac > 100 mg/dl (5.6 mmol/l) Or 2 hrs pc > 140 mg/dl (7.8 mmol/l)

pc: postcibal; ac: antecibal; SMBG: self monitoring of blood glucose; * antihyperglycemic therapy will be advanced if either the HbA1c or the SMBG "action required " criteria are met at any particular encounter

C.1.2.b) The Lipid Trial

Participants who were on a lipid- lowering agent at screening must agree to stop treatment no later than the day of randomization and be changed to simvastatin. The starting dose of simvastatin is 20 mg/day, administered once daily after the evening meal or at bedtime.

One month after randomization, the study fibrate/placebo will be started. It is recommended that simvastatin be taken in the evening and the masked fibrate/placebo be taken in the morning. If however, you feel compliance would be improved if both were taken together, that would be acceptable.

The starting dose of masked fenofibrate/placebo medication will be determined by the calculated glomerular filtration rate (GFR) using the baseline serum creatinine level and the abbreviated MDRD equation (Levey 2003). Those participants with a baseline GFR $\geq$50 ml/min/1.73m^2 will begin at a starting dose of 160 mg of fenofibrate or identical placebo tablet. Those with a calculated GFR between 30 and <50 will start at the reduced dose of 54 mg/day fenofibrate or placebo.

Implementation of baseline assignment of blinded study medication dose:

- The Coordinating Center (CC) will determine the starting dose of the blinded study medication based on calculated GFR from the MDRD equation, using Central Lab values at baseline.
- The recommended dose will appear on the participant main page below "Lipid Bottle ID" (e.g., FULL, REDUCED, or NONE).
- The CC will communicate the starting dose to the Drug Distribution Center (DDC).
- DDC will send the appropriate dose to the clinical site labeled for the specific participant.
- One-month follow-up visits for Lipid Trial participants should be scheduled at least 3 weeks after the baseline visit to allow for arrival of blinded study medication.

What to do if the Participant's GFR Falls Below Cutoff Levels

Participants in the lipid trial will have serum creatinine measured every four months during follow-up. If the participant had started on the 160 mg dose of the masked medication, this dose will be down-titrated if the participant's estimated GFR falls between 30 and <50 mL/min/1.73m^2 on two consecutive measurements taken four months apart. Participants with GFRs in this range will receive either 54 mg/day of fenofibrate or matching placebo.

Implementation of ongoing blinded study medication dose adjustment based on GFR:

- The ACCORD Coordinating Center (CC) will monitor GFR values obtained on participants at routine 4-month blood draws.
- The CC will notify the Clinical Site PI and Coordinator, the CCN and Coordinator, and the Drug Distribution Center (DDC) when a participant has met the criteria for down titration of masked study medication.
- The DDC will send a new box of reduced dose masked study medication for the participant to the Clinical Site.
- The dose of blinded study medication will be listed on the participant main page below the "Lipid Bottle ID" (e.g. REDUCED).

If the estimated GFR falls below 30 mL/min/1.73m^2 at any time, the Coordinating Center will notify the clinic site that a confirmatory blood draw for repeat estimated GFR will be required within 2 weeks. If the confirmatory estimated GFR is below 30mL/min/1.73m^2, the masked study medication will be permanently discontinued, regardless of fenofibrate or placebo assignment.

Implementation of discontinuation of blinded study medication for GFR less than 30ml/min/1.73^2 for both active and placebo Lipid Trial participants:

- The CC will notify the Clinical Site PI and Coordinator, and the CCN PI and Coordinator when a participant has a Central Lab calculated GFR less than 30ml/min/1.73m^2.
- Clinics must schedule a repeat blood draw for creatinine within 2 weeks. The participant should remain on blinded medication during the 2-week interval.
- Upon receipt of the second blood sample, the CC will determine if the participant meets the criteria to stop the blinded study medication or whether a dose reduction is required.
- An email notification will be sent from the CC to the Clinical Site at this time with dosing instructions.
- If Clinical Sites become aware of a participant who had an elevated creatinine at an outside blood draw, they should bring the participant in for an ASAP prn visit and recheck the creatinine using the ACCORD Central Lab. The CC will then notify the clinic if the participant should have a reduced dose or have their blinded medication discontinued.

C.1.3.a) Adjusting Glycemic Therapy

As noted in the following table (C.1.3), a range of approaches will be used to target the HbA1c levels shown in Table C.1.2.

C.1.3 Achieving Glycemic Goals	**Intensive Group**
Visits (1st 4 months)	Monthly
Visits (> 4 months)	Q 2 mo
Phone contact	Research staff initiated (≥1 inter-visit)
Supplemental visit	Severe hypoglycemia OR HbA1c = action req'd OR SMBG = action req'd (based on review of logbooks)
Point of Care HbA1c	Mandatory
Routine use of postprandial SMBG values to guide therapy	Yes
SMBG freq. [a] (diet/oral agent)	≥ 2/day and 4/day if glucose is > target (2 ac/day and 2 pc/day)
SMBG freq. [a] (insulin)	4-8/d (at least 2 ac/day and 2 pc/day; occasional 3 am test prn)
Self titration principles	Avoid severe hypoglycemia[b] AND Adjust therapy every 4 days AND Use CHO/patterns (if on insulin)
Initial Minimum Rx	Diet/lifestyle AND 2 oral agents
Insulin Use (when needed)	Flexible

[a]Less frequent if goals are achieved; [b] including avoiding SMBG levels < 70 mg/dl (3.9 mmol/l) on > 1/4 of the readings;

C.1.3.b) Glycemia Safety Issues/ Adjusting Therapy for Hypoglycemia

Hypoglycemic events may occur in individuals in either the intensive or standard group. Severe hypoglycemia is unusual in people with type 2 diabetes (even when normoglycemia is targeted). Mild episodes of hypoglycemia are, however, likely to occur.

All participants will be instructed to check their glucose levels regularly as described in the protocol. They will also be taught how to recognize and self-treat hypoglycemia and will be instructed to keep glucose available at all times (as tablets). Moreover, any participant who has had an episode of severe hypoglycemia will be provided with glucagon and they and any cohabiting partner will be taught how to administer it.

Severe hypoglycemia is defined as any episode of loss of consciousness/seizure or documented hypoglycemia (glucose < 50 mg/dl or 2.8 mmol/l) that also requires hospitalization or treatment by emergency personnel. If this occurs:

- Complete **Severe Hypoglycemia Action Form**. (See MOP Chapter 8, Section 8.4.4 for more details).
- For participants in either group who have an episode of severe hypoglycemia, adjust glycemic targets to achieve a fasting and 2 hour glucose (postprandial) of 100 – 140 mg/dl (5.5 – 7.8 mmol/l) and < 180 mg/dl (10 mmol/l) respectively, and a HbA1c of 7.0% - 7.9% for at least 4 weeks.
- Ensure that a complete medical assessment by the physician is completed to identify other potential causes (e.g. pituitary or adrenal insufficiency)
- Ensure that the physician reassesses the glycemic goals at subsequent visits.
- Ensure that the participant receives glucagons and tat the participant and cohabitant know how to administer it.
- Have telephone contact with participant before the next visit to assess blood glucose records and freedom from hypoglycemia.

Minor hypoglycemia is defined as self-reported transient symptoms such as lightheadedness, tremor, shaking, sweating, tingling, blurry vision, trouble concentrating etc., that are self-treated by ingestion of carbohydrates and resolve on their own. (See MOP Chapter 6, Section 6.1.6). All participants will be asked to note such episodes in their glucose logbooks and to confirm them with a blood glucose reading whenever possible. The estimated frequency (of confirmed and suspected minor hypoglycemia) will be recorded at every visit.

C.1.3.c) Self Treatment of Hypoglycemia

1. If the glucose value is < 50-70 mg/dl (3.9 mmol/l), it should be treated by ingestion of 15 grams of CHO (e.g. 3-4 glucose tablets, 5 Lifesavers, 4-6 oz. of a regular – (nondiet) – soft drink, or 8 oz. low fat milk);
2. If the glucose value is < 50 mg/dl (2.8 mmol/l), it should be treated by ingestion of 20-30 grams of CHO (e.g. 6-8 glucose tablets);
3. Blood glucose should be self-tested 15-20 minutes after therapy and therapy repeated if the level is still low (as above);
4. If no meal will be eaten within 1-2 hours, a mixed nutrient snack, including CHO, protein, and fat should be ingested right after the initial therapy to prevent another episode.
5. If the glucose value is low or there is significant cognitive or motor impairment, individuals should treat and re-test glucose value. The glucose value should be > 70 mg/dl (3.9 mmol/l) before driving a car or operating heavy machinery.

C.1.3.d) Education and Minimization of Hypoglycemia in Participants

Hypoglycemia is an inherent risk in the treatment of diabetes. It is important to inform participants of the signs and symptoms of hypoglycemia, techniques to minimize

the risk and appropriate methods of treatment. Several tools are available for use in educating participants:

1. Hypoglycemia Cartoon
2. Participant Wallet Card
3. Primer on Hypoglycemia
4. Participant Newsletters

All participants must be provided with the written material listed above at the beginning of the study. Study staff should review verbally the signs and symptoms with the participant and family members. Participants and their families should be encouraged to review the hypoglycemic video either in the clinic or at home. Both participants and family members should be educated on the appropriate treatment for symptoms, and provided with glucose tablets. Those participants suffering one severe hypoglycemic event should be provided with a glucagon kit and both the participant and the family member taught how to use it. This material must be reviewed annually with all participants and after every reported hypoglycemic event.

C.1.3.e) Safety Issues for Thiazolidinedione (TZD) Drugs

For participants on TZD (e.g. Avandia or Rosiglitazone), check for the presence of edema at every visit and obtain a Central Lab ALT every 2 months for the first year of treatment and annually thereafter.

As TZDs are contraindicated in people with stage 3 or 4 heart failure, if a participant who is taking TZD does develop heart failure, the TZD should be stopped and the heart failure treated and investigated. Depending on the results of these investigations the investigator may reconsider cautiously reinstituting TZD therapy if the heart failure resolves, and was judged to have not been directly caused by the TZD alone.

A handout to give to the participants at the discretion of the site concerning TZD use is available and can be found on page 28 at the end of this chapter.

C.1.3.f) Lipid Issues/ What to do if a Participant Exceeds LDL-C and Triglyceride Cut-points

Because the upper limit for entry LDL-C is 180 mg/dl, and because 40 mg simvastatin should provide about an average 40% reduction in LDL-cholesterol, it is expected that few participants will have an on-treatment LDL-C of more than 120 mg/dl. However, as noted below, if a participant has an LDL-cholesterol level that is persistently greater than 120 mg/dl, ACCORD will, consistent with NCEP guidelines, take the participant off the masked study medication and continue treatment with simvastatin until placed on a non-study statin by his/her primary caregiver. Triglyceride values will be maintained at a level that does not pose a risk of pancreatitis. Participants are expected to have LDL-C lower than 120 mg/dl (3.10 mmol/l) and triglycerides less than 750 mg/dl (8.47 mmol/l) during the study.

What to do if a Participant's LDL-C is Out of Range

The starting dose of open-labeled simvastatin is 20 mg/day, administered once daily after the evening meal or at bedtime. If the LDL-C is greater than 100 mg/dl (2.59 mmol/l) on two consecutive follow-up visits, the daily dose of simvastatin will be increased to 40 mg.

If the measured LDL-C goes above 120 mg/dl (3.10 mmol/l) after titrating simvastatin to 40 mg/day the Coordinating Center will send a reminder email to the Clinical Site PI and Coordinator, and the CCN PI and Coordinator who should confirm compliance with the study statin, refer the participant to a nutritionist for dietary instruction/reinforcement (if appropriate), and schedule a blood draw for the visit four months from the visit at which the LDL-C was above 120 mg/dl (3.10 mmol/l). This blood specimen needs to be sent to the ACCORD Central Chemistry Laboratory for lipid analysis.

If the participant has an LDL-C above 120 mg/dl (3.10 mmol/l) on two consecutive visits 4 months apart after titrating simvastatin to 40 mg/day (even after compliance review and dietary counseling), the following will occur:

- The CC will send an email reminder to the Clinical Site PI and Coordinator, and the CCN PI and Coordinator.
- The participant will be taken off the fibrate/placebo pills.
- The participant will remain on simvastatin 40 mg/day until placed on non-study statin by his/her primary caregiver. **[The site needs to contact the CCN office if any participant needs non-study simvastatin].**
- The site staff will make an appointment with the participant's doctor for follow-up.
- The site staff will also provide a letter for the participant to take to his/her physician for the follow-up visit. This letter will include the blood lipid values and describes the medication regimen the participant was on when the blood was drawn.
- The site staff will confirm that the participant had visited their physician.
- From that point on, the participant would be treated for their lipids by his/her personal physician and given results of any ACCORD lipid determinations to share with this physician.

If the centrally measured LDL-C is ever less than 40 mg/dl (1.03 mmol/l) during follow-up, clinic personnel should determine compliance with study statin and fibrate/placebo (to make sure that the participant is not taking more than the prescribed number of pills daily) and refer participant to nutritionist for dietary counseling to ensure that the participant is eating a balanced, adequate diet. If the centrally measured LDL-C is ever less than 40 mg/dl (1.03 mmol/l) on two consecutive measurements taken 4 months apart, the following will occur:

- The CC will send an email reminder to the Clinical Site PI and Coordinator, and the CCN PI and Coordinator.
- The participant should be taken off simvastatin.

- The participant will remain on the blinded study medication.

What to do if Triglyceride Exceeds 750 mg/dl (8.47 mmol/l)

If the centrally measured triglyceride ever exceeds 750 mg/dl (8.47 mmol/l) during follow-up, the CC will send an email reminder to the Clinical Site PI and Coordinator, and the CCN PI and Coordinator. Clinic personnel should determine compliance with study statin and fibrate/placebo, refer participant to nutritionist for dietary instruction/reinforcement (if deemed appropriate) and determine and modify potential exacerbating disorders i.e. alcohol or simple sugar intake, hypothyroidism, hyperglycemia. A follow-up blood draw should be done at the next scheduled visit.

If the triglyceride exceeds 750 mg/dl (8.47 mmol/l) on two consecutive measurements 4 months apart, even after the above measures have been conducted, the following will occur:

- The CC will send an email reminder to the Clinic Site PI and Coordinator, and the CCN PI and Coordinator.
- The participant will be taken off the simvastatin and the masked fibrate/placebo medication.
- The participant will be dispensed a 160 mg/day tablet of fenofibrate or 600 mg BID of gemfibrozil until placed on non-study fibrate by his/her primary caregiver. **[The site needs to contact the CCN office if any participant needs non-study fenofibrate].**
- The site staff will make the appointment for follow-up by the participant's physician and will confirm that the appointment was kept.
- The site staff will also provide a letter for the participant to take to their physician for the follow-up visit. This letter will include the blood lipid values and describes the medication regimen the participant was on when the blood was drawn.
- From that point on, the participant will be treated for their lipids by his/her personal physician and given results of any ACCORD lipid determinations to share with this physician.

If the masked fibrate/placebo study medication is stopped for any reason, neither the participant nor the clinic staff need to be unmasked regarding the study medication's true identity, unless there are other circumstances dictating unmasking.

C.1.3.g) Special Note Regarding the Concomitant Use of Fenofibrate and Warfarin (Coumadin)

The use of a fibrate generally necessitates a reduction in the dose of Coumadin to avoid excessive bleeding.

For persons who are on Coumadin at the start of the trial, the participant's physician should be informed both by phone and in writing of the possibility that the participant may be on a fibrate. Until the physician or someone who will manage the Coumadin dose is reached by phone or in person, the participant should not be randomized.

During the trial, you will ask about the possibility of Coumadin use at each visit and if you find that the participant is now on Coumadin, record its use in your source notes. If Coumadin has been started, the clinician prescribing it should be notified that the participant may be on a fibrate. Remember, in some cases the clinician prescribing the Coumadin may not be the clinician notified at the start of the trial of the participant's participation in the trial and randomization to fibrate or placebo.

C.2 Intensive Glycemic and Lipid Trial Visit Procedures

C.2.1 Baseline - Randomization Visit

The participants will be instructed to attend the clinic following an overnight fast (since ~10 pm the previous evening). They should not take their glycemia or lipid medication (if applicable) on the morning of this clinic visit but be instructed to bring their medications, glucose meter SMBG records, and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic (if applicable). During the visit, the following procedures will be conducted:

1. All data collected during the screening process will be reviewed.
2. Verify eligibility status for the Glycemia, Blood Pressure and Lipid Trials (including occurrence of events that may prohibit patient from participating).
   a) Review current medications including OTC, herbal remedies and vitamins.
   b) Review, evaluate and calculate the percentage of participant's compliance with at least 2 weeks of SMBG monitoring as part of the run-in procedures.
   c) Assure that the qualifying HbA1c value was obtained within the last 3 months prior to the randomization date.
3. If ineligible, the participant will be thanked for their time and dismissed from the clinic.
4. If eligible, proceed with randomization process:
   a) Verify that a full-scale consent form has been obtained and signed and HIPAA authorization obtained.
   b) Obtain and perform baseline history and physical exam, including demographics, medical history concomitant medications, weight, height, and waist circumference, visual acuity, and foot exam. Using the appropriate technique for the Omron device obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
   c) Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completes all items before end of visit.
   d) Verify that all information on the **Inclusion/Exclusion Summary Form, the Blood Pressure Screening Form,** and **the Lipid Trial Screening Form** is complete and correct both on the forms and in the computer.
   e) Click "Randomize pt" on data entry screen. A pop-up screen will appear to remind staff to provide the participant with Eye Sub-study and MIND Sub-study

(Canada, Western, Minnesota/Iowa, Ohio/Michigan, Northeast and Southeast CCNs) introductory materials.

f) Input the percent of participant's report of compliance for SMBG.

g) Verify that the **Baseline History and Physical Exam Form** has been completed.

5. The participant will be assigned a treatment regimen. The randomization screen will display this information and list target dates for the follow-up visits. It is recommended that the participant's treatment assignment and visit schedule be printed out and filed in their research record.
6. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, ALT, Creatinine, Lipid Profile, CPK and for storage of additional aliquots (where approved).
7. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Laboratory.
8. An ECG will be obtained and transmitted to the ACCORD ECG Reading Center. Retain a copy for the participant's research record.
9. Collect all glycemic related information:
   a) Measure and record POC HbA1c. Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA2000 will be required to use the Central Lab measurements of HbA1c at all times. Remember POC values should be adjusted for any systematic differences from Central Lab HbA1c values.
   b) Review screening blood glucose diary, download SMBG meter values to laptop and assess blood glucose values for implementation of the glycemia intervention.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia in the source documents. Review symptoms and therapy for hypoglycemia (See Section C.1.3.b, C.1.3.c and MOP Chapter 8, Section 8.4.4).
   d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document. Record current glycemic medications on the **Baseline History and Physical Exam Form** only by class of medication.
   e) Record name and dose of all **current** (at visit entry) glycemia medications on the **Glycemia Medications Log Form**. If on insulin, record name and dose on **Intensive Glycemia Management Form**.
   f) Conduct nutrition assessment and plan.
   g) Instruct participants on their diet, foot care, an exercise program and the relationship of medications with nutrition and exercise.
   h) Reinforce proper SMBG technique and instruct participant to test per instructions on Table A.1.3 in MOP. (4/day if diet/oral therapy (2 ac/day, 2 pc/day) and 4 -8 times/day (at least 2 ac/day and 2 pc/day; occasional 3 am test) if on insulin.
   i) Provide SMBG logbooks and instructions for their completion.
   j) Dispense glucose meter if necessary (**Canadian Sites only**).

k) Provide sufficient strips through the next visit to the participant (**Canadian Sites only**).
l) Fill out the **Unified Form** to ensure a smooth and steady flow of diabetic testing supplies being shipped by NetGroup Diabetic Services (**US Sites only**).
m) Adjust and convert all glucose lowering medications to study provided medications as needed to improve glycemic control based on POC result and screening blood glucose diary. Refer to Figure 5.3 in MOP.
n) Recommend medical ID if participant is being started on insulin.

10. For the Lipid Trial:
    a) If on lipid lowering therapy, discontinue and place on simvastatin (20 mg/day, administered once daily after the evening meal or at bedtime).
    b) Record information on the **Lipid Medications Management Form**.
    c) Refer to nutritionist for instruction/reinforcement of Step 1 diet of the National Cholesterol Education Program (NCEP).
    d) Advise participant of potential adverse effects of statin (myopathy, hepatitis). Review symptoms of myopathy and hepatitis with participant and advise on action to take if symptoms occur. Ask participant about coumadin use (see Section F.1.3.f). Review the list of prohibited medications in MOP Chapter 6, Section 6.3.5.
11. Remove labels from study medications and place on drug dispensing form then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
12. Participants assigned in the substudies (Health Related Quality of Life (HRQL), Physical Activity, Diet) will complete the appropriate questionnaires. Verify that the participant completes all items before end of visit.
13. If you have not acted upon a Central Lab HbA1c > 6%, refer to Section C.2.2. Schedule follow-up phone/fax/email/mail contact within 2 weeks and a clinic appointment in 1 month. One-month follow-up visits for Lipid Trial participants should be scheduled at least 3 weeks after the baseline visit to allow for arrival of blinded study medication.
14. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
15. Collect all related Lifestyle and Background information:
    a) Assess smoking status. Follow guidelines (if necessary) in MOP Chapter 4, section 4.3.1 for smoking cessation activities.
    b) Assess aspirin use. Recommend aspirin therapy in accordance with guidelines in chapter 4 of MOP, section 4.3.2.
16. Contact primary care provider as necessary.
17. Obtain a release of information form in case of need for subsequent events.
18. Complete the following forms and enter data as required:
    a) **Inclusion/Exclusion Summary Form**
    b) **Blood Pressure Trial Screening Form**
    c) **Lipid Trial Screening Form**
    d) **Participant Contact Information Form (if not previously completed)**
    e) **Visual Acuity Worksheet**
    f) **Ophthalmology Exam Form (as necessary)**

g) **Baseline History and Physical Exam Form**
h) **Intensive Glycemia Management Form**
i) **Glycemia Medications Log**
j) **Severe Hypoglycemia Action Form (as necessary)**
k) **Lipid Medications Management Form**
l) **Encounter and Disposition Form**
m) **Health Utilities Index Form**
n) **The Unified Form (US sites only)**
o) **Assigned Substudy Questionnaires (as necessary)**
p) **Drug Dispensing Form (as necessary)**
q) **Event Forms (as necessary)**

C.2.2 Upon Receipt of Central Lab HbA1c Values Drawn

1. If the Central HbA1c result measured at that visit returns > 6.0%, and no change in therapy was made at the time of the visit (when the Central Lab HbA1c was obtained), and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   a. Contact the participant, and intensify the therapy per protocol
      - Increase dose of current agent (if on submaximal dose) or add another agent (see Figure A.3).
   b. Complete appropriate glycemia forms regarding the changes in therapy made to achieve or maintain target levels.

C.2.3 Phone/FAX/email/mail Contact at 0.5, 1.5, 2.5 and 3.5 Months

These contacts are for participants assigned to the intensive glycemic treatment group and should occur within a +/- 1-week window. The participants will be contacted by one of the means listed above and the following procedures will be conducted:

1. Record the participant's report of their SMBG results for the previous 2 weeks if you have not already received them by phone, fax, email or mail. Encourage participants to comply with advance requests for SMBG results.
2. Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section C.1.3.b, C.1.3.c and MOP Chapter 8, Section 8.4.4).
3. Record current glycemic medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record appropriate information on the **Standard Glycemia Management Form**.
4. Adjust or maintain therapy according to the following:
   a) If < 50% of fasting levels per 4 days are > 100 mg/dl (5.6 mmol/l) **AND** < 50% per 4 days of the 2 hr levels are > 140 mg/dl (7.8 mmol/l);
      - Remain at the same dose of current medications.
   b) If > 50% of fasting levels per 4 days are > 100 mg/dl (5.6 mmol/l); **AND/OR** > 50% of the 2 hr levels per 4 days are > 140 mg/dl (7.8 mmol/l); **AND** no contraindication (See Chapter 6 of MOP) to intensify therapy:

- Increase dose of current agent (if currently on submaximal dose) or add another drug according to Figure 5.3 or 5.5 in Chapter 5 of the MOP and reinforce diet and exercise.

5. Reinforce appropriate SMBG frequency according to Table A.1.3:
   - Diet/oral therapy ($\geq$ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.
6. Instruct participants on when and how to self-titrate therapy. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.
7. Remind participant of next clinic visit.
8. Complete the following form and enter data as required:
   a) **Intensive Glycemia Management Form**
   b) **Glycemia Medications Log**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   d) **Study Status Form (as necessary)**

C.2.4 One, 2, 3, and 6 month Visits

These visits should occur within a +/- 1-week window. The participants will report to the clinic and the following procedures will be conducted:

1. Obtain weight, and record in source documentation.
2. Collect all glycemia related information:
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustment in the glycemia intervention.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section C.1.3.b, C.1.3.c and MOP Chapter 8, Section 8.4.4).
   d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
   e) Adjust or maintain therapy according to the following:
      1. If POC HbA1c < 6% **AND** < 50% of fasting levels per 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels per 4 days are > 140 mg/dl (7.8 mmol/l);
      - Maintain current therapy.

3. If POC HbA1c < 6% **BUT** > 50% of fasting levels per 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** > 50% of the 2 hour postprandial levels per 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   - Increase dose of current agent (if on submaximal dose) or add another agent (according to Figure 5.3 or 5.5 in Chapter 5 of the MOP).
4. If POC HbA1c is $\geq$ 6.0% and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   - Increase dose of current agent (if on submaximal dose) or add another agent (according to Figure 5.3 or 5.5 in Chapter 5 of the MOP).

f) **If participant was started on a TZD, check for edema at every visit**. Obtain an ALT every 2 months for the first year of treatment, annually thereafter. Provide participant information sheet on TZDs as necessary.

g) Reinforce appropriate SMBG frequency according to Table A.1.3:
   - Diet/oral therapy (> 2 times/day if at target or 4 times/day (2ac/day,2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.

h) Assess comprehension/understanding of dietary counseling.
   - Reinforce diet and exercise. Repeat at subsequent visits as necessary.

i) Instruct participants on when and how to self-titrate. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.

j) Record name and dose of all glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.

k) Provide SMBG logbooks and instructions in their completion.

3. For the Lipid Trial:

a) Determine compliance with lipid drug regimen and record information on **Lipid Medications Management Form**.

b) Record any potential side effects of lipid therapy.

c) Initiate therapy with masked fibrate/placebo **at the 1-month visit**. The starting dose of masked fenofibrate/placebo medication will be determined by the calculated glomerular filtration rate (GFR) using the baseline serum creatinine level and the abbreviated MDRD equation (Levey 2003). Those participants with a baseline GFR $\geq$50 ml/min/1.73m^2 will begin at a starting dose of 160 mg of fenofibrate or identical placebo tablet. Those with a calculated GFR between 30 and <50 will start at the reduced dose of 54 mg/day fenofibrate or placebo.

Implementation of assignment of blinded study medication dose:

- The Coordinating Center (CC) will determine the starting dose of the blinded study medication based on calculated GFR from the MDRD equation, using Central Lab values at baseline.
- The recommended dose will appear on the participant main page below "Lipid Bottle ID" (e.g., FULL, REDUCED, or NONE).
- The CC will communicate the starting dose to the Drug Distribution Center (DDC).
- DDC will send the appropriate dose to the clinical site labeled for the specific participant.

NOTE: See Section C.1.2.b if notification that the participant's GFR falls below cutoff levels is received. See Section C.1.3.f if participant's LDL-C or Triglycerides exceed cutpoints.

d) Obtain an ALT and CPK measurement to be shipped to the Central Lab **(at the 1 month visit only)**.
e) Review prohibited/discouraged medications with the participant. (See Section 6.3.5 in MOP).
f) Dispense fibrate/placebo and study statin if necessary.

5. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into the computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
6. At the month 1, 2, and 3 visits, schedule follow-up phone/fax/email/mail contact in 2 weeks and a clinic appointment in 1 month. At the 6 month visit, schedule phone/fax/email/mail contact in 1 month and a clinic appointment in 2 months
7. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
8. Complete the following forms and enter data as required:
   a) **Intensive Glycemia Management Form**
   b) **Glycemia Medications Log**
   c) **Severe Hypoglycemia Management Form (as necessary)**
   d) **Lipid Medications Management Form**
   e) **Encounter and Disposition Form**
   f) **Drug Dispensing Form (as necessary)**
   g) **Study Status Form (as necessary)**

C.2.5 Four & 8 Month Visit

The 4-month visit should occur within a +/- 1-week visit window. The 8-month visit should occur within a +/- 2-week window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia medications of lipid on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication if applicable (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stoke Report Form, Unstable Angina Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.

2. Perform the physical exam, including weight. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, Creatinine, Lipid profile, ALT, and CPK.
4. Collect all glycemia related information.
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
   - The Central Lab
   - A Bayer DCA2000, and
   - An approved local lab

   Sites that do not have an acceptable local lab or Bayer DCA2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustments in the glycemia intervention.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section C.1.3.b, C.1.3.c and MOP Chapter 8, Section 8.4.4).
   d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
   e) Adjust and maintain therapy according to the following:
      1. If POC HbA1c < 6% **AND** < 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
         - Maintain current therapy.
      2. If POC HbA1c < 6% **BUT** > 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** > 50% of the 2 hour levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
         - Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).
      3. If POC HbA1c is $\geq$ 6.0% and there is no contraindication (See MOP Chapter 6) to intensify therapy:
         - Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).
   f) **If participant was started on a TZD, check for edema at every visit**. Obtain an ALT every 2 months for the first year of treatment, annually thereafter. Provide participant information sheet on TZDs if necessary.
   g) Reinforce appropriate SMBG frequency according to Table A.1.3:
   Diet/oral therapy (> 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.

h) Assess comprehension/understanding of dietary counseling.
   - Reinforce diet and exercise. Repeat at subsequent visits as necessary.

i) Instruct participants on when and how to self-titrate. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.

j) Record name, dose, and adherence of all glycemia medications on the **Glycemia Medications Log.** If on insulin, record name and dose on the **Intensive Glycemia Management Form**.

k) Provide SMBG logbooks and instructions for their completion.

5. For the Lipid Trial:
   a) Determine compliance with lipid drug regimen and record information on **Lipid Medications Management Form**.
   b) Determine if any potential statin/fibrate related side effects are present.
   c) Review the list of prohibited medications found in MOP Chapter 5.
   d) Fasting Lipid Profile, ALT, CPK and Creatinine sent to Central Chemistry Lab.

NOTE: See Section C.1.2.b if notification that the participant's GFR falls below cutoff levels is received. See Section C.1.3.f if participant's LDL-C or Triglycerides exceed cutpoints.

6. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medications as necessary. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
7. Complete **Cost Substudy Form** for participants in the Cost Substudy.
8. Schedule follow-up phone/fax/email/mail contact in 1 month +/- 2 weeks and a clinic appointment in 2 months or any other required supplemental visits (See Chapter 6).
9. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
10. Complete the following forms and enter data as required:
    a) **Interval History and Follow-up Form**
    b) **Intensive Glycemia Management Form**
    c) **Glycemia Medications Log**
    d) **Severe Hypoglycemia Action Form (as necessary)**
    e) **Lipid Medications Management Form**
    f) **Encounter and Disposition Form**
    g) **Preliminary Event Notification Form (as necessary)**
    h) **Event Forms (as necessary)**
    i) **Drug Dispensing Form (as necessary)**
    j) **Cost Substudy Form (as necessary)**
    k) **Study Status From (as necessary)**

C.2.6 Bi-Monthly Phone/FAX/email/ mail Contacts From Month 5 visit Through End Of Study

These contacts are for participants assigned to the intensive glycemic treatment group and should occur within a +/- 2-week window. The participants will be contacted by one of the means listed above and the following procedures will be conducted:

1. Record the participant's report of their SMBG results for the previous 2 weeks if you have not already received them by phone, fax, email or mail. Encourage participants to comply with advance requests for SMBG results.
2. Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section C.1.3.b, C.1.3.c and MOP Chapter 8, Section 8.4.4).
3. Record current glycemic medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record appropriate information on the **Intensive Glycemia Management Form**.
4. Adjust or maintain therapy according to the following:
   a) If < 50% of fasting levels over 4 days are > 100 mg/dl (5.6 mmol/l) **AND** < 50% over 4 days of the 2 hr levels are > 140 mg/dl (7.8 mmol/l);
      - Remain at the same dose of current medications.
   b) If > 50% of fasting levels over 4 days are > 100 mg/dl (5.6 mmol/l); **AND/OR** > 50% of the 2 hr levels over 4 days are > 140 mg/dl (7.8 mmol/l); **AND** no contraindication (See MOP Chapter 6) to intensify therapy:
      - Increase dose of current agent (if on submaximal dose) or add another drug (See MOP Chapter 5, Figure 5.3 or 5.5) and reinforce diet and exercise.
5. Reinforce appropriate SMBG frequency according to Table A.1.3:
   - Diet/oral therapy ($\geq$ 2 times/day if at target or 4 times/day (2 ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.
6. Instruct participants on when and how to self-titrate therapy. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.
7. Remind participant of next 2-month clinic appointment.
8. Complete the following form and enter data as required:
   a) **Intensive Glycemia Management Form**
   b) **Glycemia Medications Log**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   d) **Study Status Form (as necessary)**

C.2.7 Visits at Follow-up Months 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74,78, 82, 86, 90, and 94

These visits should occur within a +/- 2-week window. The participants will report to the clinic and the following procedures will be conducted:

1. Obtain weight, and record in source documentation.
2. Collect all glycemia related information:
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.

b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustment in the glycemia intervention.

c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section C.1.3.b, C.1.3.c and MOP Chapter 8, Section 8.4.4).

d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.

e) Adjust or maintain therapy according to the following:

1. If POC HbA1c < 6% **AND** < 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
   - Maintain current therapy.
2. If POC HbA1c < 6% **BUT** > 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** > 50% of the 2 hour levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   - Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).
3. If POC HbA1c is $\geq$ 6.0% and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   - Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).

f) **If participant was started on a TZD, check for edema at every visit**. Obtain an ALT every 2 months for the first year of treatment, annually thereafter. Provide participant information sheet on TZDs if necessary.

g) Reinforce appropriate SMBG frequency according to Table A.1.3:
   - Diet/oral therapy ($\geq$ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.

h) Assess comprehension/understanding of dietary counseling.
   - Reinforce diet and exercise. Repeat at subsequent visits as necessary.

i) Instruct participants on when and how to self-titrate. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.

j) Record name and dose of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.

k) Provide SMBG logbooks and instructions in their completion.

3. Remove labels from study medications and place on drug dispensing form then dispense blood pressure-lowering study medication. Scan label bar codes into the

computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.

4. Schedule follow-up phone/fax/email/mail contact in 1 month and a clinic appointment in 2 months.
5. Remind participants to bring all their medications, glucose meter and SMBG records to each visit.
6. Remind participant to take blood pressure medications the morning of next visit.
7. Complete the following forms and enter data as required:
   a) **Intensive Glycemia Management Form**
   b) **Glycemia Medications Log**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   d) **Encounter and Disposition Form**
   e) **Drug Dispensing Form (as necessary)**
   f) **Study Status Form (as necessary)**

C.2.8 Annual Visits (12, 24, 36, 48, 60, 72, 84 Months)

This visit should occur within a +/- 2-week visit window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia or lipid medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication if applicable (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Review and update Contact Information.
2. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter the **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
3. Perform the annual physical exam, including weight, height, weight circumference, visual acuity, and foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
4. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium **(12-month, prn, and exit visit)**, Creatinine, Lipid Profile, ATL and CPK. **(Blood samples for storage of additional aliquots, where approved, should occur at the 24-month, 48-month and 72 month visits)**.
5. Review the Concomitant Medications list located in the **Annual Follow-up and Physical Exam Form** with participant to document all non-study medications currently taking.

6. Participants will be given the **Health Utilities Index Form** and instructed on how to complete it **(12-month, 36-month, and 48-month visits)**. Verify that the participant completes all items before end of visit.
7. **A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Lab for the 24-month, 48-month, and 72 month visits.**
8. **An ECG will be obtained and transmitted to the ACCORD ECG Reading Center for the 24-month, 48-month, and 72 month visits**. Retain a copy for participant's research records.
9. Collect all glycemia related information.
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustments in the glycemia intervention.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section C.1.3.b, C.1.3.c and MOP Chapter 8, Section 8.4.4).
   e) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
   f) Adjust and maintain therapy according to the following:
      1. If POC HbA1c $< 6\%$ **AND** $< 50\%$ of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** $< 50\%$ of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
         - Maintain current therapy.
      2. If POC HbA1c $< 6\%$ **BUT** $> 50\%$ of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** $> 50\%$ of the 2 hour levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
         - Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).
      3. If POC HbA1c is $\geq 6.0\%$ and there is no contraindication (See MOP Chapter 6) to intensify therapy:

      Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).
   f) **If participant was started on a TZD, check for edema at every visit**. Obtain an ALT every 2 months for the first year of treatment, annually thereafter. Provide participant information sheet on TZDs if necessary.

g) Reinforce appropriate SMBG frequency according to Table A.1.3:
Diet/oral therapy ($\geq$ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.

h) Assess comprehension/understanding of dietary counseling.
- Reinforce diet and exercise. Repeat at subsequent visits as necessary.

i) Instruct participants on when and how to self-titrate. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.

j) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Intensive Glycemia Management Form**.

k) Provide SMBG logbooks and instructions for their completion.

l) Review and update the **Unified Form** to ensure a smooth and steady flow of diabetic testing supplies being shipped by the NetGroup Diabetic Services **(US sites only)**.

10. For the Lipid Trial:
    a) Determine participant's report of compliance with lipid drug regimen and record information on **Lipid Medications Management Form**.
    b) Determine if any potential statin/fibrate related side effects are present.
    c) Fasting Lipid Profile, ALT, CPK and Creatinine sent to the Central Chemistry Lab.

NOTE: See Section C.1.2.b if notification that the participant's GFR falls below cutoff levels is received. See Section C.1.3.f if participant's LDL-C or Triglycerides exceed cutpoints.

11. Remove labels from study medications and place on drug dispensing form then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
12. Participants assigned in the substudies (Health Related Quality of Life (HRQL), Physical Activity, Diet) will complete the appropriate questionnaires. **(12-month, 36-month, and 48-month visits)**. Verify that the participant completes all items before end of visit. Complete **Cost Substudy Form** for participants in the Cost Substudy.
13. Schedule follow-up phone/fax/email/mail contact in 1 month +/- 2 weeks and a clinic appointment in 2 months or any other required supplemental visits (See MOP Chapter 6).
14. Remind participants to bring all their medications, glucose meter and SMBG records to next visit.
15. Complete the following forms and enter data as required:
    a) **Participant Contact Information Form (as necessary)**
    b) **Annual History and Follow-up Form**
    c) **Intensive Glycemia Management Form**
    d) **Glycemia Medications Log**
    e) **Severe Hypoglycemia Action Form (as necessary)**
    f) **Lipid Medications Management Form**
    g) **Encounter and Disposition Form**
    h) **Health Utilities Index (12-month, 36-month, and 48-month visits)**
    i) **The Unified Form (US Sites)**

j) **Visual Acuity Worksheet (24-month, 48-month, and 72-month)**
k) **Ophthalmology Exam Form (as necessary)**
l) **Preliminary Event Notification Form (as necessary)**
m) **Event Forms (as necessary)**
n) **Assigned Substudy Questionnaires (as necessary at 12-month, 36-month, and 48-month visits)**
o) **Drug Dispensing Form (as necessary)**
p) **Cost Substudy Form (as necessary)**
q) **Study Status Form (as necessary)**

C.2.9 Visits at Follow-up Months 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, and 92

These visits are for participants assigned to the intensive glycemia/intensive BP treatment intervention and should occur within a +/- 2- week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter the **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Obtain weight.
3. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
4. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c and Creatinine.
5. Collect all glycemia related information.
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop, and assess for medication/lifestyle adjustments in the glycemia intervention.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia.

Review symptoms and therapy for hypoglycemia (See Section C.1.3.b, C.1.3.c and MOP Chapter 8, Section 8.4.4).

d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.

e) Adjust and maintain therapy according to the following:

1. If POC HbA1c < 6% **AND** < 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND** < 50% of the 2 hour levels over 4 days are > 140 mg/dl (7.8 mmol/l);
   - Maintain current therapy.
2. If POC HbA1c < 6% **BUT** > 50% of fasting levels over 4 days are > 100 mg/dl (5.7 mmol/l) **AND/OR** > 50% of the 2 hour levels over 4 days are > 140 mg/dl/ (7.8 mmol/l) and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   - Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).
3. If POC HbA1c is $\geq$ 6.0% and there is no contraindication (See MOP Chapter 6) to intensify therapy:
   - Increase dose of current agent (if on submaximal dose) or add another agent (See MOP Chapter 5, Figure 5.3 or 5.5).

f) Reinforce appropriate SMBG frequency according to Table A.1.3:
Diet/oral therapy ($\geq$ 2 times/day if at target or 4 times/day (2ac/day, 2 pc/day) if not at target and 4-8 times/day (at least 2 ac and 2 pc tests/ day; occasional 3 am test) if on insulin.

g) Assess comprehension/understanding of dietary counseling.
   - Reinforce diet and exercise. Repeat at subsequent visits as necessary.

h) Instruct participants on when and how to self-titrate. If on insulin, instruct participant on when and how to self-titrate therapy every 4 days.

i) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log**.

j) Provide SMBG logbooks and instructions for their completion.

6. For the Lipid Trial:
   a) Determine participant's report of compliance with lipid drug regimen and record information on the **Lipid Medications Management Form.**
   b) Determine if any potential statin/fibrate related side effects are present.
   c) Review prohibited/ discouraged medications with participant (See MOP Chapter 6, Section 6.3.5).
   d) Dispense study statin and fibrate/placebo as necessary.

NOTE: See Section C.1.2.b if notification that the participant's GFR falls below cutoff levels is received. See Section C.1.3.f if participant's LDL-C or Triglycerides exceed cutpoints.

7. Remove labels from study medications and place on drug dispensing form then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
8. Complete **Cost Substudy Form** for participants in the Cost Substudy.

9. Schedule follow-up phone/fax/email/mail contact in 1 month +/- 2 weeks and a clinic appointment in 2 months or any other required supplemental visits (See MOP Chapter 6).
10. Remind participants to bring all their medications, glucose meter and SMBG records to next visit.
11. Complete the following forms and enter data as required:
    a) **Interval History and Follow-up**
    b) **Intensive Glycemia Management Form**
    c) **Glycemia Medications Log**
    d) **Severe Hypoglycemia Action Form (as necessary)**
    e) **Lipid Medications Management Form**
    f) **Encounter and Disposition Form**
    g) **Preliminary Event Notification Form (as necessary)**
    h) **Event Forms (as necessary)**
    i) **Drug Dispensing Form (as necessary)**
    j) **Cost Substudy Form (as necessary)**
    k) **Study Status Form (as necessary)**

C.2.10 Exit Visit

This visit should occur within a +/- 2-week visit window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia or lipid medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication if applicable (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter the **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the annual physical exam, including weight, height, weight circumference, visual acuity, and foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, Creatinine, Lipid Profile, ALT and CPK and for storage of additional aliquots (where approved).
4. Review the Concomitant Medications list located in the **Annual Follow-up and Physical Exam Form** with participant to document all non-study medications currently taking.

5. Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completes all items before end of visit.
6. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Lab.
7. An ECG will be obtained and transmitted to the ACCORD ECG Reading Center. Retain a copy for participant's research records.
8. Collect all glycemia related information.
   a) Measure and record POC HbA1c. [Currently there are only 3 acceptable means of attaining a HbA1c value:
      - The Central Lab
      - A Bayer DCA 2000, and
      - An approved local lab

      Sites that do not have an acceptable local lab or Bayer DCA 2000 will be required to use the Central Lab measurements of HbA1c at all times]. Remember POC values should be adjusted for any systematic differences from Central HbA1c values.
   b) Review the previous 2 weeks SMBG values in the diary, download meter values to laptop.
   c) Complete **Intensive Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section C.1.3.b, C.1.3.c and MOP Chapter 8, Section 8.4.4).
   d) Record current glycemic medications including name, dose and participant's self report of adherence in the source document.
   e) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on **Intensive Glycemia Management Form**.
9. For the Lipid Trial:
   a) Determine participant's report of compliance with lipid drug regimen and record information on the **Lipid Medications Managment Form.**
   b) Determine if any potential statin/fibrate related side effects are present.
10. Participants will be prescribed appropriate non-study antihyperglycemia and lipid therapy based on their current status and post-trial follow-up care will be arranged.
11. Complete the following forms and enter data as required:
    a) **Participant Contact Information Form (as necessary)**
    b) **Annual Follow-up and Physical Exam Form**
    c) **Intensive Glycemia Management Form**
    d) **Glycemia Medications Log**
    e) **Severe Hypoglycemia Action Form (as necessary)**
    f) **Lipid Medications Management Form**
    g) **Encounter and Disposition Form**
    h) **Health Utilities Index Form**
    i) **Visual Acuity Worksheet**
    j) **Ophthalmology Exam Form (as necessary)**
    k) **Preliminary Event Notification Form (as necessary)**
    l) **Event Forms (as necessary)**

m) **Cost Substudy Form (as necessary)**
n) **Study Status Form (as necessary)**

Figure C.3
Treatment Algorithm for Intensive Glycemic Therapy Group (Goal: HbA1c<6%)

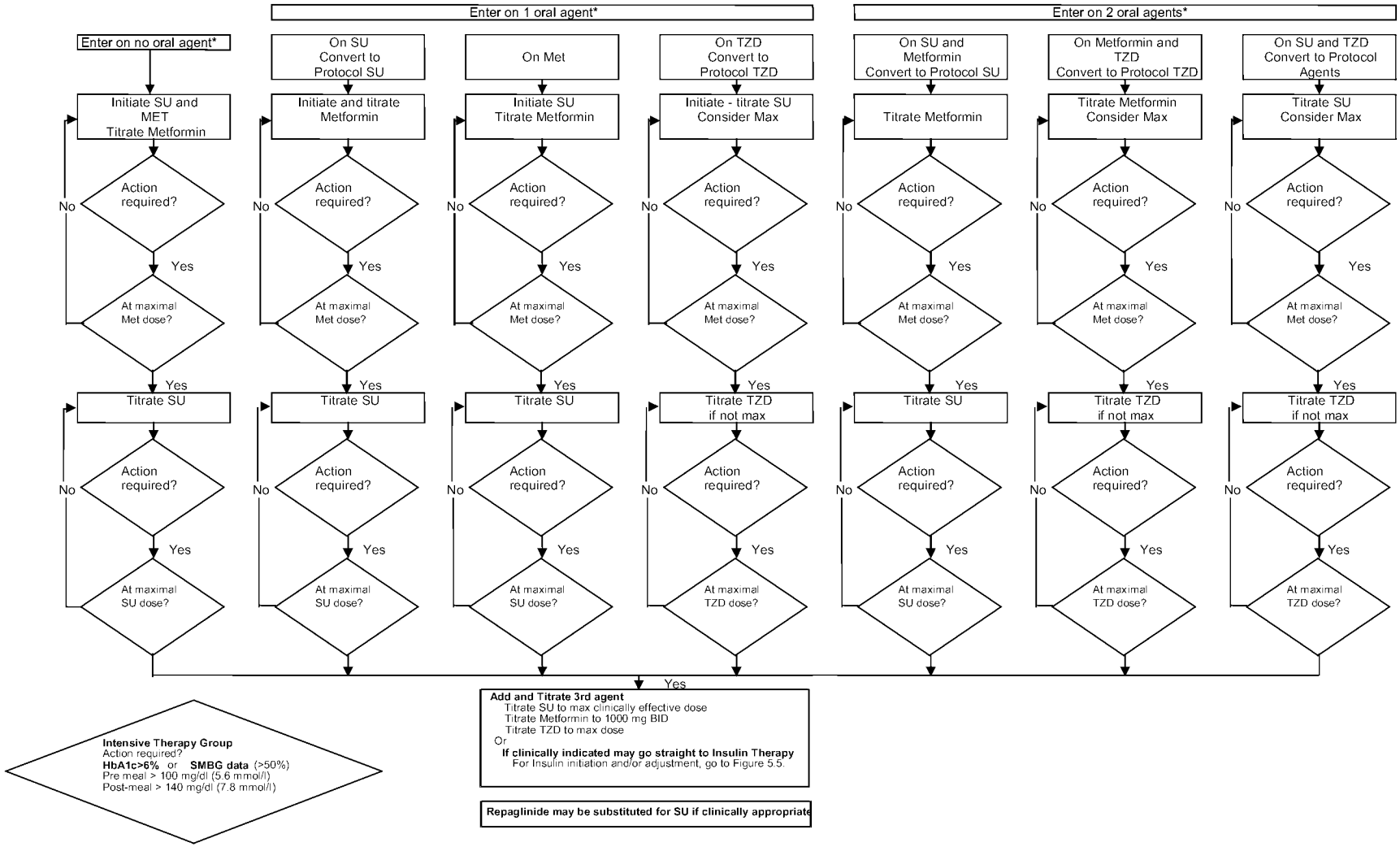
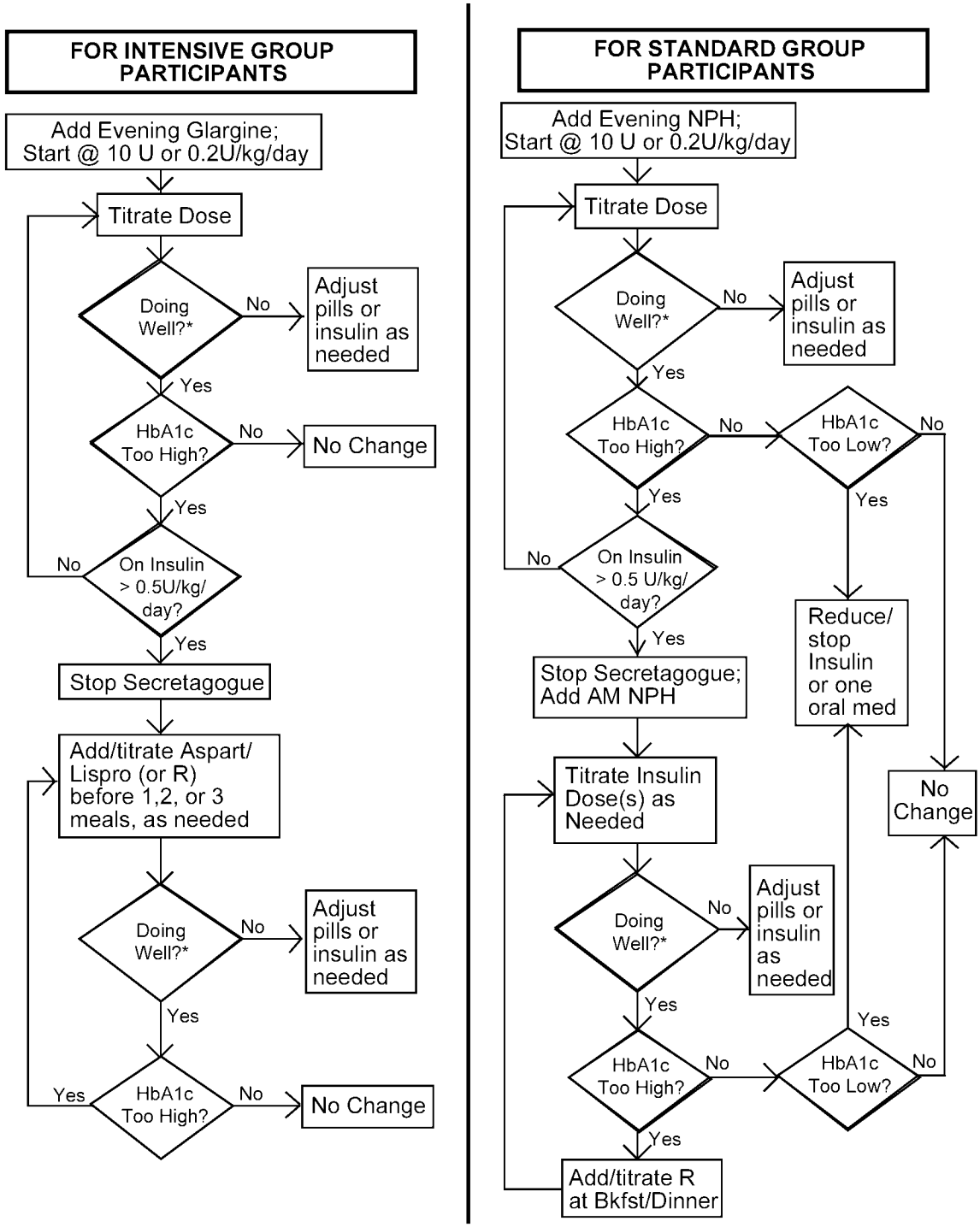


Figure 3.3:
Use of Insulin for Participants On Maximal Oral Therapy



*Doing well: no severe hypoglycemic or adverse event or no reason to reduce therapy (as described in Figure 3.2)

Thiazolidinedione Drugs (e.g. Avandia or Rosiglitazone)

ACTIONS of THIAZOLIDINEDIONES

The drug Avandia (rosiglitazone) belongs to a group of medications called thiazolidinediones (or glitazones or TZD's), and may be supplied as part of the ACCORD trial. Actos (pioglitazone) is another drug that belongs in this group. These drugs lower the blood glucose by reducing the body's resistance to the action of insulin (i.e. making your own insulin work more effectively). They can be used alone or can be combined with other diabetes pills or insulin.

COMMON SIDE EFFECTS

1. Hypoglycemia (low blood sugar)

These drugs can lead to hypoglycemia. When taken alone, the risk of hypoglycemia is low. When taken with insulin or other pills, the risk of hypoglycemia is higher.

If you do experience symptoms of a low blood sugar (such as lightheadedness, sweating, nervousness, hunger, a sensation of a racing heart, headache, or sudden fatigueat unusual times), check your blood sugar. If the level is less than 70 mg/dl (3.9 mmol/l) you may be suffering from hypoglycemia. If so, drink 4 ounces of juice or regular soda or eight ounces of milk or have three glucose tablets or five Life Savers (i.e. 15 grams of carbohydrate). Recheck your blood sugar in 15 minutes to make sure it has risen to at least 90 mg/dl (5.0 mmol/L). If low blood sugar reactions are frequent, severe or unexpected, call your doctor.

2. Weight Gain

These drugs may lead to weight gain. Weight gain is due to the lowering of blood sugar by insulin and drugs that act like insulin. This reduces the amount of sugar lost in the urine and helps the body store extra energy in fat cells. Sometimes, weight gain may be due to some fluid retention. Regardless of the cause, the amount of weight gained or lost depends on the level of physical activity and diet, or can be due to other drugs that are being taken. For example, some people gain more weight if insulin is also being taken. To minimize weight gain or to cause weight loss, exercise regularly, eat low fat foods, avoid extra snacks and large portions.

3. Fluid Retention

These drugs may lead to fluid retention. Fluid retention is generally mild with some swelling in the ankle or leg or bloating; it may be more pronounced when these drugs are used together with insulin, and rarely, the fluid retention can be severe or even life threatening. If you develop major leg swelling or especially shortness of breath either with activity or at rest, see your doctor as soon as possible. Reducing the dose, adding diuretics (water pills) or adjusting other medications (such as blood pressure pills, calcium channel blockers, non-steroidal anti-inflammatory drugs or arthritis pills) can also be used to manage this problem. ***You and your doctor should pay close attention to fluid retention if you take insulin or have heart failure or other heart problems.***

POTENTIAL SIDE EFFECTS

Because of rare cases of severe liver disease with a related medicine that is no longer available (Rezulin or troglitazone), you must have your blood drawn for liver enzyme tests (ALT) when treated with these drugs every 2 months for the first year of treatment and intermittently thereafter. If you develop persistent nausea, vomiting, belly pain, fatigue, loss of appetite, dark

urine, yellowing of the eyes or skin while treated with this drug, stop the medication and see your doctor for a blood draw within a few days.

DOSING

Avandia (rosiglitazone) can be taken once a day, but may work a bit better if taken twice daily. Actos (pioglitazone) can be taken any time of the day. Both drugs can be taken either with or without food. It may take 12 weeks to see the full effect of a dose.

7. Visit Schedule of Study Activities by Randomization Cell

D. Standard Glycemia and Intensive Blood Pressure

D.1. Overview

One of the key aims of the ACCORD study is to determine if a therapeutic strategy that targets a HbA1c of < 6.0% reduces the rate of cardiovascular disease (CVD) events more than a strategy that targets a HbA1c of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%) in high risk middle-aged or older people with type 2 diabetes. The approaches used to implement these targets, suggested algorithms for the use of pharmacologic agents and follow-up schedules are described in MOP Chapters 5 and 6. Details regarding the implementation of the protocol for the Standard Glycemia and Lipid Trial groups are described below.

The ACCORD blood pressure (BP) trial component is designed to test whether a therapeutic strategy that targets a systolic blood pressure (SBP) of < 120 mmHg reduces the rate of cardiovascular events in a middle-aged or older type 2 diabetic population at high risk for cardiovascular events compared to a strategy that targets a SBP of < 140 mmHg in the context of good glycemic control. Details regarding the implementation of the protocol for the intensive glycemia and intensive blood pressure control groups are described below.

D.1.1 Algorithms for Standard Glycemic and Intensive Blood Pressure Control; Choice of Agents

Figures D.4 and D.5 at the end of this chapter are suggested algorithms to guide changes in glycemic therapy for the standard group. The exact changes to be made whenever glycemic therapy needs to be intensified on the basis of the HbA1c or the SMBG results will be determined by the individual site using the figures as guides.

The algorithm for the intensive BP group calls for an assessment of the participants' antihypertensive medication regimen at baseline to determine the starting point on the decision tree for future monitoring and medication adjustments needed to achieve their assigned SBP goal (< 120 mmHg) (Refer to Figure D.6 at the end of this chapter).

D.1.2 Targets and Action Required Levels

D.1.2.a) Standard Glycemic Control

Table D.1.2 outlines the glycemic target for the standard group, which is identical to Table 3.1 in the protocol.

TableD.1.2: Glycemic Targets and Thresholds for Action for ACCORD			
		"Action Required" Threshold	
Group	HbA1c Targets	HbA1c	> 50% of SMBG Results/4 days
Standard Therapy	7 – 7.9%	> 7.9%* or ≤ 6.5%[#] (anytime) or 6.6%-6.9% [#] (twice consecutively)	fasting/ac < 90 mg/dl (5.0 mmol/l)[#]

pc: postcibal; ac: antecibal; SMBG: self monitoring of blood glucose;
*antihyperglycemic therapy will be advanced if either the HbA1c or the SMBG "action required" criteria are met at any participant encounter [#] therapy with drugs that increase the risk of hypoglycemia (e.g. insulin, sulfonylureas, meglitinides) will be reduced to avoid hypoglycemia if these criteria are met.

D.1.2.b) Intensive Blood Pressure Control

Participants randomized to the intensive blood pressure control will have a SBP goal of < 120 mmHg. The BP intervention will begin at the randomization visit. The investigator may choose from among the available ACCORD agents or select another as determined appropriate. It is recommended that the regimen include a drug class associated with reduced cardiovascular events in diabetes (ACE-inhibitor, beta-blocker, calcium channel blocker or diuretic). For participants in the intensive BP group, a combination of a diuretic and either an ACE inhibitor, a beta-blocker, a calcium channel blocker or an angiotensin II receptor blocker (ARB) is strongly encouraged for initial therapy at randomization. (Refer to Drug Availability List – MOP Chapter 5)

D.1.3.a) Adjusting Glycemic Therapy

As noted in the following table (D.1.3), a range of approaches will be used to target the HbA1c level shown in Table D.1.2.

TableD.1.3 Achieving Glycemic Goals	
	Standard Group
Visits (1 and 4 months)	Month 1 and 4 mo
Visits (> 4 months)	Q 4 mo
Phone contact	Participant initiated (prn)
Supplemental contact	Severe hypoglycemia/hyperglycemia HbA1c in action required range Frequent (>50%/4 days) premeal SMBG levels <90 mg/dl (5.0 mmol/l)
Point of Care HbA1c	Optional
Routine use of postprandial SMBG values to guide therapy	No
SMBG freq.[a] (not on insulin)	≤7/wk (daily at different times or >1/day on certain days)
SMBG freq.[a] (on insulin)	≤3/day

Self titration principles	Avoid severe hypoglycemia and premeal SMBG levels < 90 mg/dl (5.0 mmol/l)
Initial Minimum Rx	Diet/lifestyle
Insulin Use (when needed)	Generally ≤ 2 injections/day

[a]less frequent if goals are achieved; [b] including avoiding SMBG levels < 70 mg/dl (3.9 mmol/l) on > 1/4 of the readings.

D.1.3.b) Glycemia Safety Issues/ Adjusting Therapy for Hypoglycemia

Hypoglycemic events may occur in individuals in either the intensive or standard group. Severe hypoglycemia is unusual in people with type 2 diabetes (even when normoglycemia is targeted). Mild episodes of hypoglycemia are, however, likely to occur.

All participants will be instructed to check their glucose levels regularly as described in the protocol. They will also be taught how to recognize and self-treat hypoglycemia and will be instructed to keep glucose available at all times (as tablets). Moreover, any participant who has had an episode of severe hypoglycemia will be provided with glucagon and they and any cohabiting partner will be taught how to administer it.

Severe hypoglycemia is defined as any episode of loss of consciousness/seizure or documented hypoglycemia (glucose < 50 mg/dl or 2.8 mmol/l) that also requires hospitalization or treatment by emergency personnel. If this occurs:

- Complete **Severe Hypoglycemia Action Form**. (See MOP Chapter 8, Section 8.4.4 for more details).
- For participants in either group who have an episode of severe hypoglycemia, adjust glycemic targets to achieve a fasting and 2 hour glucose (postprandial) of 100 – 140 mg/dl (5.5 – 7.8 mmol/l) and < 180 mg/dl (10 mmol/l) respectively, and a HbA1c of 7.0% - 7.9% for at least 4 weeks.
- Ensure that a complete medical assessment by the physician is completed to identify other potential causes (e.g. pituitary or adrenal insufficiency)
- Ensure that the physician reassesses the glycemic goals at subsequent visits.
- Ensure that the participant has received glucagon and that the participant and cohabitant know how to administer it.
- Have telephone contact with participant before the next visit to assess blood glucose records and freedom from hypoglycemia.

Minor hypoglycemia is defined as self-reported transient symptoms such as lightheadedness, tremor, shaking, sweating, tingling, blurry vision, trouble concentrating etc., that are self-treated by ingestion of carbohydrates and resolve on their own (See MOP Chapter 6, Section 6.1.6). All participants will be asked to note such episodes in their glucose logbooks and to confirm them with a blood glucose reading whenever possible. The estimated frequency (of confirmed and suspected minor hypoglycemia) will be recorded at every visit.

D.1.3.c) Self Treatment of Hypoglycemia

1. If the glucose value is < 50-70 mg/dl (3.9 mmol/l), it should be treated by ingestion of 15 grams of CHO (e.g. 3-4 glucose tablets, 5 Lifesavers, 4-6 oz. of a regular – (nondiet) – soft drink, or 8 oz. low fat milk);
2. If the glucose value is < 50 mg/dl (2.8 mmol/l), it should be treated by ingestion of 20-30 grams of CHO (e.g. 6-8 glucose tablets);
3. Blood glucose should be self-tested 15-20 minutes after therapy and therapy repeated if the level is still low (as above)
4. If no meal will be eaten within 1-2 hours, a mixed nutrient snack, including CHO, protein, and fat should be ingested right after the initial therapy to prevent another episode
4. If the glucose value is low or there is significant cognitive or motor impairment, individuals should treat and re-test glucose value. The glucose value should be > 70 mg/dl (3.9 mmol/l) before driving a car or operating heavy machinery.

D.1.3.d) Education and Minimization of Hypoglycemia in Participants

Hypoglycemia is an inherent risk in the treatment of diabetes. It is important to inform participants of the signs and symptoms of hypoglycemia, techniques to minimize the risk and appropriate methods of treatment. Several tools are available for use in educating participants:

1. Hypoglycemia Cartoon
2. Participant Wallet Card
3. Primer on Hypoglycemia
4. Participant Newsletters

All participants must be provided with the written material listed above at the beginning of the study. Study staff should review verbally the signs and symptoms with the participant and family members. Participants and their families should be encouraged to review the hypoglycemic video either in the clinic or at home. Both participants and family members should be educated on the appropriate treatment for symptoms, and provided with glucose tablets. Those participants suffering one severe hypoglycemic event should be provided with a glucagon kit and both the participant and the family member taught how to use it. This material must be reviewed annually with all participants and after every reported hypoglycemic event.

D.1.3.e) Safety Issues for Thiazolidinedione (TZD) Drugs

For participants on TZD (e.g. Avandia or Rosiglitazone), check for the presence of edema at every visit and obtain a Central Lab ALT every 2 months for the first year of treatment and annually thereafter.

As TZDs are contraindicated in people with stage 3 or 4 heart failure, if a participant who is taking a TZD does develop heart failure, the TZD should be stopped and the heart failure treated and investigated. Depending on the results of these investigations the investigator may reconsider cautiously reinstituting TZD therapy if the heart failure resolves, and was judged to have not been directly cause by the TZD alone.

A handout to give to the participants at the discretion of the site concerning TZD use is available and can be found on page 22 at the end of this chapter.

D.1.3.f) Adjusting Antihypertensive Therapy

Participant's BP should be monitored at every visit. For the intensive BP group, initiation of study therapy is dependent upon the participant's medication status at baseline. If on 0 - 1 antihypertensive medication at baseline, the participant should begin a study drug combination (an ACE-I, a beta-blocker, a calcium channel blocker, or an angiotensin II receptor blocker (ARB) combined with the diuretic) and be monitored as indicated by the protocol. If the participant is on 2 or 3 medications at baseline, they may continue their present therapy if at goal (< 120 mm Hg). It is strongly encouraged that a diuretic be included as part of the study antihypertensive regimen. If the participant is not at goal (≥ 120 mm Hg) therapy should be adjusted (e.g. dosage titration, addition of another agent, or change to an alternate combination) to move toward the study goal. The SBP goal for the intensive group is < 120 mm Hg. Action must occur at each visit and is required at each **Milepost** visit (4 month intervals through the 24-month visit and annually thereafter based on date of randomization), throughout the duration of the study for those participants who remain above goal (SBP ≥ 120 mm Hg). If the SBP remains ≥ 120 mm Hg upward dose titration or an additional drug (not already in use) must be added and the participant should be seen at monthly intervals until at goal. If at a **Milepost** visit the SBP is not < 120 mm Hg, an antihypertensive medication from a different class not already in use MUST be added. If the SBP has reached the desired goal and remains < 120 mm Hg, therapy and monitoring will continue as per protocol.

D.2 Standard Glycemic and Intensive Blood Pressure Control Visit Procedures

D.2.1 Baseline – Randomization Visit

The participants will be instructed to attend the clinic following an overnight fast (since ~10 pm the previous evening). They should not take their glycemia or lipid medications on the morning of this clinic visit but be instructed to bring their medications, glucose meter SMBG records, and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic (if applicable). During the visit, the following procedures will be conducted:

1. All data collected during the screening process will be reviewed.
2. Verify eligibility status for the Glycemia, Blood Pressure and Lipid Trials (including occurrence of events that may prohibit patient from participating).

a) Review current medications including OTC, herbal remedies and vitamins.
b) Review, evaluate and calculate the percentage of participant's compliance with at least 2 weeks of SMBG monitoring as part of the run-in procedures.
c) Assure that the qualifying HbA1c value was obtained within the last 3 months prior to the randomization date.

3. If ineligible, the participant will be thanked for their time and dismissed from the clinic.
4. If eligible, proceed with randomization process:
   a) Verify that a full-scale consent form has been obtained and signed.
   b) Obtain and perform baseline history and physical exam, including demographics, medical history concomitant medications, weight, height, and waist circumference, visual acuity, and foot exam. Using the appropriate technique for the Omron device obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
   c) Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completes all items before end of visit.
   d) Verify that all information on the **Inclusion/Exclusion Summary Form, the Blood Pressure Screening Form,** and **the Lipid Trial Screening Form** is complete and correct both on the forms and in the computer.
   e) Click "Randomize pt" on data entry screen.
   f) Input the percent of participant's report of compliance for SMBG.
   g) Verify that the **Baseline History and Physical Exam Form** has been completed.
5. The participant will be assigned a treatment regimen. The randomization screen will display this information and list target dates for the follow-up visits. It is recommended that the participant's treatment assignment and visit schedule be printed out and filed in their research record.
6. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, ALT, Creatinine, Lipid Profile, CPK and for storage of additional aliquots (where approved).
7. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Laboratory.
8. An ECG will be obtained and transmitted to the ACCORD ECG Reading Center. Retain a copy for the participant's research record.
9. Collect all glycemic related information:
   a) Review screening blood glucose diary, download SMBG meter values to laptop and assess blood glucose values for implementation of the glycemia intervention.
   b) Complete **Standard Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia in source documents. Review symptoms and therapy for hypoglycemia (See Section D.1.3.b, D.1.3.c and MOP Chapter 8, Section 8.4.4).
   c) Record current glycemic medications including name, dose and participant's self report of adherence in the source document. Record current glycemia medications on the **Baseline History and Physical Exam Form** only by class of medication
   d) Record name and dose of all **current** (at visit entry) oral glycemia medications on the **Glycemia Medications Log.** If on insulin, record name and dose on the **Standard Glycemia Management Form**.

e) Conduct nutrition assessment and plan.
f) Instruct participants on their diet, foot care and exercise program and the relationship of medications with nutrition and exercise.
g) Reinforce proper SMBG technique and instruct participant to test per instructions on MOP Table D.1.3 ($\leq$ 7/wk (daily at different times or > 1/day on certain days) if diet/oral therapy and $\leq$ 3/day if on insulin).
h) Provide SMBG logbooks and instructions for their completion.
i) Dispense glucose meter if necessary (**Canadian sites only**).
j) Provide sufficient strips through to the next visit to the participant (**Canadian sites only**).
k) Fill out the **Unified Form** to ensure a smooth and steady flow of diabetic testing supplies being shipped by NetGroup Diabetic Services (**US sites only**).
l) **At baseline continue glycemia therapy that participants were regularly or routinely taking prior to the ACCORD Study.** Convert all glucose lowering medications to equivalent study provided medications.
   1. If any of the conditions in Box A apply, then reduce dose of a glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ $\geq$ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications

   2. Upon receipt of Central Lab HbA1c values, refer to MOP section D.2.2 in this chapter.
m) Record name and dose of **all** glycemia medications participant was prescribed at visit exit on the **Glycemia Medications Log.** If on insulin, record name and dose on the **Standard Glycemia Management Form**.

10. Collect all blood pressure related information:
    a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
    b) Record current BP medications on the **Baseline History and Physical Exam Form** only by class of medication.
    c) Using appropriate technique with the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
    d) If on 0 - 1 antihypertensive medication at baseline, the participant should begin a study drug combination (an ACE-I, a beta-blocker, a calcium channel blocker, or an angiotensin II receptor blocker (ARB) combined with the diuretic) and be monitored as indicated by the protocol. If the participant is on 2 or 3 medications at baseline, they may continue their present therapy if at goal (< 120 mm Hg) and the regimen includes a diuretic. If the regimen does not include a diuretic it is recommended that the current regimen be adjusted and include a diuretic. If the participant is not at goal ($\geq$ 120 mm Hg) therapy should be adjusted (e.g. dosage

titration, addition of another agent, or change to an alternate combination) to move toward the study goal.

e) Initiate or convert all blood pressure-lowering medications to study drugs (if necessary); record name of drug and dose on the **Blood Pressure Medications Log**.

f) Instruct participants on actions to limit symptomatic orthostasis.

11. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
12. Participants assigned in substudies (Health Related Quality of Life (HRQL), Physical Activity, Diet) will complete the appropriate questionnaires. Verify that the participant completes all items before end of visit. Complete **Cost Substudy Form** for participants in the Cost Substudy.
13. Schedule a clinic appointment in 1 month.
14. Remind participants to bring all their medications, glucose meters and SMBG records to each visit.
15. Remind participants to take blood pressure medications the morning of next visit.
16. Collect all related Lifestyle and Background information:

    a) Assess smoking status. Follow guidelines (if necessary) in MOP Chapter 4, Section 4.3.1 for smoking cessation activities.

    b) Assess aspirin use. Recommend aspirin therapy (if appropriate) in accordance with guidelines in MOP Chapter 4, Section 4.3.2.
17. Contact primary care provider as necessary.
18. Obtain a release of information form in case of need for subsequent events.
19. Complete the following forms and enter data as required:

    a) **Inclusion/Exclusion Summary Form**
    b) **Blood Pressure Trial Screening Form**
    c) **Lipid Trial Screening Form**
    d) **Participant Contact Information Form (if not previously completed)**
    e) **Visual Acuity Worksheet**
    f) **Ophthalmology Exam Form (as necessary)**
    g) **Baseline History and Physical Exam Form**
    h) **Intensive Glycemia Management Form**
    i) **Glycemia Medications Log**
    j) **Severe Hypoglycemia Action Form (as necessary)**
    k) **Intensive Blood Pressure Management Form**
    l) **Blood Pressure Medications Log**
    m) **Encounter and Disposition Form**
    n) **Health Utilities Index Form**
    o) **The Unified Form (US sites only)**
    p) **Assigned Substudy Questionnaires (as necessary)**
    q) **Cost Substudy Form (as necessary)**
    r) **Drug Dispensing Form (as necessary)**
    s) **Event Forms (as necessary)**

D.2.2 Upon Receipt of All Central HbA1c Values Drawn

1. If Central Lab HbA1c is 7% - 7.9% at this visit or is 6.6 %–6.9% at this visit and Central HbA1c was $\geq$ 7% at previous visit, no action is required.
2. Contact the participant if no change was made at the previous visit and the HbA1c result measured at that visit returns > 7.9% or $\leq$ 6.5%.
3. If the Central Lab HbA1c was > 9%, optimize MNT **and** increase 1 agent by 1 dose increment **or** optimize MNT and add an agent if indicated.
4. If Central Lab HbA1c $\leq$ 6.5% at this visit or < 7% on two consecutive visits **and** if on insulin or a secretagogue or any symptomatic hypoglycemia or any SMBG level < 90 mg/dl (5 mmol/l), then reduce dose of (or discontinue) a glucose lowering drug. Otherwise, if Central HbA1c $\leq$ 6.5% or < 7% on two consecutive visits, and does not meet the aforementioned medication or hypoglycemia criteria, no action required.
5. If the baseline (i.e., initial) Central Lab HbA1c is 8% - 9%, optimize MNT **and** wait for month 4 Central Lab HbA1c before increasing therapy.
6. If any subsequent Central Lab HbA1c is 8% - 9%, optimize MNT or increase one agent by one dose increment or add an agent if indicated.
7. Update record of name and dose of **all** glucose-lowering medications on **Glycemia Medications Log** if action required for HbA1c. If on insulin, record name and dose on the **Standard Glycemia Management Form**.
8. Advise the participant to contact the site if he or she is experiencing >1 episode of symptomatic hypoglycemia/week.
9. Reconfirm next clinic appointment. Remind participant to fast prior to any clinic visit requiring a fasting lipid profile.
10. Complete the following form and enter data as required:
    a) **Standard Glycemia Management Form**
    b) **Glycemia Medications Log**
    c) **Severe Hypoglycemia Action Form (as necessary)**
    c) **Drug Dispensing Form (as necessary)**

D.2.2.a The participant may be contacted by phone in two weeks (0.5 months) to check progress and adherence to protocol. This contact is not required.

D.2.3 One, 2, 3, and 6 Month Visits

This visit should occur within +/- 2-week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain the weight, and record measurement in source documentation.
2. Collect all glycemia related information:
    a) Review the previous 2 weeks SMBG values in diary, download meter values to laptop and assess for medication/lifestyle adjustment in the glycemia intervention.
    b) Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section D.1.3.b, D.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action Form**) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug.

c) Record **current** medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form (at the 1 month visit only)**.

d) If any conditions in Box A apply, then reduce dose of (or discontinue) glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications
➢ HbA1c ≤ 6.5%

e) **If any necessary adjustments to glycemia medications were not made since receipt of baseline Central Lab HbA1c results, do so now according to HbA1c Value in section D.2.2.**

f) Advise the participant to contact the site if he or she is experiencing > 1 episode of hypoglycemia/week.

g) Recommend appropriate SMBG frequency according to Table D.1.3 (≤ 7 times/wk if on diet/oral therapy and ≤ 3 times/day if on insulin).

h) Assess comprehension/understanding of dietary counseling.
- Reinforce diet and exercise. Repeat at subsequent visits as necessary.

i) Adjust the glucose lowering study drugs (if necessary) and record name and dose of **all** current glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.

j) Provide SMBG logbooks and instructions in their completion.

4. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self-report of adherence in source documents.
   c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
   d) If the SBP is at the desired goal of < 120 mm Hg, maintain current therapy
   e) If the SBP ≥ 120 mm Hg, an upward dose titration or an additional drug (not already in use) should be added. Participants should be seen at monthly intervals until at goal.
   f) Record name, dose, and adherence of **all** blood pressure medications on the **Blood Pressure Medications Log.**
5. Remove label from study medication and place on **Drug Dispensing Form** then dispense study medication. Scan label bar code into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
6. Schedule the next clinic appointment.
7. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.

8. Complete the following forms and enter data as required:
   a) **Standard Glycemia Management Form**
   b) **Glycemia Medications Log**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   d) **Intensive Blood Pressure Management Form**
   e) **Blood Pressure Medications Log**
   f) **Encounter and Disposition Form**
   g) **Drug Dispensing Form (as necessary)**
   h) **Study Status Form (as necessary)**

D.2.4 Four and 8 Month Visit

The 4-month visit should occur within a +/- 1-week visit window. The 8-month visit should occur within a +/- 2-week window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. During the visit, the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the physical exam, including weight. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, Creatinine and ALT.
4. Collect all glycemia related information.
   a) Review the previous 2 months SMBG values in the diary and download meter values to laptop, and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section D.1.3.b, D.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action** Form) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
   c) Record **current** medications including name, dose, and participant self-report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Standard Glycemia Management Form**.

d) If any conditions in Box A apply, then reduce dose of (or discontinue) glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications
➢ HbA1c ≤ 6.5%

e) **If any necessary adjustments to glycemia medications were not made since receipt of Central Lab HbA1c results, do so now according to HbA1c Value in section D.2.2.**

f) Advise the participant to contact the clinical site if he or she is experiencing > 1 episode of symptomatic hypoglycemia /week.

g) Recommend appropriate SMBG frequency according to Table D.1.3 (≤ 7times/wk if on diet/oral therapy and ≤ 3 times/day if on insulin).

h) Instruct participants on when and how to self-titrate (if applicable).

i) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log.** If on insulin, record name and dose on **Standard Glycemia Management Form**.

j) Provide SMBG logbooks and instructions for their completion.

4. **This is a Milepost Visit.** Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self- report of adherence in source document.
   c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
   d) If the SBP is at the desired goal of < 120 mm Hg, maintain current or equivalent therapy.
   e) If the SBP ≥ 120 mm Hg, **you must add an additional drug class** (not already in use) as this is considered a milepost visit for evaluation of BP goals. If in the investigator's clinical judgement, an adjustment in the medication regimen is not possible, you must complete a **Milepost Blood Pressure Drug Exception Form** explaining the reason. Participants should be seen at monthly intervals until at goal.
   f) Instruct participants on actions to limit symptomatic orthostasis.
   i) Record name, and dose of **all** blood pressure medications dispensed on the **Blood Pressure Medications Log.**
5. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medications as necessary. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
6. Schedule a clinic appointment in 4 months. Remind participant to come fasting.

7. Remind participants to bring all their medications, glucose meter and SMBG records at next visit.
8. Complete the following forms and enter data as required:
   a) **Interval History and Follow-up**
   b) **Standard Glycemia Management Form**
   c) **Glycemia Medications Log**
   d) **Severe Hypoglycemia Action Form (as necessary)**
   e) **Intensive Blood Pressure Management Form**
   f) **Blood Pressure Medications Log**
   g) **Encounter and Disposition Form**
   h) **Event Forms (as necessary)**
   i) **Milepost Blood Pressure Drug Exception Form (as necessary)**
   j) **Drug Dispensing Form (as necessary)**
   k) **Cost Substudy Form (as necessary)**
   l) **Study Status Form (as necessary)**

D.2.5 Visits at Follow-up Months 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74,78, 82, 86, 90, and 94

These visits should occur within a +/- 2-week window. The participants will report to the clinic and the following procedures will be conducted:

1. Obtain weight, and record in source documentation.
2. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, section 9.2.3).
3. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self-report of adherence in source documents.
   c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
   d) If the SBP is at the desired goal of < 120 mm Hg, maintain current therapy
   e) If the SBP $\geq$ 120 mm Hg, an upward dose titration or an additional drug (not already in use) should be added. Participants should be seen at monthly intervals until at goal.
   f) Record name, dose, and adherence of **all** blood pressure medications on the **Blood Pressure Medications Log.**

4. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
5. Schedule the next clinic appointment. Remind participant to fast prior to any clinic visit requiring a fasting lipid profile.
6. Remind participant to take blood pressure medications the morning of next visit.
7. Complete the following forms and enter data as required:
   a) **Intensive Blood Pressure Management Form**
   b) **Blood Pressure Medication Log**
   c) **Encounter and Disposition Form**
   d) **Drug Dispensing Form (as necessary)**
   e) **Study Status Form (as necessary)**

D.2.6 Annual Visits (12, 24, 36, 48, 60, 72, 84, and 96 Months)

This visit should occur within a +/- 2-week visit window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia or lipid (if applicable) medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Review and update Contact Information.
2. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
3. Perform the Annual Physical Exam, including weight, height, waist circumference, visual acuity, foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3.).
4. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium (**12 month, prn, and exit visits**), Creatinine, Lipid Profile, ALT, and CPK. **(Blood samples for storage of additional aliquots, where approved, should occur at the 24-month, 48-month 72-month and 96-month visits).**
5. Review the Concomitant Medications Inventory list located in the **Annual Follow-up and Physical Exam Form** with participant to document all non-study medications currently taking.

6. Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completes all items before end of visit **(12-month and 36-month visits).**
7. **A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Lab every 2 years for the 24-month, 48-month, 72-month and 96-month visits.**
8. **An ECG will be obtained and transmitted to the ACCORD ECG Reading Center every 2 years for the 24-month, 48-month, 72-month and 96-month visits.** Retain a copy for participant's research records.
9. Collect all glycemia related information:
   a) Review the previous 4 months SMBG values in diary, download meter values to laptop, and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Complete **Standard Glycemia Management Form**. Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section D.1.3.b, D.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action Form**) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
   c) Record **current** medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   d) If any conditions in Box A apply, then reduce dose of (or discontinue) glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications
➢ HbA1c ≤ 6.5%

   e) **If any necessary adjustments to glycemia medications were not made since receipt of Central Lab HbA1c results, do so now according to HbA1c Value in section D.2.2.**
   f) Advise participant to contact the clinical site if he or she is experiencing > 1 episode of symptomatic hypoglycemia /week.
   g) Recommend appropriate SMBG frequency according to Table D.1.3 (≤ 7 times/wk if on diet/oral therapy and ≤ 3 times/day if on insulin).
   h) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medication Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   i) Provide SMBG logbooks and instructions for their completion.
   l) Update the **Unified Form** to ensure a smooth and steady flow of diabetic testing supplies being shipped by NetGroup Diabetic Services (**US sites only**).
10. **This is a Milepost Visit.** Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not

taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.

b) Record current medications, dose and self- report of adherence.
c) Using the appropriate technique for the Omron device (See MOP Chapter 9, Section 9.2.3) obtain and evaluate blood pressure values.
d) If the SBP is at the desired goal of < 120 mm Hg, maintain current or equivalent therapy.
e) If the SBP ≥ 120 mmHg, **you must add an additional drug class** (not already in use) as this is considered a milepost visit for evaluation of BP goals. If in the investigator's clinical judgement, an adjustment in the medication regimen is not possible, you must complete a **Milepost Blood Pressure Drug Exception Form** explaining the reason. Participants should be seen at monthly intervals until at goal.
f) Instruct participants on actions to limit symptomatic orthostasis.
g) Record name, and dose of **all** blood pressure medications dispensed on the **Blood Pressure Medications Log.**

11. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after visit so that adequate inventory can be maintained at the clinical site
12. Participants assigned in the substudies (Health Related Quality of Life (HRQL), Physical Activity, Diet) will complete the appropriate questionnaires (**at 12-month, 36-month and exit visits only**). Verify that the participant completes all items before end of visit. Complete **Cost Substudy Form** for participants in the Cost Substudy.
13. Schedule follow-up clinic appointment in 2 months.
14. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
15. Complete the following forms and enter data as required:
    a) **Participant Contact Information Form (update as necessary)**
    b) **Annual History and Follow-up Form**
    c) **Standard Glycemia Management Form**
    d) **Glycemia Medications Log**
    e) **Severe Hypoglycemia Action Form (as necessary)**
    f) **Intensive Blood Pressure Management Form**
    g) **Blood Pressure Medications Log**
    h) **Encounter and Disposition Form**
    i) **Health Utilities Index Form (12-month, 36-month visits only)**
    j) **The Unified Form**
    k) **Visual Acuity Worksheet**
    l) **Ophthalmology Exam Form (as necessary)**
    m) **Assigned Substudy Questionnaires (as necessary at 12-month, 36-month visits only).**
    n) **Milepost Blood Pressure Drug Exception Form (as necessary)**
    o) **Drug Dispensing Form (as necessary)**
    p) **Cost Substudy Form (as necessary)**
    q) **Study Status Form (as necessary)**

D.2.7 Visits at Follow-up Months 16, 20, 28, 32, 40, 44, 52, 64, 68, 76, 80, 88, 92

This visit should occur within a +/- 4-week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon Completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the exam, including weight. Using appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c.
4. Collect all glycemia related information.
   a) Review the previous 4 months SMBG values in diary, download meter values to laptop and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Complete **Standard Glycemia Management Form**. Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section D.1.3.b, D.1.3.c and MOP Chapter 8, Section 8.4.4).. If any severe hypoglycemia (fill out **Severe Hypoglycemia Action** Form) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
   c) Record **current** medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   d) If any conditions in Box A apply, then reduce dose of (or discontinue) glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications
➢ HbA1c ≤ 6.5%

   e) **If any necessary adjustments to glycemia medications were not made since receipt of Central Lab HbA1c results, do so now according to HbA1c Value in section D.2.2.**
   f) Advise participant to contact the clinical site if he or she is experiencing > 1 episode of symptomatic hypoglycemia /week.
   g) Recommend appropriate SMBG frequency according to Table D.1.3 (≤ 7 times/wk if on diet/oral therapy and ≤ 3 times/day if on insulin).

h) Adjust the glucose-lowering study drug as needed and record name and dose of **all** glycemia medications on the **Glycemia Medication Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
i) Provide SMBG logbooks and instructions for their completion.

5. **This is a Milepost Visit for the 16-month and the 20-month visit.** Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self- report of adherence.
   c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
   d) If the SBP is at the desired goal of < 120 mm Hg, maintain current or equivalent therapy.
   e) If the SBP ≥ 120 mm Hg, **you must add an additional drug class** (not already in use) as this is considered a milepost visit for evaluation of BP goals for the **16-month and the 20-month visit**. If in the investigator's clinical judgement, an adjustment in the medication regimen is not possible, you must complete a **Milepost Blood Pressure Exception Form** explaining the reason.
   f) If the SBP ≥ 120 mm Hg for all the other visits, an upward dose titration or an additional drug (not already in use) should be added. Participants should be seen at monthly intervals until at goal.
   g) Instruct participants on actions to limit symptomatic orthostasis.
   h) Record name, and dose of all blood pressure medications dispensed on the **Blood Pressure Medications Log.**
6. Remove labels from study medication and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after visit so that adequate inventory can be maintained at the clinical site.
7. Complete **Cost Substudy Form** for participants in the Cost Substudy.
8. Schedule a clinic appointment in 4 months. Remind participant to fast prior to any clinic visit requiring a fasting lipid profile.
9. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
10. Complete the following forms and enter data as required.
    a) **Interval History and Follow-up Form**
    b) **Standard Glycemia Management Form**
    c) **Glycemia Medications Log**
    d) **Severe Hypoglycemia Action Form (as necessary)**
    e) **Intensive Blood Pressure Management Form**
    f) **Blood Pressure Medications Log**
    g) **Encounter Disposition Form**
    h) **Preliminary Event Notification Form (as necessary)**
    i) **Event Forms (as necessary)**

j) **Milepost Blood Pressure Drug Exception Form (as necessary for the 16-month and 20 month visit)**
k) **Drug Dispensing Form (as necessary)**
l) **Cost Substudy Form (as necessary)**
j) **Study Status Form (as necessary)**

D.2.8 Exit Visit

This visit should occur within a +/- 4-week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the exam, including weight. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, ALT, Creatinine, Lipid Profile, CPK and for storage of additional aliquots (where approved).
4. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Lab.
5. An ECG will be obtained and transmitted to the ACCORD ECG Reading Center. Retain a copy for records.
6. Collect all glycemia related information.
   a) Review the previous 4 months SMBG values in diary, download meter values to laptop and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section D.1.3.b, D.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action Form)** or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
   c) Record current medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
7. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.

b) Record current medications, dose and self- report of adherence.
c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
d) Record name, and dose of all blood pressure medications dispensed on the **Blood Pressure Medications Log.**

8. Participants will be prescribed appropriate non-study antihyperglycemia therapy and antihypertensive therapy based on their current status and post-trial follow-up care will be arranged.
9. Complete the following forms and enter data as required.
    a) **Annual History and Follow-up Form**
    b) **Glycemia Medications Log**
    c) **Standard Glycemia Management Form**
    d) **Severe Hypoglycemia Action Form (as necessary)**
    e) **Intensive Blood Pressure Management Form**
    f) **Blood Pressure Medications Log**
    e) **Encounter Disposition Form**
    f) **Preliminary Event Notification Form (as necessary)**
    g) **Event Forms (as necessary)**
    h) **Drug Dispensing Form (as necessary)**
    i) **Cost Substudy Form (as necessary)**
    j) **Study Status Form (as necessary)**

Figure D.4:
Treatment Group Algorithm for Standard Glycemia Therapy Group (Goal: HbA1c 7% to

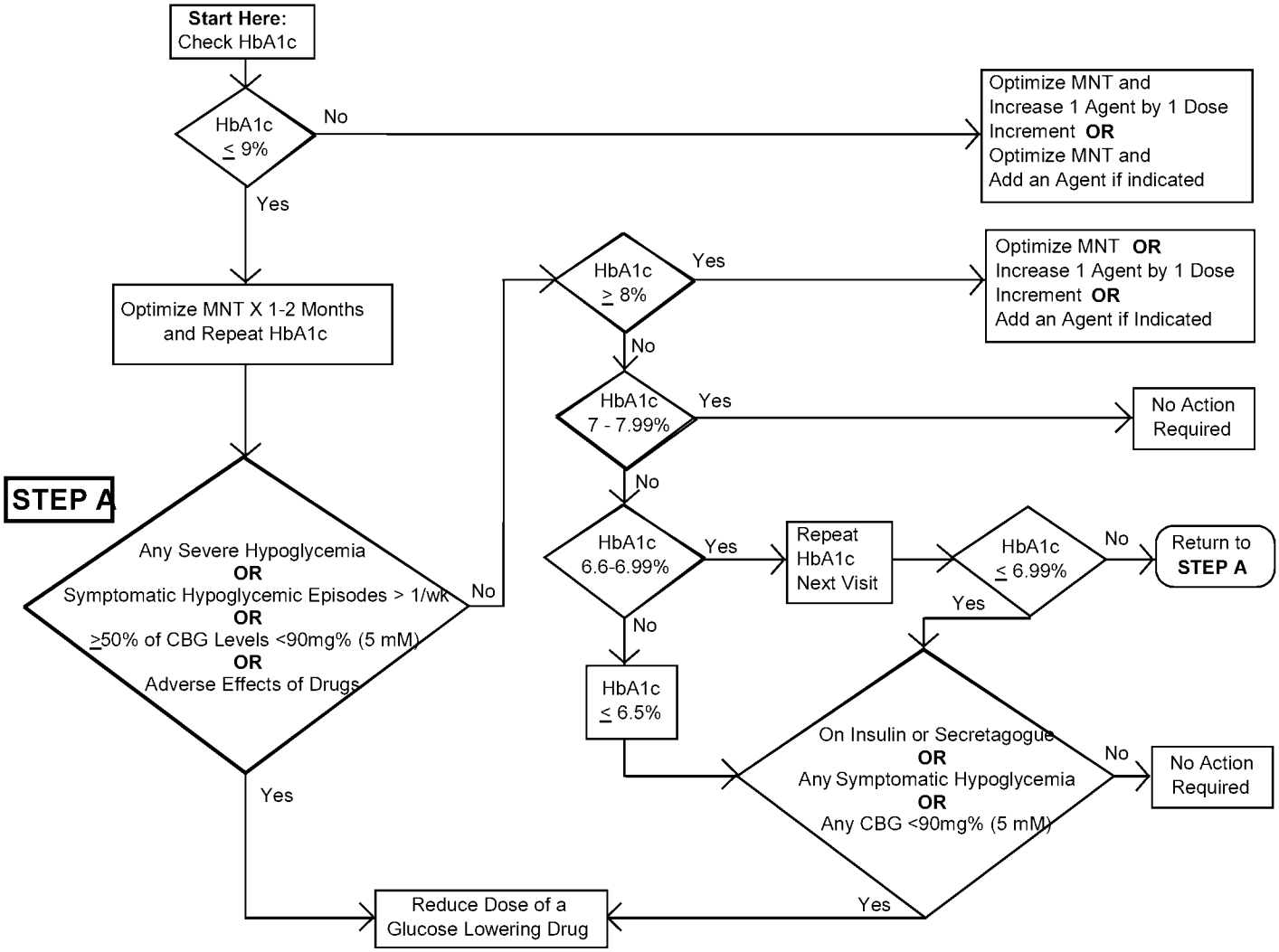
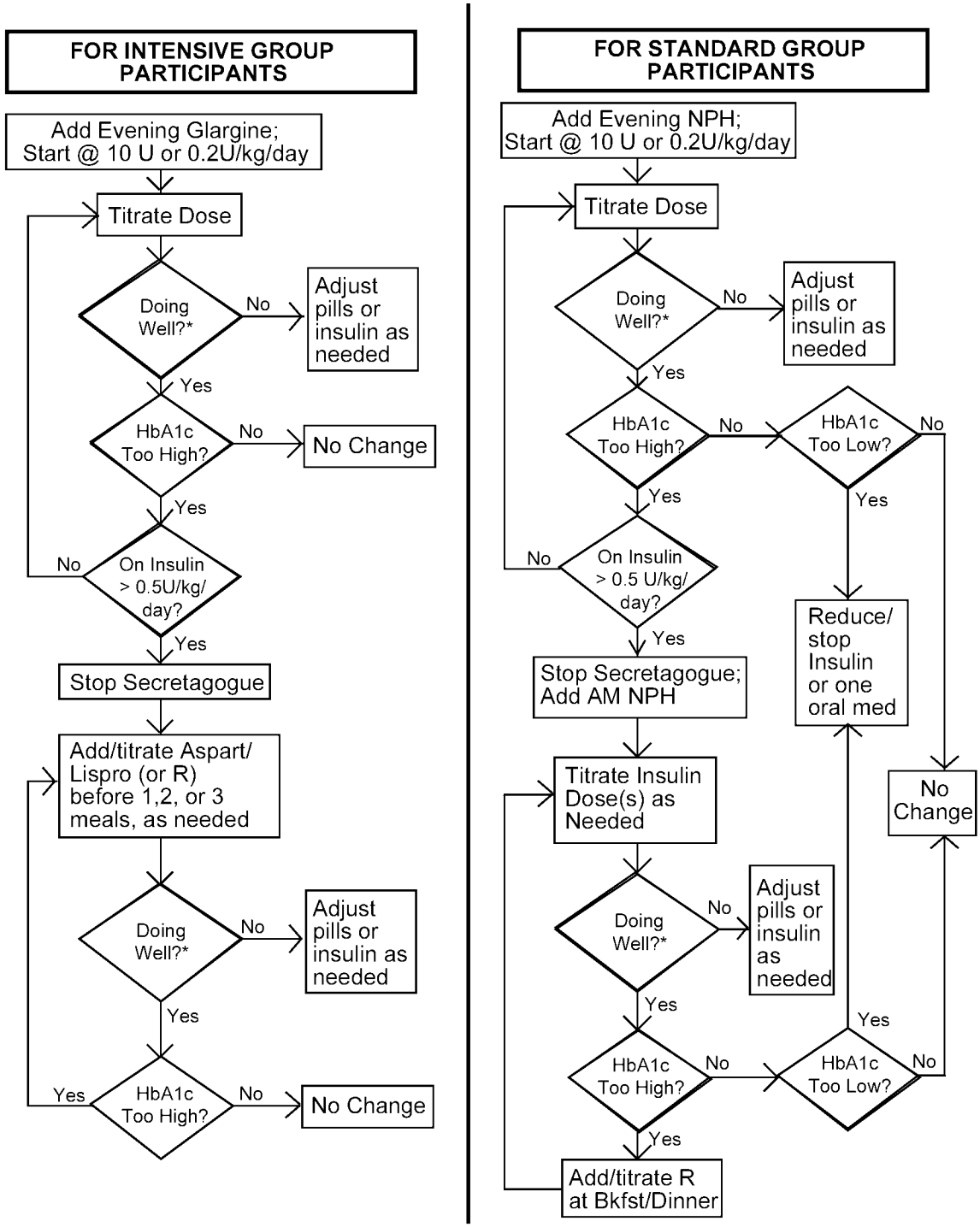


Figure 3.3:
Use of Insulin for Participants On Maximal Oral Therapy



*Doing well: no severe hypoglycemic or adverse event or no reason to reduce therapy (as described in Figure 3.2)

Thiazolidinedione Drugs (e.g. Avandia or Rosiglitazone)

ACTIONS of THIAZOLIDINEDIONES

The drug Avandia (rosiglitazone) belongs to a group of medications called thiazolidinediones (or glitazones or TZD's), and may be supplied as part of the ACCORD trial. Actos (pioglitazone) is another drug that belongs in this group. These drugs lower the blood glucose by reducing the body's resistance to the action of insulin (i.e. making your own insulin work more effectively). They can be used alone or can be combined with other diabetes pills or insulin.

COMMON SIDE EFFECTS

1. Hypoglycemia (low blood sugar)

These drugs can lead to hypoglycemia. When taken alone, the risk of hypoglycemia is low. When taken with insulin or other pills, the risk of hypoglycemia is higher.

If you do experience symptoms of a low blood sugar (such as lightheadedness, sweating, nervousness, hunger, a sensation of a racing heart, headache, or sudden fatigueat unusual times), check your blood sugar. If the level is less than 70 mg/dl (3.9 mmol/l) you may be suffering from hypoglycemia. If so, drink 4 ounces of juice or regular soda or eight ounces of milk or have three glucose tablets or five Life Savers (i.e. 15 grams of carbohydrate). Recheck your blood sugar in 15 minutes to make sure it has risen to at least 90 mg/dl (5.0 mmol/L). If low blood sugar reactions are frequent, severe or unexpected, call your doctor.

2. Weight Gain

These drugs may lead to weight gain. Weight gain is due to the lowering of blood sugar by insulin and drugs that act like insulin. This reduces the amount of sugar lost in the urine and helps the body store extra energy in fat cells. Sometimes, weight gain may be due to some fluid retention. Regardless of the cause, the amount of weight gained or lost depends on the level of physical activity and diet, or can be due to other drugs that are being taken. For example, some people gain more weight if insulin is also being taken. To minimize weight gain or to cause weight loss, exercise regularly, eat low fat foods, avoid extra snacks and large portions.

3. Fluid Retention

These drugs may lead to fluid retention. Fluid retention is generally mild with some swelling in the ankle or leg or bloating; it may be more pronounced when these drugs are used together with insulin, and rarely, the fluid retention can be severe or even life threatening. If you develop major leg swelling or especially shortness of breath either with activity or at rest, see your doctor as soon as possible. Reducing the dose, adding diuretics (water pills) or adjusting other medications (such as blood pressure pills, calcium channel blockers, non-steroidal anti-inflammatory drugs or arthritis pills) can also be used to manage this problem. ***You and your doctor should pay close attention to fluid retention if you take insulin or have heart failure or other heart problems.***

POTENTIAL SIDE EFFECTS

Because of rare cases of severe liver disease with a related medicine that is no longer available (Rezulin or troglitazone), you must have your blood drawn for liver enzyme tests (ALT) when treated with these drugs every 2 months for the first year of treatment and intermittently thereafter. If you develop persistent nausea, vomiting, belly pain, fatigue, loss of appetite, dark

urine, yellowing of the eyes or skin while treated with this drug, stop the medication and see your doctor for a blood draw within a few days.

DOSING

Avandia (rosiglitazone) can be taken once a day, but may work a bit better if taken twice daily. Actos (pioglitazone) can be taken any time of the day. Both drugs can be taken either with or without food. It may take 12 weeks to see the full effect of a dose.

7. Visit Schedule of Study Activities by Randomization Cell

E. Standard Glycemia and Standard Blood Pressure

E.1. Overview

One of the key aims of the ACCORD study is to determine if a therapeutic strategy that targets a HbA1c of < 6.0% reduces the rate of cardiovascular disease (CVD) events more than a strategy that targets a HbA1c of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%) in high risk middle-aged or older people with type 2 diabetes. The approaches used to implement these targets, suggested algorithms for the use of pharmacologic agents and follow-up schedules are described in MOP Chapters 5 and 6. Details regarding the implementation of the protocol for the Standard Glycemia and Lipid Trial groups are described below.

The ACCORD blood pressure (BP) trial component is designed to test whether a therapeutic strategy that targets a systolic blood pressure (SBP) of < 120 mm Hg reduces the rate of cardiovascular events in a middle-aged or older type 2 diabetic population at high risk for cardiovascular events compared to a strategy that targets a SBP of < 140 mm Hg in the context of good glycemic control. Details regarding the implementation of the protocol for the intensive glycemia and standard blood pressure control groups are described below.

E.1.1 Algorithms for Standard Glycemic and Intensive Blood Pressure Control; Choice of Agents

Figures E.4 and E.5 at the end of this chapter are suggested algorithms to guide changes in glycemic therapy for the standard group. The exact changes to be made whenever glycemic therapy needs to be intensified on the basis of the HbA1c or the SMBG results will be determined by the individual site using the figures as guides.

The algorithm for the standard BP group calls for an assessment of the participants' antihypertensive medication regimen at baseline to determine the starting point on the decision tree for future monitoring and medication adjustments needed to achieve their assigned SBP goal (< 140 mmHg) (Refer to Figure E.7 at the end of this chapter).

E.1.2 Targets and Action Required Levels

E.1.2.a) Standard Glycemic Control

Table E.1.2 outlines the glycemic target for the standard group, which is identical to Table 3.1 in the protocol.

Table E.1.2: Glycemic Targets and Thresholds for Action for ACCORD			
Group	HbA1c Targets	"Action Required" Threshold	
		HbA1c	> 50% of SMBG Results/4 days
Standard Therapy	7 – 7.9%	> 7.9%* or ≤ 6.5%[#] (anytime) or 6.6%-6.9% [#] (twice consecutively)	fasting/ac < 90 mg/dl (5.0 mmol/l)[#]

pc: postcibal; ac: antecibal; SMBG: self monitoring of blood glucose;
*antihyperglycemic therapy will be advanced if either the HbA1c or the SMBG "action required" criteria are met at any participant encounter [#] therapy with drugs that increase the risk of hypoglycemia (e.g. insulin, sulfonylureas, meglitinides) will be reduced to avoid hypoglycemia if these criteria are met.

E.1.2.b) Standard Blood Pressure Control

Participants randomized to the standard blood pressure control will have a SBP goal of < 140 mm Hg. The BP intervention will begin at the randomization visit. The investigator may choose from among the available ACCORD agents or select another as determined appropriate. It is recommended that the regimen include a drug class associated with reduced cardiovascular events in diabetes (ACE-inhibitor, beta-blocker, calcium channel blocker or diuretic). (Refer to Drug Availability List – MOP Chapter 5)

E.1.3.a) Adjusting Glycemic Therapy

As noted in the following table (E.1.3), a range of approaches will be used to target the HbA1c level shown in Table E.1.2.

TableE.1.3 Achieving Glycemic Goals	
	Standard Group
Visits (1 and 4 months)	Month 1 and 4 mo
Visits (> 4 months)	Q 4 mo
Phone contact	Participant initiated (prn)
Supplemental contact	Severe hypoglycemia/hyperglycemia HbA1c in action required range Frequent (>50%/4 days) premeal SMBG levels <90 mg/dl (5.0 mmol/l)
Point of Care HbA1c	Optional
Routine use of postprandial SMBG values to guide therapy	No
SMBG freq.[a] (not on insulin)	≤7/wk (daily at different times or >1/day on certain days)
SMBG freq.[a] (on insulin)	≤3/day
Self titration principles	Avoid severe hypoglycemia and premeal SMBG levels < 90 mg/dl (5.0 mmol/l)

Initial Minimum Rx	Diet/lifestyle
Insulin Use (when needed)	Generally ≤ 2 injections/day

[a]less frequent if goals are achieved; [b] including avoiding SMBG levels < 70 mg/dl (3.9 mmol/l) on > 1/4 of the readings

E.1.3.b) Glycemia Safety Issues/ Adjusting Therapy for Hypoglycemia

Hypoglycemic events may occur in individuals in either the intensive or standard group. Severe hypoglycemia is unusual in people with type 2 diabetes (even when normoglycemia is targeted). Mild episodes of hypoglycemia are, however, likely to occur.

All participants will be instructed to check their glucose levels regularly as described in the protocol. They will also be taught how to recognize and self-treat hypoglycemia and will be instructed to keep glucose available at all times (as tablets). Moreover, any participant who has had an episode of severe hypoglycemia will be provided with glucagon and they and any cohabiting partner will be taught how to administer it.

Severe hypoglycemia is defined as any episode of loss of consciousness/seizure or documented hypoglycemia (glucose < 50 mg/dl or 2.8 mmol/l) that also requires hospitalization or treatment by emergency personnel. If this occurs:

- Complete **Severe Hypoglycemia Action Form**. (See MOP Chapter 8, Section 8.4.4 for more details).
- For participants in either group who have an episode of severe hypoglycemia, adjust glycemic targets to achieve a fasting and 2 hour glucose (postprandial) of 100 – 140 mg/dl (5.5 – 7.8 mmol/l) and < 180 mg/dl (10 mmol/l) respectively, and a HbA1c of 7.0% - 7.9% for at least 4 weeks.
- Ensure that a complete medical assessment by the physician is completed to identify other potential causes (e.g. pituitary or adrenal insufficiency)
- Ensure that the physician reassesses the glycemic goals at subsequent visits.
- Ensure that participant has received glucagon and that the participant and cohabitant know how to administer it.
- Have telephone contact with the participant before the next visit to assess blood glucose records and freedom from hypoglycemia.

Minor hypoglycemia is defined as self-reported transient symptoms such as lightheadedness, tremor, shaking, sweating, tingling, blurry vision, trouble concentrating etc., that are self-treated by ingestion of carbohydrates and resolve on their own (See MOP Chapter 6, Section 6.1.6). All participants will be asked to note such episodes in their glucose logbooks and to confirm them with a blood glucose reading whenever possible. The estimated frequency (of confirmed and suspected minor hypoglycemia) will be recorded at every visit.

E.1.3.c) Self Treatment of Hypoglycemia

1. If the glucose value is < 50-70 mg/dl (3.9 mmol/l), it should be treated by ingestion of 15 grams of CHO (e.g. 3-4 glucose tablets, 5 Lifesavers, 4-6 oz. of a regular – (nondiet) – soft drink, or 8 oz. low fat milk);
2. If the glucose value is < 50 mg/dl (2.8 mmol/l), it should be treated by ingestion of 20-30 grams of CHO (e.g. 6-8 glucose tablets);
3. Blood glucose should be self-tested 15-20 minutes after therapy and therapy repeated if the level is still low (as above)
4. If no meal will be eaten within 1-2 hours, a mixed nutrient snack, including CHO, protein, and fat should be ingested right after the initial therapy to prevent another episode
5. If the glucose value is low or there is significant cognitive or motor impairment, individuals should treat and re-test glucose value. The glucose value should be > 70 mg/dl (3.9 mmol/l) before driving a car or operating heavy machinery.

E.1.3.d) Education and Minimization of Hypoglycemia in Participants

Hypoglycemia is an inherent risk in the treatment of diabetes. It is important to inform participants of the signs and symptoms of hypoglycemia, techniques to minimize the risk and appropriate methods of treatment. Several tools are available for use in educating participants:

1. Hypoglycemia Cartoon
2. Participant Wallet Card
3. Primer on Hypoglycemia
4. Participant Newsletters

All participants must be provided with the written material listed above at the beginning of the study. Study staff should review verbally the signs and symptoms with the participant and family members. Participants and their families should be encouraged to review the hypoglycemic video either in the clinic or at home. Both participants and family members should be educated on the appropriate treatment for symptoms, and provided with glucose tablets. Those participants suffering one severe hypoglycemic event should be provided with a glucagon kit and both the participant and the family member taught how to use it. This material must be reviewed annually with all participants and after every reported hypoglycemic event.

E.1.3.e) Safety Issues for Thiazolidinedione (TZD) Drugs

For participants on TZD (e.g. Avandia or Rosiglitazone), check for the presence of edema at every visit and obtain a Central Lab ALT every 2 months for the first year of treatment and annually thereafter.

As TZDs are contraindicated in people with stage 3 or 4 heart failure, if a participant who is taking a TZD does develop heart failure, the TZD should be stopped and the heart failure treated and investigated. Depending on the results of these

investigations the investigator may reconsider cautiously reinstituting TZD therapy if the heart failure resolves, and was judged to have not been directly cause by the TZD alone.

A handout to give to the participants at the discretion of the site concerning TZD use is available and can be found on page 24 at the end of this chapter.

E.1.3.f) Adjusting Antihypertensive Therapy

The participants' BP should be monitored at each protocol-scheduled visit. It is strongly encouraged that a diuretic be the drug of choice for initial therapy or be a component of any multi-drug antihypertensive regimen. The standard participants' blood pressure will be measured and assessed for progress toward the goal (SBP < 140 mm Hg). Should the SBP fall under 130 mm Hg at a single visit, or under 135 mm Hg on two consecutive visits, step-down therapy (a reduction of dose or number of antihypertensive drugs) is indicated at the discretion of the ACCORD therapist, after consultation with the participant. However, if the SBP $\geq$ 160 mm Hg at a single visit or $\geq$ 140 mm Hg on two consecutive visits, upward dose titration or an additional drug (not already in use) must be added. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg. If the SBP is 130-139 mm Hg at a single visit or 135 –139 mm Hg for 2 consecutive visits, one should continue therapy and monitor as prescribed by the protocol.

E.2 Standard Glycemic and Standard BP Procedures

E.2.1 Baseline – Randomization Visit

The participants will be instructed to attend the clinic following an overnight fast (since ~10 pm the previous evening). They should not take their glycemia or lipid (if applicable) medications on the morning of this clinic visit but be instructed to bring their medications, glucose meter SMBG records, and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. All data collected during the screening process will be reviewed.
2. Verify eligibility status for the Glycemia, Blood Pressure and Lipid Trials (including occurrence of events that may prohibit patient from participating).
   a) Review current medications including OTC, herbal remedies and vitamins.
   b) Review, evaluate and calculate the percentage of participant's compliance with at least 2 weeks of SMBG monitoring as part of the run-in procedures.
   c) Assure that the qualifying HbA1c value was obtained within the last 3 months prior to the randomization date.
3. If ineligible, the participant will be thanked for their time and dismissed from the clinic.
4. If eligible, proceed with randomization process:
   a) Verify that a full-scale consent form has been obtained and signed.

b) Obtain and perform baseline history and physical exam, including demographics, medical history concomitant medications, weight, height, and waist circumference, visual acuity, and foot exam. Using the appropriate technique for the Omron device obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
c) Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completes all items before end of visit.
d) Verify that all information on the **Inclusion/Exclusion Summary Form, the Blood Pressure Screening Form,** and **the Lipid Trial Screening Form** is complete and correct both on the forms and in the computer.
e) Click "Randomize pt" on data entry screen.
f) Input the percent of participant's report of compliance for SMBG.
g) Verify that the **Baseline History and Physical Exam Form** has been completed.

5. The participant will be assigned a treatment regimen. The randomization screen will display this information and list target dates for the follow-up visits. It is recommended that the participant's treatment assignment and visit schedule be printed out and filed in their research record.
6. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, ALT, Creatinine, Lipid Profile, CPK and for storage of additional aliquots (where approved).
7. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Laboratory.
8. An ECG will be obtained and transmitted to the ACCORD ECG Reading Center. Retain a copy for the participant's research record.
9. Collect all glycemic related information:
   a) Review screening blood glucose diary, download SMBG meter values to laptop and assess blood glucose values for implementation of the glycemia intervention.
   b) Complete **Standard Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia in source documents. Review symptoms and therapy for hypoglycemia (See Section E.1.3.b, E.1.3.c and MOP Chapter 8, Section 8.4.4).
   c) Record current glycemic medications including name, dose and participant's self report of adherence in the source document. Record current glycemia medications on the **Baseline History and Physical Exam Form** only by class of medication.
   d) Record name and dose of all **current** (at visit entry) oral glycemia medications on the **Glycemia Medications Log.** If on insulin, record name and dose on the **Standard Glycemia Management Form**.
   e) Conduct nutrition assessment and plan.
   f) Instruct participants on their diet, foot care and exercise program and the relationship of medications with nutrition and exercise.
   g) Reinforce proper SMBG technique and instruct participant to test per instructions on MOP Table E.1.3 ($\leq$ 7/wk (daily at different times or > 1/day on certain days) if diet/oral therapy and $\leq$ 3/day if on insulin).
   h) Provide SMBG logbooks and instructions for their completion.
   i) Dispense glucose meter if necessary.
   j) Provide sufficient strips through to the next visit to the participant.

k) Fill out the **Unified Form** to ensure a smooth and steady flow of diabetic testing supplies being shipped by NetGroup Diabetic Services (**US sites only**).

l) **At baseline continue glycemia therapy that participants were regularly or routinely taking prior to the ACCORD Study.** Convert all glucose lowering medications to equivalent study provided medications.

1. If any of the conditions in Box A apply, then reduce dose of a glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications

2. Upon receipt of Central Lab HbA1c values, refer to MOP section E.2.2 in this chapter.

m) Record name and dose of **all** glycemia medications participant was prescribed at visit exit on the **Glycemia Medications Log.** If on insulin, record name and dose on the **Standard Glycemia Management Form**.

10. Collect all blood pressure related information:
    a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
    b) Record current BP medications on the **Baseline History and Physical Exam Form** only by class of medication.
    c) Using appropriate technique with the Omron device, obtain and evaluate blood pressure values (See Mop Chapter 9, Section 9.2.3).
    d) If the SBP is 131- 160 mm Hg, maintain current or equivalent therapy.
    e) If SBP ≥ 160 mm Hg at this visit titrate or add therapy not already in use. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg.
    f) If SBP < 130 mm Hg at this visit, consider stepping down BP therapy.
11. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
12. Participants assigned in the substudies (Health Related Quality of Life (HRQL), Physical Activity, Diet) will complete the appropriate questionnaires. Verify that the participant completes all items before end of visit. Complete **Cost Substudy Form** for participants in the Cost Substudy.
13. Schedule a clinic appointment in 1 month.
14. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
15. Collect all related Lifestyle and Background information:
    d) Assess smoking status. Follow guidelines (if necessary) in MOP Chapter 4, section 4.3.1 for smoking cessation activities.

e) Assess aspirin use. Recommend aspirin therapy in accordance with guidelines in chapter 4, section 4.3.2.

16. Contact primary care provider as necessary.
17. Obtain a release of information form in case of need for subsequent events.
18. Complete the following forms and enter data as required:
    a) **Inclusion/Exclusion Summary Form**
    b) **Blood Pressure Trial Screening Form**
    c) **Lipid Trial Screening Form**
    d) **Participant Contact Information Form (if not previously completed)**
    e) **Visual Acuity Worksheet**
    f) **Ophthalmology Exam Form (as necessary)**
    g) **Baseline History and Physical Exam Form**
    h) **Standard Glycemia Management Form**
    i) **Glycemia Medications Log**
    j) **Severe Hypoglycemia Action Form (as necessary)**
    k) **Standard Blood Pressure Management Form**
    l) **Blood Pressure Medications Log**
    m) **Encounter and Disposition Form**
    n) **Health Utilities Index Form**
    o) **The Unified Form (US Sites only)**
    p) **Assigned Substudy Questionnaires (as necessary)**
    q) **Cost Substudy Form (as necessary)**
    r) **Drug Dispensing Form (as necessary)**
    s) **Event Forms (as necessary)**

E.2.2 Upon Receipt of All Central HbA1c Values Drawn

1. If Central Lab HbA1c is 7% - 7.9% at this visit or is 6.6 %–6.9% at this visit and Central HbA1c was $\geq$ 7% at previous visit, no action is required.
2. Contact the participant if no change was made at the previous visit and the HbA1c result measured at that visit returns > 7.9% or $\leq$ 6.5%.
3. If the Central Lab HbA1c was > 9%, optimize MNT **and** increase 1 agent by 1 dose increment **or** optimize MNT and add an agent if indicated.
4. If Central Lab HbA1c $\leq$ 6.5% at this visit or < 7% on two consecutive visits **and** if on insulin or a secretagogue or any symptomatic hypoglycemia or any SMBG level < 90 mg/dl (5 mmol/l), then reduce dose of (or discontinue) a glucose lowering drug. Otherwise, if Central HbA1c $\leq$ 6.5% or < 7% on two consecutive visits, and does not meet the aforementioned medication or hypoglycemia criteria, no action required.
5. If the baseline (i.e., initial) Central Lab HbA1c is 8% - 9%, optimize MNT **and** wait for month 4 Central Lab HbA1c before increasing therapy.
6. If any subsequent Central Lab HbA1c is 8% - 9%, optimize MNT or increase one agent by one dose increment or add an agent if indicated.
7. Update record of name and dose of **all** glucose-lowering medications on **Glycemia Medications Log** if action required for HbA1c. If on insulin, record name and dose on the **Standard Glycemia Management Form**.

8. Advise the participant to contact the site if he or she is experiencing >1 episode of symptomatic hypoglycemia/week.
9. Reconfirm next clinic appointment. Remind participant to fast prior to any clinic visit requiring a fasting lipid profile.
10. Complete the following form and enter data as required:
    a) **Standard Glycemia Management Form**
    b) **Glycemia Medications Log**
    c) **Severe Hypoglycemia Action Form (as necessary)**
    d) **Drug Dispensing Form (as necessary)**

E.2.2.a The participant may be contacted by phone in two weeks (0.5 months) to check progress and adherence to protocol. This contact is not required.

E.2.3 One-Month Visit

This visit should occur within +/- 1-week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain the weight, and record measurement in source documentation.
2. Collect all glycemia related information:
    a) Review the previous 2 weeks SMBG values in diary, download meter values to laptop and assess for medication/lifestyle adjustment in the glycemia intervention.
    b) Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section E.1.3.b, E.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action Form**) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug.
    c) Record **current** medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
    d) If any conditions in Box A apply, then reduce dose or discontinue glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications
➢ HbA1c ≤ 6.5%

    e) **If any necessary adjustments to glycemia medications were not made since receipt of baseline Central Lab HbA1c results, do so now according to the HbA1c value in section E.2.2.**
    f) Advise the participant to contact the site if he or she is experiencing > 1 episode of hypoglycemia/week.
    g) Recommend appropriate SMBG frequency according to Table E.1.3 (≤ 7 times/wk if on diet/oral therapy and ≤ 3 times/day if on insulin).
    h) Assess comprehension/understanding of dietary counseling.

- Reinforce diet and exercise. Repeat at subsequent visits as necessary.

i) Adjust the glucose lowering study drugs (if necessary) and record name and dose of **all** current glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
j) Provide SMBG logbooks and instructions in their completion.

4. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self-report of adherence.
   c) Using the appropriate technique for the Omron device, obtain and evaluate blood pressure values (See MOP Chapter 9, Section 9.2.3).
   d) If the SBP is 130 –139 mm Hg at this visit and was > 135 mm Hg at previous visit, maintain current therapy.
   e) If the SBP < 130 mm Hg at this visit or < 135 mm Hg on 2 consecutive visits, step down therapy is indicated.
   f) If SBP is ≥ 160 mm Hg at this visit or ≥140 mm Hg on 2 consecutive visits, an upward dose titration or an additional drug (not already in use) must be added. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg.
   g) Complete **Standard Blood Pressure Management Form**
   h) Record name, dose, and adherence of **all** blood pressure medications on the **Blood Pressure Medications Log.**
5. Remove label from study medication and place on **Drug Dispensing Form** then dispense study medication. Scan label bar code into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
6. Schedule a 4-month clinic appointment. Remind the participant to come fasting.
7. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
8. Complete the following forms and enter data as required:
   a) **Standard Glycemia Management Form**
   b) **Glycemia Medications Log**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   d) **Standard Blood Pressure Management Form**
   e) **Blood Pressure Medications Log**
   f) **Encounter and Disposition Form**
   g) **Drug Dispensing Form (as necessary)**
   f) **Study Status Form (as necessary)**

E.2.4 Four and 8 Month Visit

These visits should occur within a +/- 2-week visit window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia or lipid (if applicable) medications on the

morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the physical exam, including weight. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, Creatinine, and ALT.
4. Collect all glycemia related information.
   a) Review the previous 2 months SMBG values in the diary and download meter values to laptop, and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section E.1.3.b, E.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action** Form) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
   c) Record **current** medications including name, dose, and participant self-report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Standard Glycemia Management Form**.
   d) If any conditions in Box A apply, then reduce dose or discontinue glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications
➢ HbA1c ≤ 6.5%

   e) **If any necessary adjustments to glycemia medications were not made since receipt of Central Lab HbA1c results, do so now according to the HbA1c value in section E.2.2.**
   f) Advise the participant to contact the clinical site if he or she is experiencing > 1 episode of symptomatic hypoglycemia /week.
   g) Recommend appropriate SMBG frequency according to Table E.1.3 (≤ 7times/wk if on diet/oral therapy and ≤ 3 times/day if on insulin).

h) Instruct participants on when and how to self-titrate (if applicable).
i) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log.** If on insulin, record name and dose on **Standard Glycemia Management Form**.
i) Provide SMBG logbooks and instructions for their completion.

5. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self- report of adherence.
   c) Using the appropriate technique for the Omron device (See MOP Chapter 9, Section 9.2.3), obtain and evaluate blood pressure values.
   d) If SBP is 130 – 139 mm Hg at this visit and was > 135 mm Hg at previous visit, maintain current therapy.
   e) If SBP is 140 – 159 mm Hg at this visit and < 140 mm Hg at previous visit, maintain current therapy.
   f) If SBP is < 130 mm Hg at this visit or < 135 mm hg on 2 consecutive visits, step down therapy is indicated..
   g) If SBP is ≥ 160 mm Hg at this visit or ≥ 140 mm Hg on 2 consecutive visits, an upward dose titration or an additional drug (not already in use) must be added. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg.
   h) Instruct participants on actions to limit symptomatic orthostasis.
   i) Complete **Standard Blood Pressure Management Form**.
   j) Record name, and dose of **all** blood pressure medications dispensed on the **Blood Pressure Medications Log.**
6. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medications as necessary. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
7. Schedule a clinic appointment in 4 months. Remind participant to come fasting.
8. Remind participants to bring all their medications, glucose meter and SMBG records at next visit.
9. Complete the following forms and enter data as required:
   a) **Interval History and Follow-up**
   b) **Standard Glycemia Management Form**
   c) **Glycemia Medication Log**
   d) **Severe Hypoglycemia Action Form (as necessary)**
   e) **Standard Blood Pressure Management Form**
   f) **Blood Pressure Medications Log**
   g) **Encounter and Disposition Form**
   h) **Event Forms (as necessary)**
   i) **Drug Dispensing Form (as necessary)**
   j) **Cost Substudy Form (as necessary)**

k) **Study Status Form (as necessary)**

E.2.5 Annual Visits (12, 24, 36, 48, 60, 72, 84, and 96 Months)

These visits should occur within a +/- 2-week visit window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia or lipid (if applicable) medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Review and update Contact Information.
2. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documnetation are mailed to the Coordinating Center.
3. Perform the Annual Physical Exam, including weight, height, waist circumference, visual acuity, foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3.).
4. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium (**12 month, prn, and exit visits**), Creatinine, Lipid Profile, ALT, and CPK. **(Blood samples for storage of additional aliquots, where approved, should occur at the 24-month, 48-month 72-month and 96-month visits)**.
5. Review the Concomitant Medications Inventory list located in the **Annual Follow-up and Physical Exam Form** with participant to document all non-study medications currently taking.
6. Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completes all items before end of visit **(12-month and 36-month visits).**
7. **A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Lab every 2 years for the 24-month, 48-month, 72-month and 96-month visits.**
8. **An ECG will be obtained and transmitted to the ACCORD ECG Reading Center every 2 years for the 24-month, 48-month, 72-month and 96-month visits**. Retain a copy for participant's research records.
9. Collect all glycemia related information:
   a) Review the previous 4 months SMBG values in diary, download meter values to laptop, and assess for medication/lifestyle adjustment in the glycemia intervention.

b) Complete **Standard Glycemia Management Form**. Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section E.1.3.b, E.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action Form**) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.

c) Record **current** medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.

d) If any conditions in Box A apply, then reduce dose or discontinue glucose lowering drug:

BOX A
- Any severe hypoglycemia
- Symptomatic hypoglycemia episodes > 1/week
- ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
- Any adverse effects of glycemia medications
- HbA1c ≤ 6.5%

e) **If any necessary adjustments to glycemia medications were not made since receipt of Central Lab HbA1c results, do so now according to the HbA1c value in section E.2.2.**

f) Advise participant to contact the clinical site if he or she is experiencing > 1 episode of symptomatic hypoglycemia /week.

g) Recommend appropriate SMBG frequency according to Table E.1.3 (≤ 7 times/wk if on diet/oral therapy and ≤ 3 times/day if on insulin).

h) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medication Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.

i) Provide SMBG logbooks and instructions for their completion.

j) Update the **Unified Form** to ensure a smooth and steady flow of diabetic testing supplies being shipped by NetGroup Diabetic Services (**US sites only**).

10. Collect all blood pressure related information:

a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.

b) Record current medications, dose and self- report of adherence.

c) Using the appropriate technique for the Omron device (See MOP Chapter 9, Section 9.2.3) obtain and evaluate blood pressure values.

   a) If SBP is 130 –139 mm Hg at this visit and was > 135 mm Hg at previous visit, maintain current therapy.

e) If the SBP is 140 – 159 mm Hg at this visit and SBP < 140 at previous visit, maintain current therapy.

f) If the SBP is < 130 mm Hg at this visit or < 135 mm Hg on 2 consecutive visits, step down therapy is indicated..

g) If SBP is $\geq$ 160 mm Hg at this visit or $\geq$ 140 mm Hg on 2 consecutive visits, an upward dose titration or an additional drug (not already in use) must be added. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg.
h) Instruct participants on actions to limit symptomatic orthostasis.
i) Complete **Standard Blood Pressure Management Form**.
j) Record name, and dose of **all** blood pressure medications dispensed on the **Blood Pressure Medications Log.**

11. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after visit so that adequate inventory can be maintained at the clinical site
12. Participants assigned in the substudies (Health Related Quality of Life (HRQL), Physical Activity, Diet) will complete the appropriate questionnaires (**at 12-month, 36-month and exit visits only**). Verify that the participant completes all items before end of visit. Complete **Cost Substudy Form** for participants in the Cost Substudy.
13. Schedule follow-up clinic appointment in 4 months.
14. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
15. Complete the following forms and enter data as required:
    a) **Participant Contact Information Form (update as necessary)**
    b) **Annual History and Follow-up Form**
    c) **Standard Glycemia Management Form**
    d) **Glycemia Medications Log**
    e) **Severe Hypoglycemia Action Form (as necessary)**
    f) **Standard Blood Pressure Management Form**
    g) **Blood Pressure Medications Log**
    h) **Encounter and Disposition Form**
    i) **Health Utilities Index Form (12-month, 36-month visits only)**
    j) **The Unified Form**
    k) **Visual Acuity Worksheet**
    l) **Ophthalmology Exam Form (as necessary)**
    m) **Assigned Substudy Questionnaires (as necessary at 12-month, 36-month visits only)**
    n) **Drug Dispensing Form (as necessary)**
    o) **Cost Substudy Form (as necessary)**
    p) **Study Status Form (as necessary)**

F.2.6 Sixteen and 20 Month Visit

This visit should occur within a +/- 4-week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and

request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.

2. Perform the exam, including weight. Using appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c.
4. Collect all glycemia related information.
   a) Review the previous 4 months SMBG values in diary, download meter values to laptop and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Complete **Standard Glycemia Management Form**. Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section E.1.3.b, E.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action** Form) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
   c) Record **current** medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   d) If any conditions in Box A apply, then reduce dose or discontinue glucose lowering drug:

   BOX A
   - Any severe hypoglycemia
   - Symptomatic hypoglycemia episodes > 1/week
   - $\geq$ 50% SMBG levels < 90 mg/dl (5 mmol/l)
   - Any adverse effects of glycemia medications
   - HbA1c $\leq$ 6.5%

   e) **If any necessary adjustments to glycemia medications were not made since receipt of Central Lab HbA1c results, do so now according to the HbA1c value in section E.2.2.**
   f) Advise participant to contact the clinical site if he or she is experiencing > 1 episode of symptomatic hypoglycemia /week.
   g) Recommend appropriate SMBG frequency according to Table E.1.3 ($\leq$ 7 times/wk if on diet/oral therapy and $\leq$ 3 times/day if on insulin).
   h) Adjust the glucose-lowering study drug as needed and record name, dose of **all** glycemia medications, on the **Glycemia Medication Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   i) Provide SMBG logbooks and instructions for their completion.
5. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.

b) Record current medications, dose and self- report of adherence.
c) Using the appropriate technique for the Omron device (See MOP Chapter 9, Section 9.2.3), obtain and evaluate blood pressure values.
d) If SBP is 130 –139 mm Hg at this visit and was > 135 mm Hg at previous visit, maintain current therapy.
e) If SBP is 140 – 159 mm Hg at this visit and SBP < 140 mm Hg at previous visit, maintain current therapy.
f) If SBP is < 130 mm Hg at this visit or < 135 mm Hg on 2 consecutive visits, step down therapy is indicated..
g) If SBP is ≥ 160 mm Hg at this visit or ≥ 140 mm Hg on 2 consecutive visits, an upward dose titration or an additional drug (not already in use) must be added. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg.
h) Instruct participants on actions to limit symptomatic orthostasis.
i) Complete **Standard Blood Pressure Management Form**.
j) Record name, and dose of all blood pressure medications dispensed on the **Blood Pressure Medications Log.**

6. Remove labels from study medication and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after visit so that adequate inventory can be maintained at the clinical site.
7. Complete **Cost Substudy Form** for participants in the Cost Substudy.
8. Schedule the next clinic appointment. Remind participant to come fasting for the 24 month visit.
9. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
10. Complete the following forms and enter data as required.
    a) **Interval History and Follow-up Form**
    b) **Standard Glycemia Management Form**
    j) **Glycemia Medications Log**
    d) **Severe Hypoglycemia Action Form (as necessary)**
    k) **Standard Blood Pressure Management Form**
    l) **Blood Pressure Medications Log**
    m) **Encounter Disposition Form**
    n) **Preliminary Event Notification Form (as necessary)**
    o) **Event Forms (as necessary)**
    p) **Drug Dispensing Form (as necessary)**
    k) **Cost Substudy Form (as necessary)**
    l) **Study Status Form (as necessary)**

E.2.7 Subsequent 4 Month Visits (28, 32, 40, 44, 52, 64, 68, 76, 80, 88, 92)

This visit should occur within a +/- 4-week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event,

obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.

2. Perform the exam, including weight. Using appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c.
4. Collect all glycemia related information.
   a) Review the previous 4 months SMBG values in diary, download meter values to laptop and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Complete **Standard Glycemia Management Form**. Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section E.1.3.b, E.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action** Form) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
   c) Record **current** medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   d) If any conditions in Box A apply, then reduce dose or discontinue glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications
➢ HbA1c ≤ 6.5%

   e) **If any necessary adjustments to glycemia medications were not made since receipt of baseline Central Lab HbA1c results, do so now according to the HbA1c value in section E.2.2.**
   f) Advise participant to contact the clinical site if he or she is experiencing > 1 episode of symptomatic hypoglycemia /week.
   g) Recommend appropriate SMBG frequency according to Table E.1.3 (≤ 7 times/wk if on diet/oral therapy and ≤ 3 times/day if on insulin).
   h) Adjust the glucose-lowering study drug as needed and record name and dose of **all** glycemia medications on the **Glycemia Medication Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   i) Provide SMBG logbooks and instructions for their completion.
5. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the

participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.

b) Record current medications, dose and self- report of adherence.
c) Using the appropriate technique for the Omron device (See MOP Chapter 9, Section 9.2.3), obtain and evaluate blood pressure values.
d) If SBP is 130 –139 mm Hg at this visit and was > 135 mm Hg at previous visit, maintain current therapy.
e) If SBP is 140 – 159 mm Hg at this visit and SBP < 140 mm Hg at previous visit, maintain current therapy.
f) If SBP is < 130 mm Hg at this visit or < 135 mm Hg on 2 consecutive visits, step down therapy is indicated..
g) If SBP is ≥ 160 mm Hg at this visit or ≥ 140 mm Hg on 2 consecutive visits, an upward dose titration or an additional drug (not already in use) must be added. It is reasonable to see the participant at monthly intervals for adjustment of therapy until the SBP is < 160 mm Hg.
h) Instruct participants on actions to limit symptomatic orthostasis.
i) Complete **Standard Blood Pressure Management Form**.
j) Record name, and dose of all blood pressure medications dispensed on the **Blood Pressure Medications Log.**

6. Remove labels from study medication and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after visit so that adequate inventory can be maintained at the clinical site.
7. Complete **Cost Substudy Form** for participants in the Cost Substudy.
8. Schedule a clinic appointment in 4 months. Remind participant to fast prior to any clinic visit requiring a fasting lipid profile.
9. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
10. Complete the following forms and enter data as required.
    a) **Interval History and Follow-up Form**
    b) **Standard Glycemia Management Form**
    c) **Glycemia Medications Log**
    d) **Severe Hypoglycemia Action Form**
    e) **Standard Blood Pressure Management Form**
    f) **Blood Pressure Medications Log**
    g) **Encounter Disposition Form**
    h) **Preliminary Event Notification Form (as necessary)**
    i) **Event Forms (as necessary)**
    j) **Drug Dispensing Form (as necessary)**
    k) **Cost Substudy Form (as necessary)**
    l) **Study Status Form (as necessary)**

E.2.8 Exit Visit

This visit should occur within a +/- 4-week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the exam, including weight. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, ALT, Creatinine, Lipid Profile, CPK and for storage of additional aliquots (where approved).
4. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Lab.
5. An ECG will be obtained and transmitted to the ACCORD ECG Reading Center. Retain a copy for records.
6. Collect all glycemia related information.
   a) Review the previous 4 months SMBG values in diary, download meter values to laptop and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section E.1.3.b, E.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action Form)** or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
   c) Record current medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
7. Collect all blood pressure related information:
   a) Verify prior to taking the BP measurements, that the participant has taken their BP medication that morning prior to coming to the visit. If the participant has not taken the medication but has brought the medication with them, have the participant take the medication and then measure their study BP 2-3 hours following the administration of the medication.
   b) Record current medications, dose and self- report of adherence.
   c) Obtain, review and evaluate blood pressure values using the appropriate technique for the Omron device (See MOP Chapter 9, Section 9.2.3).
   d) Complete **Standard Blood Pressure Management Form**.
   e) Record name, and dose of all blood pressure medications dispensed on the **Blood Pressure Medications Log.**
8. Participants will be prescribed appropriate non-study antihyperglycemia therapy and lipid-lowering therapy based on their current status and post-trial follow-up care will be arranged.
9. Complete the following forms and enter data as required.
   a) **Interval History and Follow-up Form**

b) **Standard Glycemia Management Form**
c) **Glycemia Medications Log**
d) **Severe Hypoglycemia Action Form (as necessary)**
e) **Standard Blood Pressure Management Form**
f) **Blood Pressure Medications Log**
g) **Encounter Disposition Form**
h) **Preliminary Event Notification Form (as necessary)**
i) **Event Forms (as necessary)**
j) **Drug Dispensing Form (as necessary)**
k) **Cost Substudy Form (as necessary)**
l) **Study Status Form (as necessary)**

Figure E.4:
Treatment Group Algorithm for Standard Glycemia Therapy Group (Goal: HbA1c 7% to

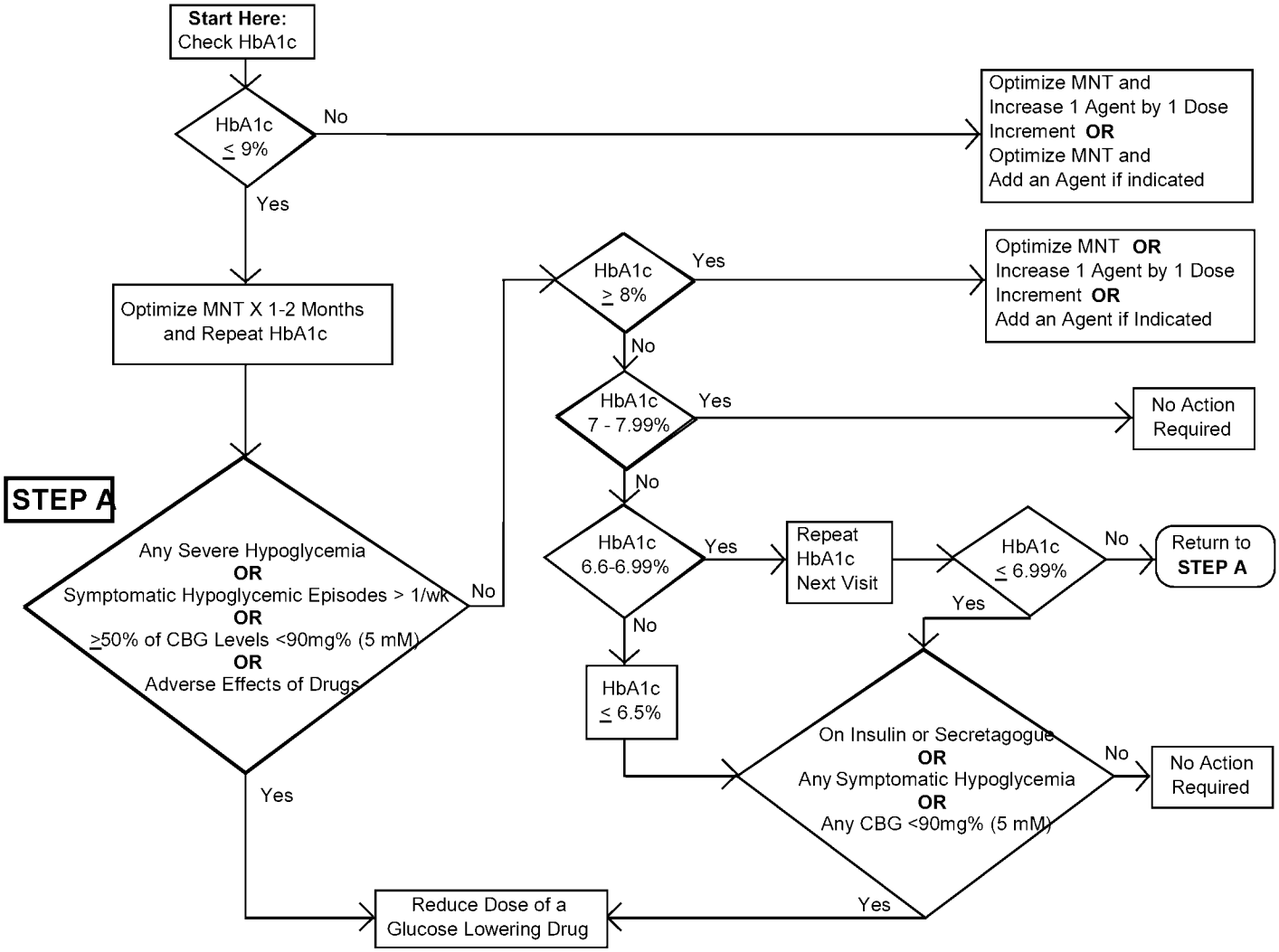
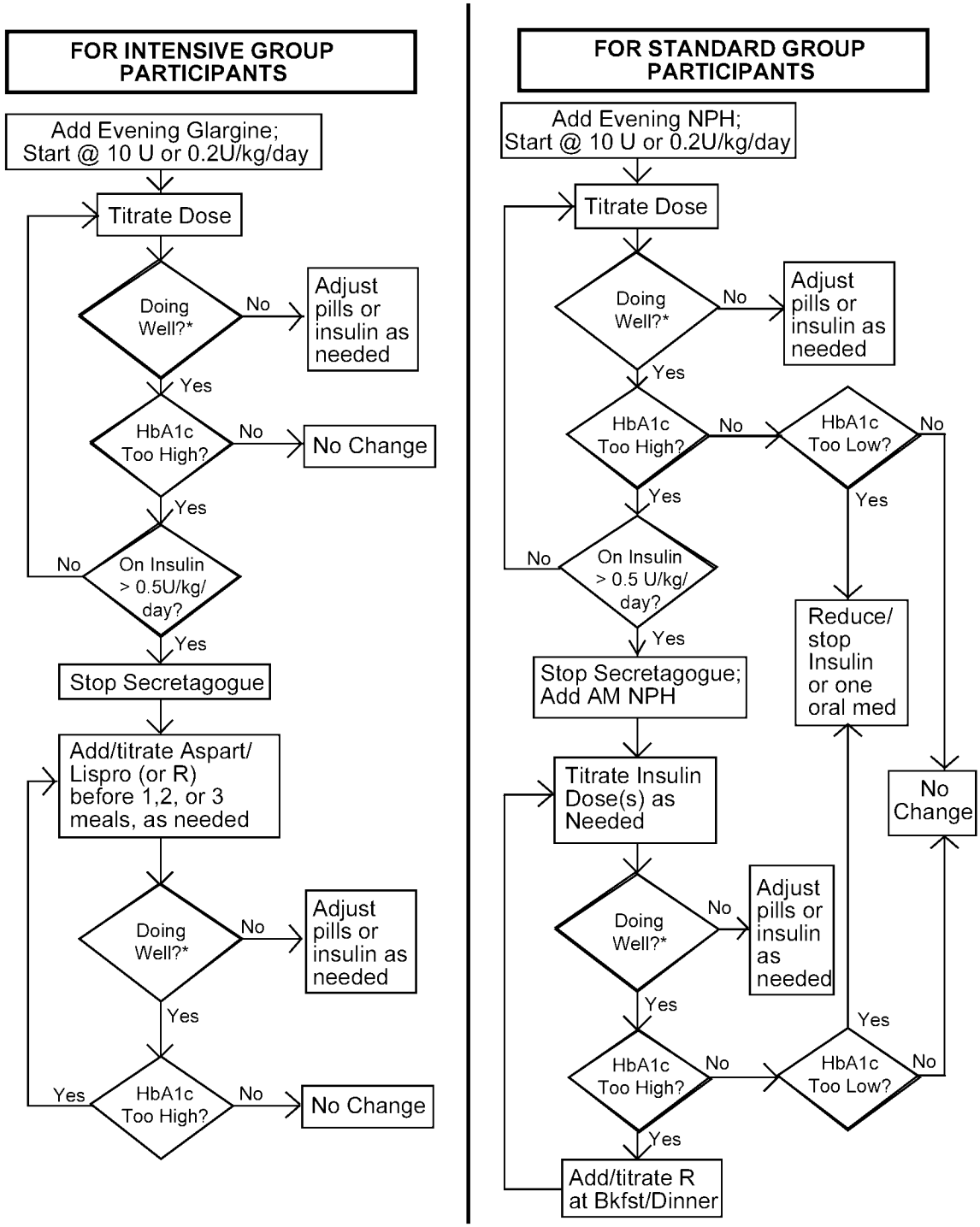
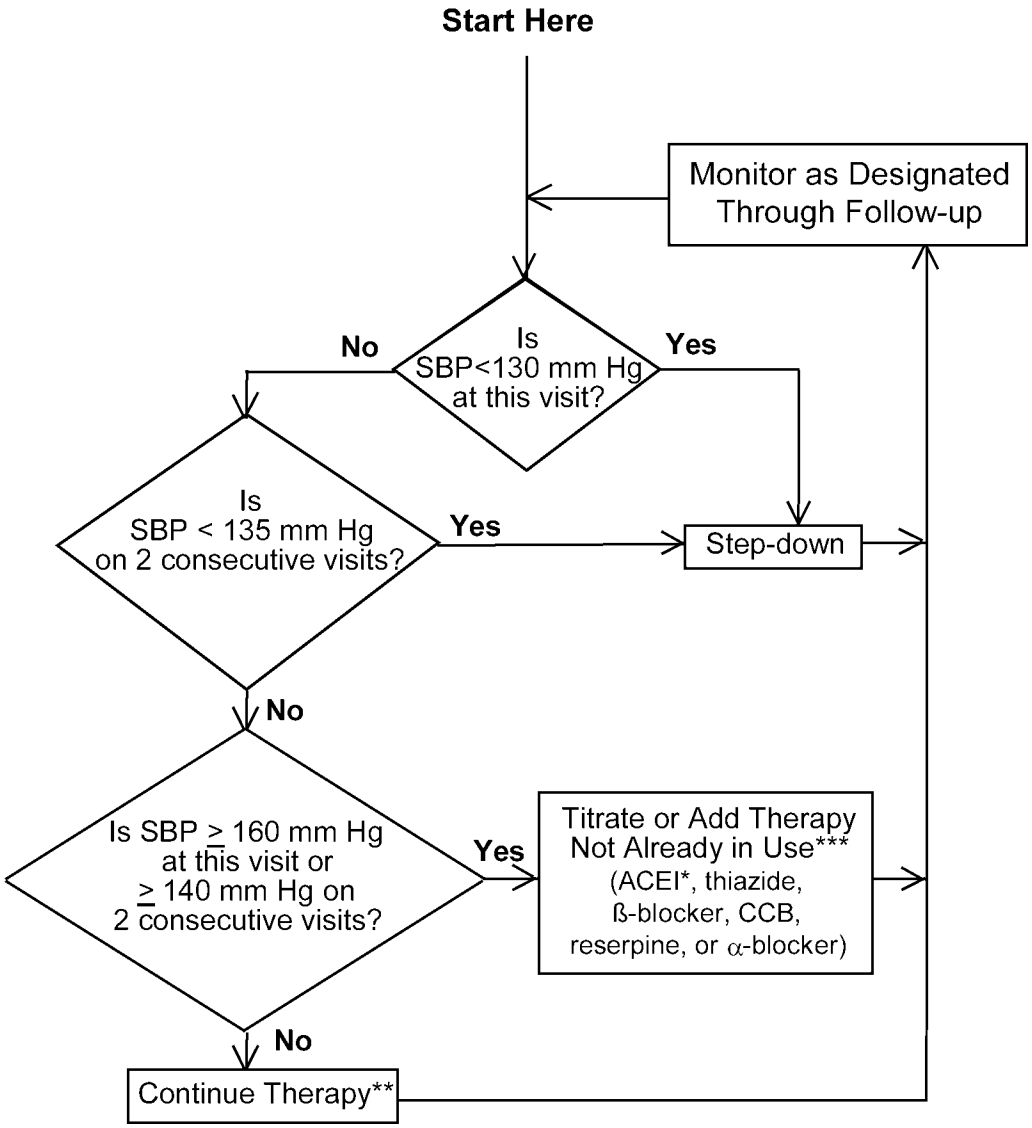


Figure 3.3:
Use of Insulin for Participants On Maximal Oral Therapy



*Doing well: no severe hypoglycemic or adverse event or no reason to reduce therapy (as described in Figure 3.2)

Figure E.7: Treatment Algorithm for Standard Blood Pressure (Goal: SBP < 140 mm Hg)



* ARB can be considered as a substitute for participants who do not tolerate ACEI therapy
** Unless side effects warrant change in therapy
*** Consult with the Clinical Center Network before adding a fifth antihypertensive medication

Thiazolidinedione Drugs (e.g. Avandia or Rosiglitazone)

ACTIONS of THIAZOLIDINEDIONES

The drug Avandia (rosiglitazone) belongs to a group of medications called thiazolidinediones (or glitazones or TZD's), and may be supplied as part of the ACCORD trial. Actos (pioglitazone) is another drug that belongs in this group. These drugs lower the blood glucose by reducing the body's resistance to the action of insulin (i.e. making your own insulin work more effectively). They can be used alone or can be combined with other diabetes pills or insulin.

COMMON SIDE EFFECTS

1. Hypoglycemia (low blood sugar)

These drugs can lead to hypoglycemia. When taken alone, the risk of hypoglycemia is low. When taken with insulin or other pills, the risk of hypoglycemia is higher.

If you do experience symptoms of a low blood sugar (such as lightheadedness, sweating, nervousness, hunger, a sensation of a racing heart, headache, or sudden fatigueat unusual times), check your blood sugar. If the level is less than 70 mg/dl (3.9 mmol/l) you may be suffering from hypoglycemia. If so, drink 4 ounces of juice or regular soda or eight ounces of milk or have three glucose tablets or five Life Savers (i.e. 15 grams of carbohydrate). Recheck your blood sugar in 15 minutes to make sure it has risen to at least 90 mg/dl (5.0 mmol/L). If low blood sugar reactions are frequent, severe or unexpected, call your doctor.

2. Weight Gain

These drugs may lead to weight gain. Weight gain is due to the lowering of blood sugar by insulin and drugs that act like insulin. This reduces the amount of sugar lost in the urine and helps the body store extra energy in fat cells. Sometimes, weight gain may be due to some fluid retention. Regardless of the cause, the amount of weight gained or lost depends on the level of physical activity and diet, or can be due to other drugs that are being taken. For example, some people gain more weight if insulin is also being taken. To minimize weight gain or to cause weight loss, exercise regularly, eat low fat foods, avoid extra snacks and large portions.

3. Fluid Retention

These drugs may lead to fluid retention. Fluid retention is generally mild with some swelling in the ankle or leg or bloating; it may be more pronounced when these drugs are used together with insulin, and rarely, the fluid retention can be severe or even life threatening. If you develop major leg swelling or especially shortness of breath either with activity or at rest, see your doctor as soon as possible. Reducing the dose, adding diuretics (water pills) or adjusting other medications (such as blood pressure pills, calcium channel blockers, non-steroidal anti-inflammatory drugs or arthritis pills) can also be used to manage this problem. ***You and your doctor should pay close attention to fluid retention if you take insulin or have heart failure or other heart problems.***

POTENTIAL SIDE EFFECTS

Because of rare cases of severe liver disease with a related medicine that is no longer available (Rezulin or troglitazone), you must have your blood drawn for liver enzyme tests (ALT) when treated with these drugs every 2 months for the first year of treatment and intermittently thereafter. If you develop persistent nausea, vomiting, belly pain, fatigue, loss of appetite, dark

urine, yellowing of the eyes or skin while treated with this drug, stop the medication and see your doctor for a blood draw within a few days.

DOSING

Avandia (rosiglitazone) can be taken once a day, but may work a bit better if taken twice daily. Actos (pioglitazone) can be taken any time of the day. Both drugs can be taken either with or without food. It may take 12 weeks to see the full effect of a dose.

7. Visit Schedule of Study Activities by Randomization Cell

F. Standard Glycemia and Lipid Trial

F.1. Overview

One of the key aims of the ACCORD study is to determine if a therapeutic strategy that targets a HbA1c of < 6.0% reduces the rate of cardiovascular disease (CVD) events more than a strategy that targets a HbA1c of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%) in high risk middle-aged or older people with type 2 diabetes. The approaches used to implement these targets, suggested algorithms for the use of pharmacologic agents and follow-up schedules are described in MOP Chapters 5 and 6. Details regarding the implementation of the protocol for the Standard Glycemia and Lipid Trial groups are described below.

The ACCORD lipid component is designed to test whether lowering plasma triglyceride and increasing plasma HDL cholesterol levels with a fibrate in addition to lowering LDL cholesterol levels with an HMG CoA reductase inhibitor (hereafter referred to as "statin") will reduce the rate of CVD events more than statin alone. The specific fibrate to be used in ACCORD is fenofibrate and the specific statin is simvastatin.

F.1.1 Algorithms for Standard Glycemic and Lipid Trial Control; Choice of Agents

Figures F.4 and F.5 at the end of this chapter are suggested algorithms to guide changes in glycemic therapy for the standard group. The exact changes to be made whenever glycemic therapy needs to be intensified on the basis of the HbA1c or the SMBG results will be determined by the individual site using the figures as guides.

Eligible participants in the lipid trial will be randomized to micronized fenofibrate or placebo. All participants will be treated with simvastatin.

F.1.2 Targets and Action Required Levels

F.1.2.a) Standard Glycemic Control

Table F.1.2 outlines the glycemic target for the standard group, which is identical to Table 3.1 in the protocol.

Table F.1.2: Glycemic Targets and Thresholds for Action for ACCORD			
		"Action Required" Threshold	
Group	HbA1c Targets	HbA1c	> 50% of SMBG Results/4 days
Standard Therapy	7 – 7.9%	> 7.9%* or ≤ 6.5%[#] (anytime) or 6.6%-6.9% [#] (twice consecutively)	fasting/ac < 90 mg/dl (5.0 mmol/l)[#]

pc: postcibal; ac: antecibal; SMBG: self monitoring of blood glucose; *antihyperglycemic therapy will be advanced if either the HbA1c or the SMBG "action required" criteria are met at any participant encounter
[#] therapy with drugs that increase the risk of hypoglycemia (e.g. insulin, sulfonylureas, meglitinides) will be reduced to avoid hypoglycemia if these criteria are met

F.1.2.b) Lipid Trial

Participants who were on a lipid- lowering agent at screening must agree to stop treatment no later than the day of randomization and be changed to simvastatin. The starting dose of simvastatin is 20 mg/day, administered once daily after the evening meal or at bedtime.

One month after randomization, the study fibrate/placebo will be started. It is recommended that simvastatin be taken in the evening and the masked fibrate/placebo be taken in the morning. If however, you feel compliance would be improved if both were taken together, that would be acceptable.

The starting dose of masked fenofibrate/placebo medication will be determined by the calculated glomerular filtration rate (GFR) using the baseline serum creatinine level and the abbreviated MDRD equation (Levey 2003). Those participants with a baseline GFR ≥50 ml/min/1.73m^2 will begin at a starting dose of 160 mg of fenofibrate or identical placebo tablet. Those with a calculated GFR between 30 and <50 will start at the reduced dose of 54 mg/day fenofibrate or placebo.

Implementation of baseline assignment of blinded study medication dose:

- The Coordinating Center (CC) will determine the starting dose of the blinded study medication based on calculated GFR from the MDRD equation, using Central Lab values at baseline.
- The recommended dose will appear on the participant main page below "Lipid Bottle ID" (e.g., FULL, REDUCED, or NONE).
- The CC will communicate the starting dose to the Drug Distribution Center (DDC).
- DDC will send the appropriate dose to the clinical site labeled for the specific participant.

- One-month follow-up visits for Lipid Trial participants should be scheduled at least 3 weeks after the baseline visit to allow for arrival of blinded study medication.

What to do if the Participant's GFR Falls Below Cutoff Levels

Participants in the lipid trial will have serum creatinine measured every four months during follow-up. If the participant had started on the 160 mg dose of the masked medication, this dose will be down-titrated if the participant's estimated GFR falls between 30 and <50 mL/min/1.73m^2 on two consecutive measurements taken four months apart. Participants with GFRs in this range will receive either 54 mg/day of fenofibrate or matching placebo.

Implementation of ongoing blinded study medication dose adjustment based on GFR:

- The ACCORD Coordinating Center (CC) will monitor GFR values obtained on participants at routine 4-month blood draws.
- The CC will notify the Clinical Site PI and Coordinator, the CCN and Coordinator, and the Drug Distribution Center (DDC) when a participant has met the criteria for down titration of masked study medication.
- The DDC will send a new box of reduced dose masked study medication for the participant to the Clinical Site.
- The dose of blinded study medication will be listed on the participant main page below the "Lipid Bottle ID" (e.g. REDUCED).

If the estimated GFR falls below 30 mL/min/1.73m^2 at any time, the Coordinating Center will notify the clinic site that a confirmatory blood draw for repeat estimated GFR will be required within 2 weeks. If the confirmatory estimated GFR is below 30mL/min/1.73m^2, the masked study medication will be permanently discontinued, regardless of fenofibrate or placebo assignment.

Implementation of discontinuation of blinded study medication for GFR less than 30ml/min/1.73^2 for both active and placebo Lipid Trial participants:

- The CC will notify the Clinical Site PI and Coordinator, and the CCN PI and Coordinator when a participant has a Central Lab calculated GFR less than 30ml/min/1.73m^2.
- Clinics must schedule a repeat blood draw for creatinine within 2 weeks. The participant should remain on blinded medication during the 2-week interval.
- Upon receipt of the second blood sample, the CC will determine if the participant meets the criteria to stop the blinded study medication or whether a dose reduction is required.
- An email notification will be sent from the CC to the Clinical Site at this time with dosing instructions.
- If Clinical Sites become aware of a participant who had an elevated creatinine at an outside blood draw, they should bring the participant in for an ASAP prn visit and recheck the creatinine using the ACCORD Central Lab. The CC will then

notify the clinic if the participant should have a reduced dose or have their blinded medication discontinued.

F.1.3.a) Adjusting Glycemic Therapy

As noted in the following table (F.1.3), a range of approaches will be used to target the HbA1c level shown in Table F.1.2.

TableF.1.3 Achieving Glycemic Goals	
	Standard Group
Visits (1 and 4 months)	Month 1 and 4 mo
Visits (> 4 months)	Q 4 mo
Phone contact	Participant initiated (prn)
Supplemental contact	Severe hypoglycemia/hyperglycemia HbA1c in action required range Frequent (>50%/4 days) premeal SMBG levels <90 mg/dl (5.0 mmol/l)
Point of Care HbA1c	Optional
Routine use of postprandial SMBG values to guide therapy	No
SMBG freq.[a] (not on insulin)	≤7/wk (daily at different times or >1/day on certain days)
SMBG freq.[a] (on insulin)	≤3/day
Self titration principles	Avoid severe hypoglycemia and premeal SMBG levels < 90 mg/dl (5.0 mmol/l)
Initial Minimum Rx	Diet/lifestyle
Insulin Use (when needed)	Generally ≤ 2 injections/day

[a]less frequent if goals are achieved; [b] including avoiding SMBG levels < 70 mg/dl (3.9 mmol/l) on > 1/4 of the readings.

F.1.3.b) Glycemia Safety Issues/ Adjusting Therapy for Hypoglycemia

Hypoglycemic events may occur in individuals in either the intensive or standard group. Severe hypoglycemia is unusual in people with type 2 diabetes (even when normoglycemia is targeted). Mild episodes of hypoglycemia are, however, likely to occur.

All participants will be instructed to check their glucose levels regularly as described in the protocol. They will also be taught how to recognize and self-treat hypoglycemia and will be instructed to keep glucose available at all times (as tablets). Moreover, any participant who has had an episode of severe hypoglycemia will be provided with glucagon and they and any cohabiting partner will be taught how to administer it.

Severe hypoglycemia is defined as any episode of loss of consciousness/seizure or documented hypoglycemia (glucose < 50 mg/dl or 2.8 mmol/l) that also requires hospitalization or treatment by emergency personnel. If this occurs:

- Complete **Severe Hypoglycemia Action Form**. (See MOP Chapter 8, Section 8.4.4 for more details).
- For participants in either group who have an episode of severe hypoglycemia, adjust glycemic targets to achieve a fasting and 2 hour glucose (postprandial) of 100 – 140 mg/dl (5.5 – 7.8 mmol/l) and < 180 mg/dl (10 mmol/l) respectively, and a HbA1c of 7.0% - 7.9% for at least 4 weeks.
- Ensure that a complete medical assessment by the physician is completed to identify other potential causes (e.g. pituitary or adrenal insufficiency)
- Ensure that the physician reassesses the glycemic goals at subsequent visits.
- Ensure that participant has received glucagon and that the participant and cohabitant know how to administer it.
- Have telephone contact with participant before the next visit to assess blood glucose records and freedom from hypoglycemia.

Minor hypoglycemia is defined as self-reported transient symptoms such as lightheadedness, tremor, shaking, sweating, tingling, blurry vision, trouble concentrating etc., that are self-treated by ingestion of carbohydrates and resolve on their own (See MOP Chapter 6, Section 6.1.6). All participants will be asked to note such episodes in their glucose logbooks and to confirm them with a blood glucose reading whenever possible. The estimated frequency (of confirmed and suspected minor hypoglycemia) will be recorded at every visit.

F.1.3.c) Self Treatment of Hypoglycemia

1. If the glucose value is < 50 - 70 mg/dl (3.9 mmol/l), it should be treated by ingestion of 15 grams of CHO (e.g. 3-4 glucose tablets, 5 Lifesavers, 4-6 oz. of a regular – (nondiet) – soft drink, or 8 oz. low fat milk);
2. If the glucose value is < 50 mg/dl (2.8 mmol/l), it should be treated by ingestion of 20-30 grams of CHO (e.g. 6-8 glucose tablets);
3. Blood glucose should be self-tested 15-20 minutes after therapy and therapy repeated if the level is still low (as above)
4. If no meal will be eaten within 1-2 hours, a mixed nutrient snack, including CHO, protein, and fat should be ingested right the initial therapy to prevent another episode
4. If the glucose value is low or there is significant cognitive or motor impairment, individuals should treat and re-test glucose value. The glucose value should be > 70 mg/dl (3.9 mmol/l) before driving a car or operating heavy machinery.

F.a.3.d) Education and Minimization of Hypoglycemia in Participants

Hypoglycemia is an inherent risk in the treatment of diabetes. It is important to inform participants of the signs and symptoms of hypoglycemia, techniques to minimize the risk and appropriate methods of treatment. Several tools are available for use in educating participants:

1. Hypoglycemia Cartoon
2. Participant Wallet Card
3. Primer on Hypoglycemia
4. Participant Newsletters

All participants must be provided with the written material listed above at the beginning of the study. Study staff should review verbally the signs and symptoms with the participant and family members. Participants and their families should be encouraged to review the hypoglycemic video either in the clinic or at home. Both participants and family members should be educated on the appropriate treatment for symptoms, and provided with glucose tablets. Those participants suffering one severe hypoglycemic event should be provided with a glucagon kit and both the participant and the family member taught how to use it. This material must be reviewed annually with all participants and after every reported hypoglycemic event.

F.1.3.e) Safety Issues for Thiazolidinedione (TZD) Drugs

For participants on TZD (e.g. Avandia or Rosiglitazone), check for the presence of edema at every visit and obtain a Central Lab ALT every 2 months for the first year of treatment and annually thereafter.

As TZDs are contraindicated in people with stage 3 or 4 heart failure, if a participant who is taking a TZD does develop heart failure, the TZD should be stopped and the heart failure treated and investigated. Depending on the results of these investigations the investigator may reconsider cautiously reinstituting TZD therapy if the heart failure resolves, and was judged to have not been directly cause by the TZD alone.

A handout to give to the participants at the discretion of the site concerning TZD use is available and can be found on page 25 at the end of this chapter.

F.1.3.f) Lipid Issues/ What to do if a Participant Exceeds LDL-C and Triglyceride Cut-points

Because the upper limit for entry LDL-C is 180 mg/dl, and because 40 mg simvastatin should provide about an average 40% reduction in LDL-cholesterol, it is expected that few participants will have an on-treatment LDL-C of more than 120 mg/dl. However, as noted below, if a participant has an LDL-cholesterol level that is persistently greater than 120 mg/dl, ACCORD will, consistent with NCEP guidelines, take the participant off the masked study medication and continue treatment with simvastatin until placed on a non-study statin by his/her primary caregiver. Triglyceride values will be maintained at a level that does not pose a risk of pancreatitis. Participants are expected to have LDL-C lower than 120 mg/dl (3.10 mmol/l) and triglycerides less than 750 mg/dl (8.47 mmol/l) during the study.

What to do if a Participant's LDL-C is Out of Range

The starting dose of open-labeled simvastatin is 20 mg/day, administered once daily after the evening meal or at bedtime. If the LDL-C is greater than 100 mg/dl (2.59 mmol/l) on two consecutive follow-up visits, the daily dose of simvastatin will be increased to 40 mg.

If the measured LDL-C goes above 120 mg/dl (3.10 mmol/l) after titrating simvastatin to 40 mg/day the Coordinating Center will send a reminder email to the Clinical Site PI and Coordinator, and the CCN PI and Coordinator who should confirm compliance with the study statin, refer the participant to a nutritionist for dietary instruction/reinforcement (if appropriate), and schedule a blood draw for the visit four months from the visit at which the LDL-C was above 120 mg/dl (3.10 mmol/l). This blood specimen needs to be sent to the ACCORD Central Chemistry Laboratory for lipid analysis.

If the participant has an LDL-C above 120 mg/dl (3.10 mmol/l) on two consecutive visits 4 months apart after titrating simvastatin to 40 mg/day (even after compliance review and dietary counseling), the following will occur:

- The CC will send an email reminder to the Clinical Site PI and Coordinator, and the CCN PI and Coordinator.
- The participant will be taken off the fibrate/placebo pills.
- The participant will remain on simvastatin 40 mg/day until placed on non-study statin by his/her primary caregiver. **[The site needs to contact the CCN office if any participant needs non-study simvastatin].**
- The site staff will make an appointment with the participant's doctor for follow-up.
- The site staff will also provide a letter for the participant to take to his/her physician for the follow-up visit. This letter will include the blood lipid values and describes the medication regimen the participant was on when the blood was drawn.
- The site staff will confirm that the participant had visited their physician.
- From that point on, the participant would be treated for their lipids by his/her personal physician and given results of any ACCORD lipid determinations to share with this physician.

If the centrally measured LDL-C is ever less than 40 mg/dl (1.03 mmol/l) during follow-up, clinic personnel should determine compliance with study statin and fibrate/placebo (to make sure that the participant is not taking more than the prescribed number of pills daily) and refer participant to nutritionist for dietary counseling to ensure that the participant is eating a balanced, adequate diet. If the centrally measured LDL-C is ever less than 40 mg/dl (1.03 mmol/l) on two consecutive measurements taken 4 months apart, the following will occur:

- The CC will send an email reminder to the Clinical Site PI and Coordinator, and the CCN PI and Coordinator.
- The participant should be taken off simvastatin.

- The participant will remain on the blinded study medication.

What to do if Triglyceride Exceeds 750 mg/dl (8.47 mmol/l)

If the centrally measured triglyceride ever exceeds 750 mg/dl (8.47 mmol/l) during follow-up, the CC will send an email reminder to the Clinical Site PI and Coordinator, and the CCN PI and Coordinator. Clinic personnel should determine compliance with study statin and fibrate/placebo, refer participant to nutritionist for dietary instruction/reinforcement (if deemed appropriate) and determine and modify potential exacerbating disorders i.e. alcohol or simple sugar intake, hypothyroidism, hyperglycemia. A follow-up blood draw should be done at the next scheduled visit.

If the triglyceride exceeds 750 mg/dl (8.47 mmol/l) on two consecutive measurements 4 months apart, even after the above measures have been conducted, the following will occur:

- The CC will send an email reminder to the Clinic Site PI and Coordinator, and the CCN PI and Coordinator.
- The participant will be taken off the simvastatin and the masked fibrate/placebo medication.
- The participant will be dispensed a 160 mg/day tablet of fenofibrate or 600 mg BID of gemfibrozil until placed on non-study fibrate by his/her primary caregiver. **[The site needs to contact the CCN office if any participant needs non-study fenofibrate].**
- The site staff will make the appointment for follow-up by the participant's physician and will confirm that the appointment was kept.
- The site staff will also provide a letter for the participant to take to their physician for the follow-up visit. This letter will include the blood lipid values and describes the medication regimen the participant was on when the blood was drawn.
- From that point on, the participant will be treated for their lipids by his/her personal physician and given results of any ACCORD lipid determinations to share with this physician.

If the masked fibrate/placebo study medication is stopped for any reason, neither the participant nor the clinic staff need to be unmasked regarding the study medication's true identity, unless there are other circumstances dictating unmasking.

F.1.3.g) Special Note Regarding the Concomitant Use of Fenofibrate and Warfarin (Coumadin)

The use of a fibrate generally necessitates a reduction in the dose of Coumadin to avoid excessive bleeding.

For persons who are on Coumadin at the start of the trial, the participant's physician should be informed both by phone and in writing of the possibility that the participant may be on a fibrate. Until the physician or someone who will manage the Coumadin dose is reached by phone or in person, the participant should not be randomized.

During the trial, you will ask about the possibility of Coumadin use at each visit and if you find that the participant is now on Coumadin, record its use in your source notes. If Coumadin has been started, the clinician prescribing it should be notified that the participant may be on a fibrate. Remember, in some cases the clinician prescribing the Coumadin may not be the clinician notified at the start of the trial of the participant's participation in the trial and randomization to fibrate or placebo.

F.2 Standard Glycemic and Lipid Trial Visit Procedures

F.2.1 Baseline – Randomization Visit

The participants will be instructed to attend the clinic following an overnight fast (since ~10 pm the previous evening). They should not take their glycemia or lipid medications on the morning of this clinic visit but be instructed to bring their medications, glucose meter SMBG records, and significant other or support person with them. They should, however, take their blood pressure medication (with water) prior to coming to clinic (if applicable). During the visit, the following procedures will be conducted:

1. All data collected during the screening process will be reviewed.
2. Verify eligibility status for the Glycemia, Blood Pressure and Lipid Trials (including occurrence of events that may prohibit patient from participating).
   a) Review current medications including OTC, herbal remedies and vitamins.
   b) Review, evaluate and calculate the percentage of participant's compliance with at least 2 weeks of SMBG monitoring as part of the run-in procedures.
   c) Assure that the qualifying HbA1c value was obtained within the last 3 months prior to the randomization date.
3. If ineligible, the participant will be thanked for their time and dismissed from the clinic.
4. If eligible, proceed with randomization process:
   a) Verify that a full-scale consent form has been obtained and signed and HIPAA authorization obtained.
   b) Obtain and perform baseline history and physical exam, including demographics, medical history concomitant medications, weight, height, and waist circumference, visual acuity, and foot exam. Using the appropriate technique for the Omron device obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
   c) Participants will be given the **Health Utilities Index Form** and instructed on how to complete it. Verify that the participant completes all items before end of visit.
   d) Verify that all information on the **Inclusion/Exclusion Summary Form, the Blood Pressure Screening Form,** and **the Lipid Trial Screening Form** is complete and correct both on the forms and in the computer.
   e) Click "Randomize pt" on data entry screen. . A pop-up screen will appear to remind staff to provide the participant with Eye Sub-study and MIND Sub-study

(Canada, Western, Minnesota/Iowa, Ohio/Michigan, Northeast and Southeast CCNs) introductory materials.

f) Input the percent of participant's report of compliance for SMBG.

g) Verify that the **Baseline History and Physical Exam Form** has been completed.

5. The participant will be assigned a treatment regimen. The randomization screen will display this information and list target dates for the follow-up visits. It is recommended that the participant's treatment assignment and visit schedule be printed out and filed in their research record.
6. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, ALT, Creatinine, Lipid Profile, CPK and for storage of additional aliquots (where approved).
7. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Laboratory.
8. An ECG will be obtained and transmitted to the ACCORD ECG Reading Center. Retain a copy for the participant's research record.
9. Collect all glycemic related information:
   a) Review screening blood glucose diary, download SMBG meter values to laptop and assess blood glucose values for implementation of the glycemia intervention.
   b) Complete **Standard Glycemia Management Form.** Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia in source documents. Review symptoms and therapy for hypoglycemia (See Section F.1.3.b, F.1.3.c and MOP Chapter 8, Section 8.4.4).
   c) Record current glycemic medications including name, dose and participant's self report of adherence in the source document. Record current glycemia medications on the **Baseline History and Physical Exam Form** only by class of medication.
   d) Record name and dose of all **current** (at visit entry) oral glycemia medications on the **Glycemia Medications Log.** If on insulin, record name and dose on the **Standard Glycemia Management Form**.
   e) Conduct nutrition assessment and plan.
   f) Instruct participants on their diet, foot care and exercise program and the relationship of medications with nutrition and exercise.
   g) Reinforce proper SMBG technique and instruct participant to test per instructions on MOP Table F.1.3 ($\leq$ 7/wk (daily at different times or > 1/day on certain days) if diet/oral therapy and $\leq$ 3/day if on insulin).
   h) Provide SMBG logbooks and instructions for their completion.
   i) Dispense glucose meter if necessary (**Canadian Sites only**).
   j) Provide sufficient strips through to the next visit to the participant (**Canadian Sites only**).
   k) Fill out the **Unified Form** to ensure a smooth and steady flow of diabetic testing supplies being shipped by NetGroup Diabetic Services (**US sites only**).
   l) **At baseline continue glycemia therapy that participants were regularly or routinely taking prior to the ACCORD Study.** Convert all glucose lowering medications to equivalent study provided medications.
      1. If any of the conditions in Box A apply, then reduce dose of a glucose lowering drug:

BOX A
- Any severe hypoglycemia
- Symptomatic hypoglycemia episodes > 1/week
- ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
- Any adverse effects of glycemia medications

2. Upon receipt of Central Lab HbA1c values, refer to MOP section F.2.2 in this chapter.

m) Record name and dose of **all** glycemia medications participant was prescribed at visit exit on the **Glycemia Medications Log.** If on insulin, record name and dose on the **Standard Glycemia Management Form**.

10. For the Lipid Trial:
    a) If on lipid lowering therapy, discontinue and place on simvastatin (20 mg/day, administered once daily after the evening meal or at bedtime).
    b) Record information on the **Lipid Medications Management Form**.
    c) Refer to nutritionist for instruction/reinforcement of Step 1 diet of the National Cholesterol Education Program (NCEP).
    d) Advise participant of potential adverse effects of statin (myopathy, hepatitis). Review symptoms of myopathy and hepatitis with participant and advise on action to take if symptoms occur. Ask participant about coumadin use (see Section F.1.3.f). Review the list of prohibited medications in MOP Chapter 6, Section 6.3.5.
11. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
12. Participants assigned in the substudies (Health Related Quality of Life (HRQL), Physical Activity, Diet) will complete the appropriate questionnaires. Verify that the participant completes all items before end of visit.
13. Schedule a clinic appointment in 1 month. One-month follow-up visits for Lipid Trial participants should be scheduled at least 3 weeks after the baseline visit to allow for arrival of blinded study medication.
14. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
15. Collect all related Lifestyle and Background information:
    d) Assess smoking status. Follow guidelines (if necessary) in MOP Chapter 4, section 4.3.1 for smoking cessation activities.
    e) Assess aspirin use. Recommend aspirin therapy in accordance with guidelines in chapter 4, section 4.3.2.
16. Contact primary care provider as necessary.
17. Obtain a release of information form in case of need for subsequent events.
18. Complete the following forms and enter data as required:
    a) **Inclusion/Exclusion Summary Form**
    b) **Blood Pressure Trial Screening Form**
    c) **Lipid Trial Screening Form**
    d) **Participant Contact Information Form (if not previously completed)**
    e) **Visual Acuity Worksheet**
    f) **Ophthalmology Exam Form (as necessary)**

g) **Baseline History and Physical Exam Form**
h) **Standard Glycemia Management Form**
i) **Glycemia Medications Log**
j) **Severe Hypoglycemia Action Form (as necessary)**
k) **Lipid Medications Management Form**
l) **Encounter and Disposition Form**
m) **Health Utilities Index Form**
n) **The Unified Form (US Sites only)**
o) **Assigned Substudy Questionnaires (as necessary)**
p) **Drug Dispensing Form (as necessary)**
q) **Event Forms (as necessary)**

F.2.2 Upon Receipt of All Central HbA1c Values Drawn

1. If Central Lab HbA1c is 7% - 7.9% at this visit or is 6.6 %–6.9% at this visit and Central HbA1c was $\geq$ 7% at previous visit, no action is required.
2. Contact the participant if no change was made at the previous visit and the HbA1c result measured at that visit returns > 7.9% or $\leq$ 6.5%.
3. If the Central Lab HbA1c was > 9%, optimize MNT **and** increase 1 agent by 1 dose increment **or** optimize MNT and add an agent if indicated.
4. If Central Lab HbA1c $\leq$ 6.5% at this visit or < 7% on two consecutive visits **and** if on insulin or a secretagogue or any symptomatic hypoglycemia or any SMBG level < 90 mg/dl (5 mmol/l), then reduce dose of (or discontinue) a glucose lowering drug. Otherwise, if Central HbA1c $\leq$ 6.5% or < 7% on two consecutive visits, and does not meet the aforementioned medication or hypoglycemia criteria, no action required.
5. If the baseline (i.e., initial) Central Lab HbA1c is 8% - 9%, optimize MNT **and** wait for month 4 Central Lab HbA1c before increasing therapy.
6. If any subsequent Central Lab HbA1c is 8% - 9%, optimize MNT or increase one agent by one dose increment or add an agent if indicated.
7. Update record of name and dose of **all** glucose-lowering medications on **Glycemia Medications Log** if action required for HbA1c. If on insulin, record name and dose on the **Standard Glycemia Management Form**.
8. Advise the participant to contact the site if he or she is experiencing >1 episode of symptomatic hypoglycemia/week.
9. Reconfirm next clinic appointment. Remind participant to fast prior to any clinic visit requiring a fasting lipid profile.
10. Complete the following form and enter data as required:
    a) **Standard Glycemia Management Form**
    b) **Glycemia Medications Log**
    c) **Severe Hypoglycemia Action Form (as necessary)**
    d) **Drug Dispensing Form (as necessary)**

F.2.2.a The participant may be contacted by phone in two weeks (0.5 months) to check progress and adherence to protocol. This contact is not required.

F.2.3 One-Month Visit

This visit should occur within +/- 1-week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain the weight, and record measurement in source documentation.
2. Blood samples will be obtained, processed and shipped to the Central Lab for measurement of ALT and CPK.
3. Collect all glycemia related information:
   a) Review the previous 2 weeks SMBG values in diary, download meter values to laptop and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia. Review symptoms and therapy for hypoglycemia (See Section F.1.3.b, F.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action Form**) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug.
   c) Record **current** medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   d) If any conditions in Box A apply, then reduce dose or discontinue glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications
➢ HbA1c ≤ 6.5%

   e) **If any necessary adjustments to glycemia medications were not made since receipt of baseline Central Lab HbA1c results, do so now according to the HbA1c value in Section F.2.2.**
   f) Advise the participant to contact the site if he or she is experiencing > 1 episode of hypoglycemia/week.
   g) Recommend appropriate SMBG frequency according to Table F.1.3 (≤ 7 times/wk if on diet/oral therapy and ≤ 3 times/day if on insulin).
   h) Assess comprehension/understanding of dietary counseling.
      - Reinforce diet and exercise. Repeat at subsequent visits as necessary.
   i) Adjust the glucose lowering study drugs (if necessary) and record name and dose of **all** current glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   j) Provide SMBG logbooks and instructions in their completion.
4. For the Lipid Trial:
   a) Determine compliance with lipid drug regimen and record information on **Lipids Medication Form**.
   b) Record any potential side effects of lipid therapy.
   c) Initiate therapy with masked fibrate/placebo. The starting dose of masked fenofibrate/placebo medication will be determined by the calculated glomerular

filtration rate (GFR) using the baseline serum creatinine level and the abbreviated MDRD equation (Levey 2003). Those participants with a baseline GFR $\geq$50 ml/min/1.73m^2 will begin at a starting dose of 160 mg of fenofibrate or identical placebo tablet. Those with a calculated GFR between 30 and <50 will start at the reduced dose of 54 mg/day fenofibrate or placebo.

Implementation of assignment of blinded study medication dose:

- The Coordinating Center (CC) will determine the starting dose of the blinded study medication based on calculated GFR from the MDRD equation, using Central Lab values at baseline.
- The recommended dose will appear on the participant main page below "Lipid Bottle ID" (e.g., FULL, REDUCED, or NONE).
- The CC will communicate the starting dose to the Drug Distribution Center (DDC).
- DDC will send the appropriate dose to the clinical site labeled for the specific participant.

d) Obtain an ALT and CPK measurement to be shipped to the Central Lab.

e) Review prohibited/discouraged medications with the participant. (See MOP Chapter 6, Section 6.3.5).

NOTE: See Section F.1.2.b if notification that the participant's GFR falls below cutoff levels is received. See Section F.1.3.f if participant's LDL-C or Triglycerides exceed cutpoints.

f) Dispense fibrate/placebo and study statin if necessary.

5. Remove label from study medication and place on **Drug Dispensing Form** then dispense study medication. Scan label bar code into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
6. Schedule a 4-month clinic appointment. Remind the participant to come fasting.
7. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
8. Complete the following forms and enter data as required:
   a) **Standard Glycemia Management Form**
   b) **Glycemia Medications Log**
   c) **Severe Hypoglycemia Action Form (as necessary)**
   d) **Lipid Medication Form**
   e) **Encounter and Disposition Form**
   f) **Drug Dispensing Form (as necessary)**
   g) **Study Status Form (as necessary)**

F.2.4 Four and 8 Month Visit

This visit should occur within a +/- 2-week window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia or lipid medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication if applicable (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the physical exam, including weight. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, Creatinine, Lipid Profile, ALT and CPK.
4. Collect all glycemia related information.
   a) Review the previous 2 months SMBG values in the diary and download meter values to laptop, and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section F.1.3.b, F.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action** Form) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
   c) Record **current** medications including name, dose, and participant self-report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on the **Standard Glycemia Management Form**.
   d) If any conditions in Box A apply, then reduce dose or discontinue glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications
➢ HbA1c ≤ 6.5%

   e) **If any necessary adjustments to glycemia medications were not made since receipt of Central Lab HbA1c results, do so now according to the HbA1c value in Section F.2.2.**
   f) Advise the participant to contact the clinical site if he or she is experiencing > 1 episode of symptomatic hypoglycemia /week.
   g) Recommend appropriate SMBG frequency according to Table F.1.3 (≤ 7times/wk if on diet/oral therapy and ≤ 3 times/day if on insulin).
   h) Instruct participants on when and how to self-titrate (if applicable).
   i) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medications Log.** If on insulin, record name and dose on **Standard Glycemia Management Form**.

j) Provide SMBG logbooks and instructions for their completion.

5. For the Lipid Trial:
   a) Determine compliance with lipid drug regimen and record information on **Lipid Medications Management Form**.
   b) Determine if any potential statin/fibrate related side effects are present.
   c) Ask participant about coumadin use (see Section F.1.3.f). Review the list of prohibited medications found in MOP Chapter 5.
   d) Fasting Lipid Profile, ALT, CPK and Creatinine sent to Central Chemistry Lab.

   NOTE: See Section F.1.2.b if notification that the participant's GFR falls below cutoff levels is received. See Section F.1.3.f if participant's LDL-C or Triglycerides exceed cutpoints.
6. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medications as necessary. Scan label bar codes into computer as soon as possible after the visit so that adequate inventory can be maintained at the clinical site.
7. Schedule a clinic appointment in 4 months. Remind participant to come fasting.
8. Remind participants to bring all their medications, glucose meter and SMBG records at next visit.
9. Complete the following forms and enter data as required:
   a) **Interval History and Follow-up**
   b) **Standard Glycemia Management Form**
   c) **Glycemia Medications Log**
   d) **Severe Hypoglycemia Action Form (as necessary)**
   e) **Lipid Medications Management Form**
   f) **Encounter and Disposition Form**
   g) **Event Forms (as necessary)**
   h) **Drug Dispensing Form (as necessary)**
   i) **Cost Substudy Form (as necessary)**
   j) **Study Status Form (as necessary)**

F.2.5 Annual Visits (12, 24, 36, 48, 60, 72, 84, and 96 Months)

This visit should occur within a +/- 2-week visit window. The participants will be instructed to attend the clinic following an overnight fast (since ~ 10 p.m. the previous evening). They should not take their glycemia or lipid medications on the morning of this clinic visit but should be instructed to bring their medications, glucose meter, SMBG records and significant other or support person with them. They should, however, take their blood pressure medication if applicable (with water) prior to coming to clinic. During the visit, the following procedures will be conducted:

1. Review and update Contact Information.
2. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the

Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.

3. Perform the Annual Physical Exam, including weight, height, waist circumference, visual acuity, foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3.).
4. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium (**12 month, prn, and exit visits**), Creatinine, Lipid Profile, ALT, and CPK. **(Blood samples for storage of additional aliquots, where approved, should occur at the 24-month, 48-month 72-month and 96-month visits).**
5. Review the Concomitant Medications Inventory list located in the **Annual Follow-up and Physical Exam Form** with participant to document all non-study medications currently taking.
6. Participants will be given the **Health Utilities Index Form** and instructed on how to complete it **(12-month, 36-month and 48-month visits)**. Verify that the participant completes all items before end of visit **(12-month and 36-month visits)**
7. **A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Lab every 2 years for the 24-month, 48-month, 72-month and 96-month visits.**
8. **An ECG will be obtained and transmitted to the ACCORD ECG Reading Center every 2 years for the 24-month, 48-month, 72-month and 96-month visits.** Retain a copy for participant's research records.
9. Collect all glycemia related information:
   a) Review the previous 4 months SMBG values in diary, download meter values to laptop, and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Complete **Standard Glycemia Management Form**. Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section F.1.3.b, F.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action Form**) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
   c) Record **current** medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   d) If any conditions in Box A apply, then reduce dose or discontinue glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ $\geq$ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications
➢ HbA1c $\leq$ 6.5%

e) **If any necessary adjustments to glycemia medications were not made since receipt of Central Lab HbA1c results, do so now according to the HbA1c value in Section F.2.2.**
f) Advise participant to contact the clinical site if he or she is experiencing > 1 episode of symptomatic hypoglycemia /week.
g) Recommend appropriate SMBG frequency according to Table F.1.3 ($\leq$ 7 times/wk if on diet/oral therapy and $\leq$ 3 times/day if on insulin).
h) Record name, dose, and adherence of **all** glycemia medications on the **Glycemia Medication Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
i) Provide SMBG logbooks and instructions for their completion.
j) Update the **Unified Form** to ensure a smooth and steady flow of diabetic testing supplies being shipped by NetGroup Diabetic Services (**US sites only**).

10. For the Lipid Trial:
    a) Determine participant's report of compliance with lipid drug regimen and record information on **Lipid Medications Management Form**.
    b) Ask participant about coumadin use (see Section F.1.3.f). Determine if any potential statin/fibrate related side effects are present.
    c) Fasting Lipid Profile, ALT, CPK and Creatinine sent to the Central Chemistry Lab.

    NOTE: See Section F.1.2.b if notification that the participant's GFR falls below cutoff levels is received. See Section F.1.3.f if participant's LDL-C or Triglycerides exceed cutpoints.
11. Remove labels from study medications and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after visit so that adequate inventory can be maintained at the clinical site
12. Participants assigned in the substudies (Health Related Quality of Life (HRQL), Physical Activity, Diet) will complete the appropriate questionnaires (**at 12-month, 36-month and 48-month visits**). Verify that the participant completes all items before end of visit. Complete **Cost Substudy Form** for participants in the Cost Substudy.
13. Schedule follow-up clinic appointment in 4 months.
14. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
15. Complete the following forms and enter data as required:
    a) **Participant Contact Information Form (update as necessary)**
    b) **Annual History and Follow-up Form**
    c) **Standard Glycemia Management Form**
    d) **Glycemia Medications Log**
    e) **Severe Hypoglycemia Action Form (as necessary)**
    f) **Lipid Medications Management Form**
    g) **Encounter and Disposition Form**
    h) **Health Utilities Index Form (12-month, 36-month, and 48-month visits)**
    i) **The Unified Form (US Sites)**
    j) **Visual Acuity Worksheet (24-month, 36-month, and 72-month visits)**
    k) **Ophthalmology Exam Form (as necessary)**

l) **Assigned Substudy Questionnaires (as necessary at 12-month, 36-month, and 48-month visits)** .
m) **Drug Dispensing Form (as necessary)**
n) **Cost Substudy Form (as necessary)**
o) **Study Status Form (as necessary)**

F.2.6 Sixteen and 20 Month Visit

This visit should occur within a +/- 4-week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the exam, including weight. Using appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c and Creatinine.
4. Collect all glycemia related information.
   a) Review the previous 4 months SMBG values in diary, download meter values to laptop and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Complete **Standard Glycemia Management Form**. Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section F.1.3.b, F.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action** Form) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
   c) Record **current** medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   d) Upon receipt of the Central Lab HbA1c value, refer to section F.2.2 in this chapter.
   e) Advise participant to contact the clinical site if he or she is experiencing > 1 episode of symptomatic hypoglycemia /week.
   f) Recommend appropriate SMBG frequency according to Table F.1.3 ($\leq$ 7 times/wk if on diet/oral therapy and $\leq$ 3 times/day if on insulin).
   g) Adjust the glucose-lowering study drug as needed and record name, dose of **all** glycemia medications, on the **Glycemia Medication Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   m) Provide SMBG logbooks and instructions for their completion.

5. For the Lipid Trial:
   a) Determine participant's report of compliance with lipid drug regimen and record information on the **Lipid Medications Management Form.**
   b) Ask participant about coumadin use (see Section F.1.3.f).Determine if any potential statin/fibrate related side effects are present.
   c) Review prohibited/ discouraged medications with participant (See MOP Chapter 6, Section 6.3.5).

   NOTE: See Section F.1.2.b if notification that the participant's GFR falls below cutoff levels is received. See Section F.1.3.f if participant's LDL-C or Triglycerides exceed cutpoints.
   d) Dispense study statin and fibrate/placebo as necessary.
6. Remove labels from study medication and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after visit so that adequate inventory can be maintained at the clinical site.
7. Complete **Cost Substudy Form** for participants in the Cost Substudy.
8. Schedule the next clinic appointment. Remind participant to come fasting for the 24 month visit.
9. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
10. Complete the following forms and enter data as required.
    a) **Interval History and Follow-up Form**
    b) **Standard Glycemia Management Form**
    c) **Glycemia Medications Log**
    d) **Severe Hypoglycemia Action Form (as necessary)**
    e) **Lipid Medications Management Form**
    f) **Encounter Disposition Form**
    g) **Preliminary Event Notification Form (as necessary)**
    h) **Event Forms (as necessary)**
    i) **Drug Dispensing Form (as necessary)**
    j) **Cost Substudy Form (as necessary)**
    k) **Study Status Form (as necessary)**

F.2.7 Subsequent 4 Month Visits (28, 32, 40, 44, 52, 64, 68, 76, 80, 88, 92)

This visit should occur within a +/- 4-week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.

2. Perform the exam, including weight. Using appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c and Creatinine.
4. Collect all glycemia related information.
   a) Review the previous 4 months SMBG values in diary, download meter values to laptop and assess for medication/lifestyle adjustment in the glycemia intervention.
   b) Complete **Standard Glycemia Management Form**. Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section F.1.3.b, F.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action** Form) or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
   c) Record **current** medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   d) If any conditions in Box A apply, then reduce dose or discontinue glucose lowering drug:

BOX A
➢ Any severe hypoglycemia
➢ Symptomatic hypoglycemia episodes > 1/week
➢ ≥ 50% SMBG levels < 90 mg/dl (5 mmol/l)
➢ Any adverse effects of glycemia medications
➢ HbA1c ≤ 6.5%

   e) **If any necessary adjustments to glycemia medications were not made since receipt of Central Lab HbA1c results, do so now according to the HbA1c value in Section F.2.2.**
   f) Advise participant to contact the clinical site if he or she is experiencing > 1 episode of symptomatic hypoglycemia /week.
   g) Recommend appropriate SMBG frequency according to Table F.1.3 (≤ 7 times/wk if on diet/oral therapy and ≤ 3 times/day if on insulin).
   h) Adjust the glucose-lowering study drug as needed and record name and dose of **all** glycemia medications on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.
   i) Provide SMBG logbooks and instructions for their completion.
5. For the Lipid Trial:
   a) Determine participant's report of compliance with lipid drug regimen and record information on the **Lipid Medications Management Form.**
   b) Ask participant about coumadin use (see Section F.1.3.f). Determine if any potential statin/fibrate related side effects are present.
   c) Review prohibited/ discouraged medications with participant (See MOP Chapter 6, Section 6.3.5).

   NOTE: See Section F.1.2.b if notification that the participant's GFR falls below cutoff levels is received. See Section F.1.3.f if participant's LDL-C or Triglycerides exceed cutpoints.
   d) Dispense study statin and fibrate/placebo as necessary.

6. Remove labels from study medication and place on **Drug Dispensing Form** then dispense study medication. Scan label bar codes into computer as soon as possible after visit so that adequate inventory can be maintained at the clinical site.
7. Complete **Cost Substudy Form** for participants in the Cost Substudy.
8. Schedule a clinic appointment in 4 months. Remind participant to fast prior to any clinic visit requiring a fasting lipid profile.
9. Remind participants to bring all their medications, glucose meter and SMBG records at each visit.
10. Complete the following forms and enter data as required.
    a) **Interval History and Follow-up Form**
    b) **Standard Glycemia Management Form**
    c) **Glycemia Medications Log**
    d) **Severe Hypoglycemia Action Form (as necessary)**
    e) **Lipid Medications Management Form**
    f) **Encounter Disposition Form**
    g) **Preliminary Event Notification Form (as necessary)**
    h) **Event Forms (as necessary)**
    i) **Drug Dispensing Form (as necessary)**
    j) **Cost Substudy Form (as necessary)**
    k) **Study Status Form (as necessary)**

F.2.8 Exit Visit

This visit should occur within a +/- 4-week window. The participants will attend the clinic and the following procedures will be conducted:

1. Obtain interval history, including adverse, hypoglycemic and outcome events. If the participant has had a myocardial infarction or stroke, or other reportable event, obtain preliminary information and complete and data enter outcome form- **Preliminary Event Notification Form**. Obtain a release of information if not already done, and request the additional required information for the event needed to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form** or **Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed to the Coordinating Center.
2. Perform the exam, including weight. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 9, Section 9.2.3).
3. Blood samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, Fasting Plasma Glucose, Potassium, ALT, Creatinine, Lipid Profile, CPK and for storage of additional aliquots (where approved).
4. A spot urine sample for urinalysis will be obtained, processed and shipped to the ACCORD Central Chemistry Lab.
5. An ECG will be obtained and transmitted to the ACCORD ECG Reading Center. Retain a copy for records.
6. Collect all glycemia related information.

a) Review the previous 4 months SMBG values in diary, download meter values to laptop and assess for medication/lifestyle adjustment in the glycemia intervention.
b) Record occurrence of any severe hypoglycemia as well as the occurrence and frequency of hypoglycemia (See Section F.1.3.b, F.1.3.c and MOP Chapter 8, Section 8.4.4). If any severe hypoglycemia (fill out **Severe Hypoglycemia Action Form)** or symptomatic hypoglycemia episodes > 1/wk occurred, reduce dose of a glucose lowering drug. Review symptoms and therapy for hypoglycemia.
c) Record current medications including name, dose and participant's self report of adherence on the **Glycemia Medications Log**. If on insulin, record name and dose on **Standard Glycemia Management Form**.

7. For the Lipid Trial:
   a) Determine participant's report of compliance with lipid drug regimen and record information on the **Lipid Medications Management Form.**
   b) Determine if any potential statin/fibrate related side effects are present.
8. Participants will be prescribed appropriate non-study antihyperglycemia therapy and lipid-lowering therapy based on their current status and post-trial follow-up care will be arranged.
9. Complete the following forms and enter data as required.
   a) **Participant Contact Information (as necessary)**
   b) **Annual History and Follow-up Form**
   c) **Standard Glycemia Management Form**
   d) Glycemia Medications Log
   e) **Severe Hypoglycemia Action Form (as necessary)**
   f) **Lipid Medications Management Form**
   g) **Encounter Disposition Form**
   h) **Health Utilities Index Form**
   i) **Visual Acuity**
   j) **Ophthalmology Exam Form (as necessary)**
   k) **Preliminary Event Notification Form (as necessary)**
   l) **Event Forms (as necessary)**
   m) **Cost Substudy Form (as necessary)**
   n) **Study Status Form (as necessary)**

Figure F.4:
Treatment Group Algorithm for Standard Glycemia Therapy Group (Goal: HbA1c 7% to

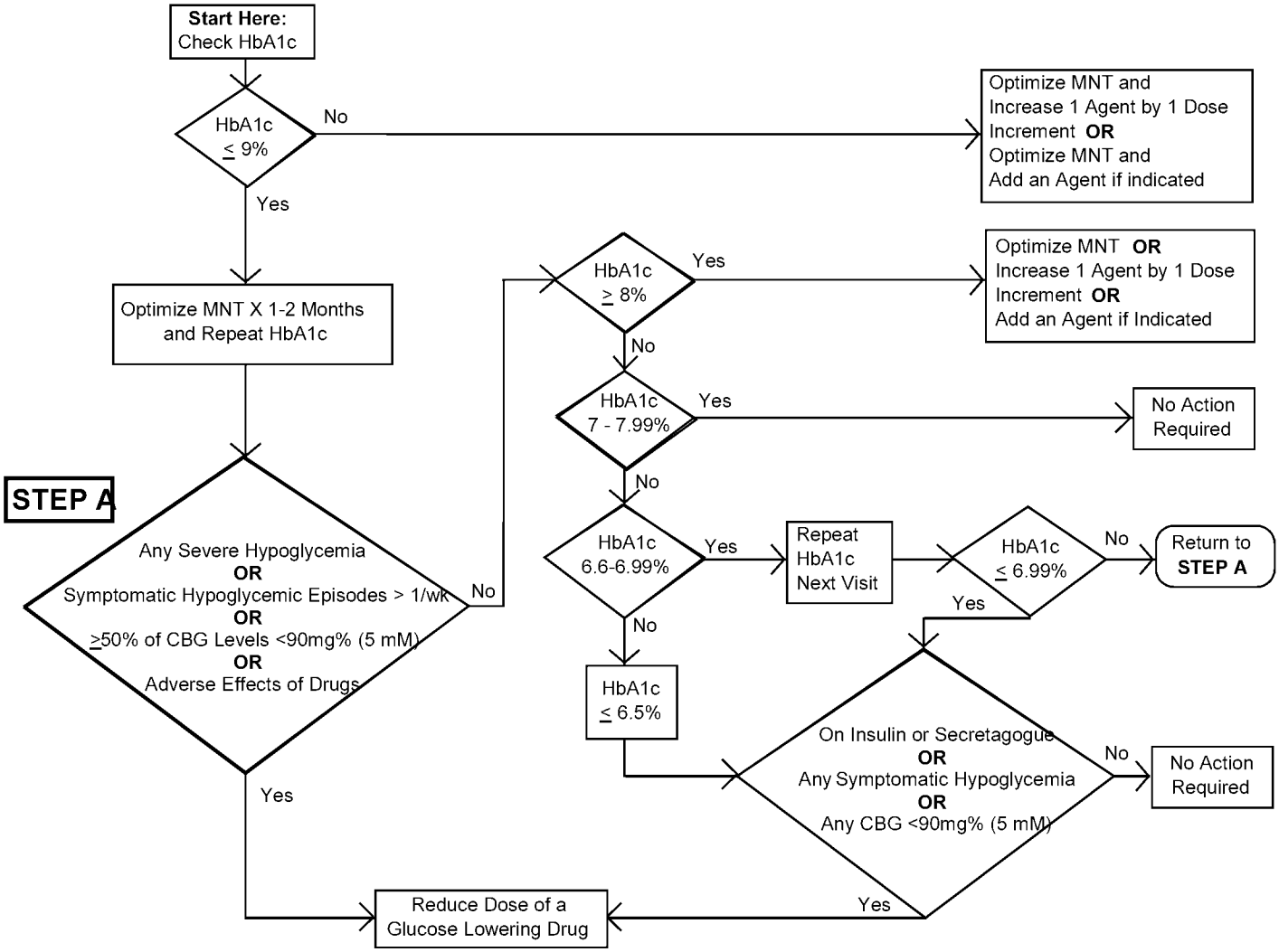
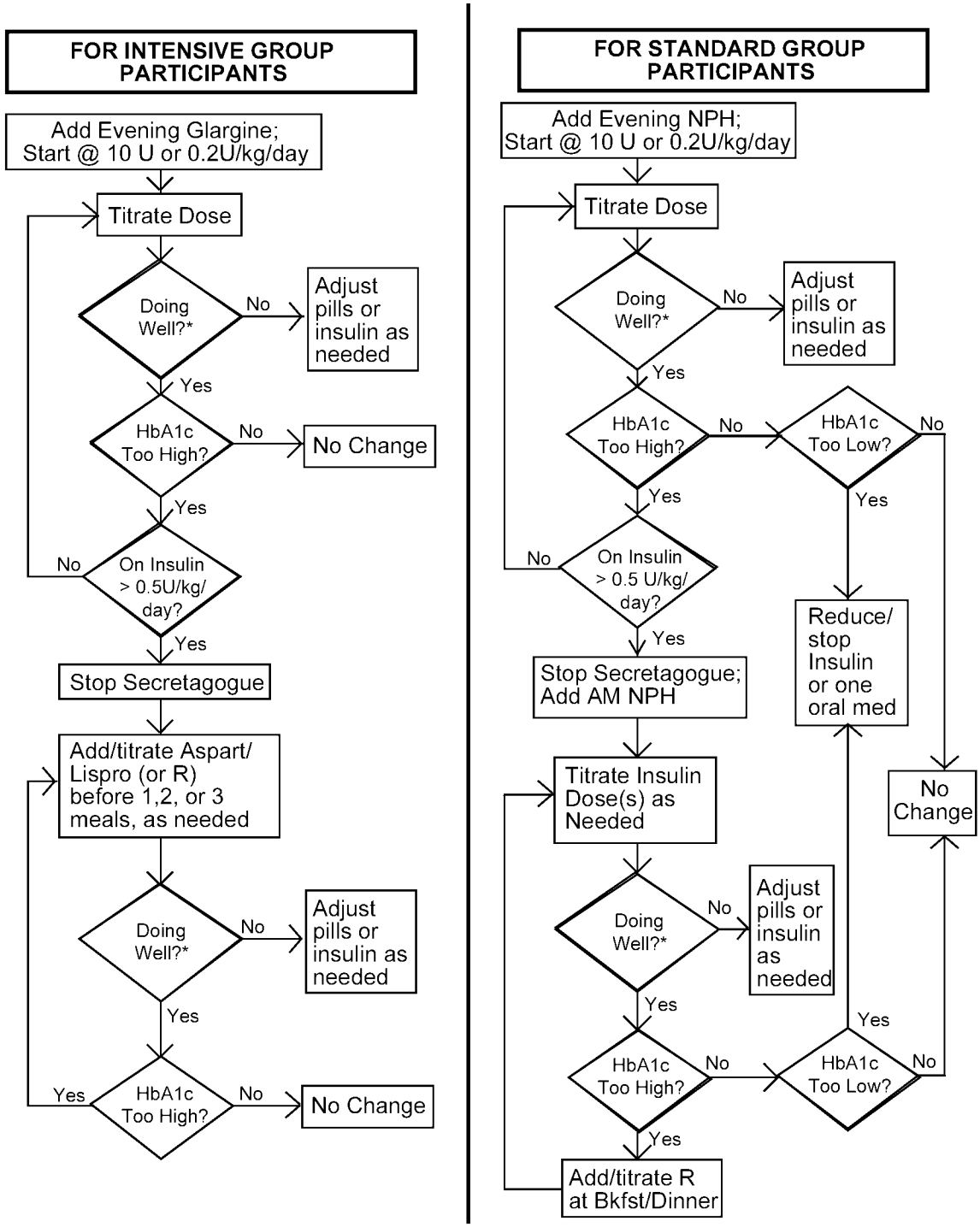


Figure 3.3:
Use of Insulin for Participants On Maximal Oral Therapy



*Doing well: no severe hypoglycemic or adverse event or no reason to reduce therapy (as described in Figure 3.2)

Thiazolidinedione Drugs (e.g. Avandia or Rosiglitazone)

ACTIONS of THIAZOLIDINEDIONES

The drug Avandia (rosiglitazone) belongs to a group of medications called thiazolidinediones (or glitazones or TZD's), and may be supplied as part of the ACCORD trial. Actos (pioglitazone) is another drug that belongs in this group. These drugs lower the blood glucose by reducing the body's resistance to the action of insulin (i.e. making your own insulin work more effectively). They can be used alone or can be combined with other diabetes pills or insulin.

COMMON SIDE EFFECTS

1. Hypoglycemia (low blood sugar)

These drugs can lead to hypoglycemia. When taken alone, the risk of hypoglycemia is low. When taken with insulin or other pills, the risk of hypoglycemia is higher.

If you do experience symptoms of a low blood sugar (such as lightheadedness, sweating, nervousness, hunger, a sensation of a racing heart, headache, or sudden fatigueat unusual times), check your blood sugar. If the level is less than 70 mg/dl (3.9 mmol/l) you may be suffering from hypoglycemia. If so, drink 4 ounces of juice or regular soda or eight ounces of milk or have three glucose tablets or five Life Savers (i.e. 15 grams of carbohydrate). Recheck your blood sugar in 15 minutes to make sure it has risen to at least 90 mg/dl (5.0 mmol/L). If low blood sugar reactions are frequent, severe or unexpected, call your doctor.

2. Weight Gain

These drugs may lead to weight gain. Weight gain is due to the lowering of blood sugar by insulin and drugs that act like insulin. This reduces the amount of sugar lost in the urine and helps the body store extra energy in fat cells. Sometimes, weight gain may be due to some fluid retention. Regardless of the cause, the amount of weight gained or lost depends on the level of physical activity and diet, or can be due to other drugs that are being taken. For example, some people gain more weight if insulin is also being taken. To minimize weight gain or to cause weight loss, exercise regularly, eat low fat foods, avoid extra snacks and large portions.

3. Fluid Retention

These drugs may lead to fluid retention. Fluid retention is generally mild with some swelling in the ankle or leg or bloating; it may be more pronounced when these drugs are used together with insulin, and rarely, the fluid retention can be severe or even life threatening. If you develop major leg swelling or especially shortness of breath either with activity or at rest, see your doctor as soon as possible. Reducing the dose, adding diuretics (water pills) or adjusting other medications (such as blood pressure pills, calcium channel blockers, non-steroidal anti-inflammatory drugs or arthritis pills) can also be used to manage this problem. ***You and your doctor should pay close attention to fluid retention if you take insulin or have heart failure or other heart problems.***

POTENTIAL SIDE EFFECTS

Because of rare cases of severe liver disease with a related medicine that is no longer available (Rezulin or troglitazone), you must have your blood drawn for liver enzyme tests (ALT) when treated with these drugs every 2 months for the first year of treatment and intermittently thereafter. If you develop persistent nausea, vomiting, belly pain, fatigue, loss of appetite, dark urine, yellowing of the eyes or skin while treated with this drug, stop the medication and see your doctor for a blood draw within a few days.

DOSING

Avandia (rosiglitazone) can be taken once a day, but may work a bit better if taken twice daily. Actos (pioglitazone) can be taken any time of the day. Both drugs can be taken either with or without food. It may take 12 weeks to see the full effect of a dose.

8. Assessment, Management, and Reporting of Adverse Events

8.1 Overview

Management of adverse events, or potential side effects, is based on the philosophy of protecting the safety of the participant, while at the same time making every effort to adhere to the treatment programs. In those instances where deviations from the treatment protocol are necessary in the judgment of the clinic physician, these deviations should be as minimal as possible. The procedures for managing adverse events reflect these philosophies. Suggested approaches to some of the more notable potential problems are specified in some detail. Other, less common problems are not described, reflecting the philosophy that each clinic physician will need the flexibility to use his or her own judgment for handling the wide variety of situations that may develop, in a way that will maintain both the safety of the participant and the integrity of the trial.

8.2 Definitions

Serious Adverse Experiences must be reported to the Coordinating Center. A Serious Adverse Experience (SAE) is defined as any adverse experience that is significantly life threatening and/or results in death, permanent disability, hospitalization or prolongation of hospitalization, myositis/myopathy, or hepatitis. If an event meets the definition for a serious adverse experience, a **Serious Adverse Experience Form** must be completed and reported within 24 hours of discovering the event.

The eight specific types of serious adverse experience that are of interest are:

- Death
- Any life threatening event – any event that posed a significant risk of death
- Any event resulting in persistent or significant disability
- Any hospitalization
- Any prolongation of hospital stay
- Myositis/myopathy
- Hepatitis
- Hypoglycemia event – requiring medical/paramedical attention; response of "1" (a-d) is marked in Part 1 of the **Severe Hypoglycemia Action Form**

Events that are part of the primary and secondary ACCORD outcomes (examples: MI, stroke, unstable angina) are NOT to be considered adverse events unless the Investigator believes that an ACCORD study drug or device caused the event or contributed to the immediate cause of the event.

8.3 Assessment of symptoms

8.3.1 Allergy, syncope or severe dermatitis

Development of an allergy (such as asthma, or a generalized rash) to any of the ACCORD medications, syncope, or severe dermatitis, requires that the medications be

discontinued. Such participants will often be suitable for subsequent rechallenge. Ultimately, they may need to be withdrawn permanently from the medication.

8.3.2 Angioedema, neutropenia, or necrotizing vasculitis

Development of angioedema, neutropenia, or necrotizing vasculitis requires that the suspect ACCORD study medication be discontinued. Such participants will need to be withdrawn permanently from the medication.

8.3.3 Clinical hepatitis

Participants developing clinical hepatitis that are taking a thiazolidinedione or dihydropyridine calcium channel blocker will need to have their medication discontinued.

In the lipid arm of ACCORD, consideration must be given to discontinuation of the statin and blinded medication. The role of ALT monitoring is discussed in Section 8.4.1.

8.3.4 Lactic acidosis

Development of lactic acidosis, or high suspicion of its development, requires that metformin be discontinued.

8.3.5 Muscle pain—in the lipid arm of ACCORD

If the patient reports diffuse muscle pain or weakness, or pain in two or more unrelated muscle groups, a creatine kinase (CK) should be obtained locally (see Section 8.4.2 for suggested management).

8.4 Blood tests

Physician investigators will routinely receive reports of all Central Laboratory determinations except lipid values (for that component of ACCORD), which will be masked after randomization.

8.4.1 Serum ALT

The Central Laboratory will routinely provide ALT levels to study investigators in a timely manner. ALT levels exceeding three times the upper limit of normal will be flagged as "alert" values. When ALT is in the alert range, blood should be redrawn and sent to the Central Laboratory for repeat measurement. If the alert value is not explained by other factors, the investigator should consider stopping one or more study medications (thiazolidinedione, HMG coA reductase inhibitor, blinded fibrate/placebo) as appropriate.

In the lipid arm of ACCORD, participants will be taking a statin and masked medication (either fibrate or placebo). These participants will need to have their

medication discontinued for persistently elevated ALT. After the ALT returns to normal or pre-treatment levels, the participant may be encouraged first to resume the masked study medication but not the simvastatin. After continued ALT monitoring shows stability at normal levels, the patient may be re-challenged with simvastatin.

8.4.2 Serum creatine phosphokinase (CPK) in the lipid arm of ACCORD

If the CPK (sometimes abbreviated 'CK') concentration is ever in excess of 5 times the upper limit of normal, another measurement should be obtained immediately. If the second value is also greater than 5 times the upper limit of normal, the ACCORD lipid medications will be permanently discontinued if the participant experienced out of the ordinary muscle aches and pains at the time of the first elevated CK. If the participant has not experienced these symptoms and there is a second elevated CK, the ACCORD lipid medications should be temporarily stopped and CK checked weekly. The participant's lipid medications can be restarted beginning with the masked study drug (followed by the simvastatin) once there has been 2 consecutive measures less than or equal to 5 times the upper limit of normal.

If the CK measurement is ever in excess of 10 times the upper limit of normal, *with* or *without symptoms*, the ACCORD lipid medications should be temporarily stopped and CK rechecked immediately. If the second CK is also greater than 10 times the upper limit of normal, lipid medications are permanently discontinued. If the second CK is greater than 5 times but less than ten times the upper limit of normal and the participant reported out of the ordinary severe muscle aches and pains at the time of the first CK, the lipid medication is also permanently discontinued. If the second CK measurement is greater than 5 but less than 10 times the upper limit of normal and the participant did not experience symptoms with the first elevated CK, then recheck the CK weekly and re-challenge when the CK is less than or equal to 5 times the upper limit of normal on 2 consecutive measures. If the second CK measurement is less than or equal to 5 times the upper limit of normal, the ACCORD lipid medications can be re-challenge immediately. As stated above, restart the masked medication first followed by the simvastatin.

8.4.3 Potassium and Creatinine

Participants in the BP component of the trial who are treated with ACE inhibitors, AII receptor blockers, or diurectics will be monitored for hypo- or hyperkalemia or renal dysfunction by monitoring the potassium and creatinine levels.

ACCORD investigators are also expected to use their judgment and reduce or, if necessary, to discontinue selected ACCORD study medications in the presence of other medically significant side effects that are judged to be attributable to study drug, and to rechallenge (if judged appropriate) with a reduced dosage when the side effects subside.

Other chapters in the Manual of Procedures contain information on the management of non-serious side effects including most episodes of hypoglycemia, myopathy, weight gain. (See MOP Chapter 6).

8.4.4 Severe Hypoglycemia – Medical or Paramedical

The ACCORD policy defines a severe hypoglycemic event as any hypoglycemia requiring assistance. A serious hypoglycemic event is defined as "any episode requiring medical or paramedical attention in which there was either a documented capillary glucose level <50 mg/dl (<2.8 mmol/l) or prompt recovery with oral carbohydrate, intravenous glucose or glucagon."

When a clinical site is informed of a severe hypoglycemia event, they must:

1) Complete a Severe Hypoglycemia Action Form (SHAF)
2) Enter relevant data from the SHAF into the ACCORD web site

If the information entered on the SHAF indicates that the event meets the criteria for a serious event an **SAE Form** must be completed. Additionally, the Coordinating Center will initiate an automated process to assist with monitoring the clinical management of the participant. The automated process for monitoring initial events was initiated on October 6, 2003 and is described below. Automated processes for monitoring participant management after second and third events can be found in Section 4 of attached policy at the end of the chapter.

The monitoring process following initial severe hypoglycemia events is comprised of five steps as follows:

a) An automated email system notifies the site PI, site Coordinator, CCN PI, CCN Coordinator and CCN Glycemia Working Group representative of the event by email. The Glycemia Working Group representatives from each CCN that are notified with these emails are shown below:

Glycemia Working Group Representatives Notified in Serious Hypoglycemia Monitoring Process

CCN	Glycemia Working Group Representative
Canada	
Western	
Minnesota/Iowa	
Ohio/Michigan	
Northeast	
Southeast	
VA	

b) In response to the email, the site PI must complete and data enter an SAE form within 24 hours.

c) Also in response to the email, either the CCN PI or Glycemia Working Group representative reviews the data entered by the clinical site on the Severe Hypoglycemia Action Form and Serious Adverse Experience Form on the ACCORD web site. The automated email provides directions on how to access the correct data.

d) The CCN PI/Glycemia Working Group representative determines if the data entered and response to the event requires direct contact with the site; if so, then he/she initiates that contact to review the case.

e) The CCN PI/Glycemia Working Group representative completes the review form on the ACCORD Web site by following a link provided in the notification email.

If you have any questions about this procedure, please contact
at the Coordinating Center.

8.5 Reporting Serious Adverse Experiences Thought to be Related to Study Meds

8.5.1 Reporting to the ACCORD Coordinating Center

Most apparent side effects will not be serious. However, some apparent side effects may be one of the eight serious adverse experiences of interest in ACCORD. These eight types are listed MOP Section 8.2. Specifically, any of these eight events that are **deemed by the investigator to be definitely or possibly caused by any study drug (blinded or open-labeled)** must be reported to the Coordinating Center within 24 hours via the **ACCORD Serious Adverse Experience Form** (described below in Section 8.6) filling the **Serious Adverse Experience Form** out completely. If the Investigator feels that the SAE is not due to study drug, then the SAE form should be signed and data entry questions 1-3 only. Also this form must be completed if a response of "1" (a-d) is marked in Part 1 of the **Severe Hypoglycemia Action Form**. This process (including the completion of the **ACCORD Serious Adverse Experience Form**) is described below in Section 8.6. The Coordinating Center may be notified by telephone, e-mail, fax or by data entry.

8.5.2 Reporting to the Food and Drug Administration

The Coordinating Center and the NHLBI Project Office will review investigator reports of serious adverse experiences thought to be related to a study drug.

In addition to individual case safety reports, the Project Office and Coordinating Center will prepare an annual summary of safety reviews as part of the annual report to the FDA on the ACCORD IND for fenofibrate and simvastatin.

8.5.3 Reporting to IRBs

ACCORD Investigators are expected to follow any requirements from their own IRB regarding which case reports of adverse events the IRB expects to receive. Investigators will

be given summaries of the DSMB review of the accumulating ACCORD safety data (see Section 8.7, below) within one month of the DSMB meeting, to forward to their IRB.

8.6 ACCORD Serious Adverse Experience Form

8.6.1 General Instructions

An **ACCORD Serious Adverse Experience Form** (form SAESP) must be completed:

- If an ACCORD participant has a serious adverse experience (SAE) that fits into one of the eight categories noted below (and in Question 1 on the form)
- If the Investigator feels that the SAE may definitely or possibly be caused by one of the study drugs.

The eight types of adverse experience that are of interest are:

- Death
- Any life threatening event
- Any event resulting in persistent or significant disability
- Any hospitalization
- Any prolongation of hospital stay
- Myositis/myopathy
- Hepatitis
- Hypoglycemia event ("1" (a-d) is checked in Part 1 of the Severe Hypoglycemia Action Form)

If the investigator does not think that there is any relationship between the SAE and an ACCORD study medication, then the Principal Investigator must sign the form and data enter questions 1-3 on the form.

All SAEs must be reported to the Coordinating Center **within 24 hours** of discovering the event. Any supplemental information/attachments can be faxed to the ACCORD SAE Monitor ( ) at the Coordinating Center at if requested.

8.6.2 Specific Instructions Regarding Form Completion

As with all ACCORD forms, place the patient's ID label in the space provided. Complete today's date (the date the form was completed, i.e. the date the SAE was discovered) as mm/dd/yy, using leading zeros as necessary (i.e., 07/06/01).

Type of Adverse Experience. From the list of eight types of SAEs, select all that apply. The outcome of the serious adverse experience may fall into one or more of the categories as listed in the first item. Thus, more than one adverse experience for a single patient can be listed per form.

Duration of this experience. Record the start and end dates of the SAE. If the SAE is an ongoing experience, please indicate by checking the box labeled "Ongoing". If "Ongoing" is

checked, please review the event periodically and enter an end date when the event and/or sequelae have ended. A change from "Ongoing" to an end date should be data entered when available; however a new form does not need to be faxed.

Relationship of SAE to the ACCORD Medication. For each adverse experience, indicate whether in the PI's opinion that the experience was definitely or possibly due to an ACCORD study medication. For this purpose, the ACCORD study medications include all medications dispensed by ACCORD Investigators and staff for management of Glycemia and either blood pressure or lipids. If the SAE is determined to <u>not</u> be due to an ACCORD study medication, answer only questions 1-3. The Principal Investigator must sign the form and the form must be data entered. If the SAE is suspected to be due to an ACCORD study medication, please complete the remainder of the SAE Form and record the suspected medication(s) in the box indicated. The Principal Investigator must sign the form and the form must be data entered.

Patient's Age at Time of SAE. Put the patient's age in this space.

Patient's weight at time of SAE. In the space provided, enter the patient's weight, being careful to note the decimal point to the left of the right-most space. Indicate whether the recorded weight was in pounds or kilograms.

Please list any relevant history, including pre-existing medical conditions. This includes (but is not limited to) any chronic diseases, allergies, race, pregnancy, smoking and/or alcohol use, any indication of hepatic or renal dysfunction. For instance, all ACCORD participants have Type II diabetes and either hypertension or hyperlipidemia.

Record the participant's acrostic (first three letters of the last name, first two letters of the first name and middle initial or "-" if no middle initial) or place a current pre-printed label over the 'Acrostic' boxes.

List Study Drug. List all study drugs that apply. List the dosing schedule in the Time/Day column.

Concomitant Medications. List all concomitant medications in the boxes indicated. This includes all prescription medications, over the counter medications and complementary medications including ACCORD Study medications not listed in # 7 on the form. Use a separate line for each medication. When listing the dosage be sure to include the unit of measure. List the dosing schedule and the route of administration.

Record the participant's acrostic (first three letters of the last name, first two letters of the first name and middle initial or "-" if no middle initial) or place a current pre-printed label over the 'Acrostic' boxes.

Action Taken. Checking all that apply, report whether the dose of study medication was reduced, whether symptomatic therapy was given, and/or whether the study medication was discontinued. If nothing was done, check "No Action Taken."

Record the participant's acrostic (first three letters of the last name, first two letters of the first name and middle initial or "-" if no middle initial) or place a current pre-printed label over the 'Acrostic' boxes.

Patient's Current Condition. Please record the participant's current condition, checking all that apply.

Classification of Body System Affected. Checking all that apply, report the systems that were affected. If you need to, you can select "Other" to report a system not on the list.

Please Describe this Adverse Experience. Use this space to provide details regarding the SAE, including (but not limited to) any relevant lab values and clinical information, including your observations regarding what happens if action was taken (e.g., if the suspected drug was discontinued or down-titrated, or if other therapy had some sort of effect on the SAE). Note, any form without something written in this section will be automatically queried by the Coordinating Center.

It is very important to describe the event in detail, including a description of what happened and a summary of all relevant clinical information (medical status prior to the event; signs and/or symptoms; differential diagnosis for the event in question; clinical course; treatment; outcome, etc.). If available and if relevant, include synopses of any office visit notes or the hospital discharge summary. To save time and space (and if permitted by your institution), please attach copies of these records with any confidential information deleted. DO NOT identify any patient, physician, or institution by name.

INVESTIGATOR Signature: The clinic Principal Investigator must review and sign the completed form prior to data entry. At the time of data entry, please document that the PI reviewed and signed this from by checking the box labeled "Reviewed". Please file the original of this form in the participant's chart and copy to your IRB as appropriate per your IRB's regulations.

8.7 Role of the Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will play the central role in the review of adverse events for ACCORD as part of its responsibility for protection of the participants. Because it can review data aggregated from all clinical centers and broken down by treatment assignment, the DSMB has the best chance to detect treatment-related adverse events. A local IRB has almost no chance of detecting treatment related excess adverse events in ACCORD because it only reviews the data from its own center (less than 5% of the total data) and does not have access to data according to treatment assignment.

At each of its meetings, the Data and Safety Monitoring Board will review adverse events tabulated by treatment groups. If a trend for a greater incidence of an adverse effect is suspected, the Data and Safety Monitoring Board can request additional safety summaries between semi-annual meetings. Also, the Board reviews things like treatment group-specific laboratory values, weight change, etc. After each meeting, the ACCORD Project Office will

send a letter to each clinical center principal investigator indicating the results of the DSMB's safety assessment. Each principal investigator will send a copy of the letter to the Institutional Review Board that governs ACCORD at his/her center. Intervention related serious adverse events that change the risk/benefit of ACCORD will be reported promptly to the Institutional Review Board for each clinical center. Accumulating safety data may require the need to revise consent forms.

8.8 ACCORD Processes for Dealing with Severe Hypoglycemia

Introduction

A key side effect of the ACCORD glycemic intervention is that of severe hypoglycemia. As ACCORD is targeting physiologic glucose levels in high cardiovascular risk individuals, episodes of severe hypoglycemia are expected to happen. Moreover, they are expected to happen more frequently in the intensive glycemia group than in the standard glycemia group.

The ACCORD study has created a set of procedures to respond to every episode of severe hypoglycemia and to minimize the risk and incidence of recurrent episodes of severe hypoglycemia. These procedures include: a) provision of clear instructions to every participant regarding strategies to avoid severe hypoglycemia as well as instructions to treat and report any episodes of severe hypoglycemia to the site; b) a requirement for research personnel to complete SAE forms for any event requiring medical or paramedical attention as well as report severe hypoglycemic episodes promptly; c) mandatory review of each episode of severe hypoglycemia requiring medical or paramedical attention by the relevant CCN PI or his delegated member on the glycemia working group; d) mandatory completion of a narrative report by the site PI with review and interaction with the CCN PI (or his delegate) in response to every second or subsequent episode of severe hypoglycemia requiring medical or paramedical attention in an individual participant; e) the removal of any glycemic titration requirements for individuals having 3 or more events requiring medical or paramedical attention.

The status of severe hypoglycemia (i.e. rates, consequences and therapeutic response to each episode) overall and by CCN and site is reviewed monthly by the entire Glycemia Working Group and at least one other time per month by the CCN Glycemia representative. Moreover, the Severe Hypoglycemia Group reviews these data within each randomized glycemia intervention arm regularly.

The detailed algorithms are described below and in the flow charts.

1. Definitions of Severe Hypoglycemia in ACCORD

An episode of severe hypoglycemia can satisfy one of 3 mutually exclusive criteria. These include:

a) any episode requiring medical or paramedical attention in which there was either a documented capillary glucose level <50 mg/dl (2.8 mmol/l) OR prompt recovery with oral carbohydrate, intravenous glucose or glucagon;
b) any episode requiring the assistance of another person *(but not requiring medical or paramedical attention)* in which there was a documented capillary glucose level <50 mg/dl (2.8 mmol/l);

c) any episode requiring the assistance of another person *(but not requiring medical or paramedical attention)* in which there was prompt recovery with oral carbohydrate or glucagon BUT no documented capillary glucose level <50 mg/dl (2.8 mmol/l).

2. Clinical Site Response to any Severe Hypoglycemia Episode

As soon as a site is notified of an episode of severe hypoglycemia (i.e. any episode that meets any of the above definitions) by a participant (or other source), it is the responsibility of the site PI to review the episode and take appropriate action to reduce the risk of a subsequent one. Moreover, a Severe Hypoglycemia Action Form must be immediately completed and the relevant data entered into the ACCORD website. These actions may include one or more of the following:

- revision of the participant's medical status and presence of co-morbid conditions;
- revision of education regarding prevention and treatment of hypoglycemia including the use of glucagon;
- revision of the pharmacotherapeutic regimen;
- revision of physical activity and nutritional patterns;
- additional participant visits to the site, additional phone calls with the participant, supplementary nutritional education, and additional or modified glucose testing instructions;
- consultation with an ACCORD endocrinologist or member of the Glycemia Working Group;
- interaction with the primary (community) physician, local community health nurses, or family members;
- temporary relaxation of glycemic targets.
- For an expanded list of follow-up recommendations go to glycemia management> "Recommended Clinic Follow-up Procedures After a Severe Hypoglycemic Event in ACCORD".

As noted above, severe hypoglycemia status (overall, and by CCN and site) is reviewed by the Glycemia Working Group, Severe Hypoglycemia Group and CCN Glycemia representative at least once/month. Sites following participants who have had multiple episodes satisfying any definition (a, b, or c above) are also identified and contacted as needed. Moreover, as definition (a) is the one that is most likely to result in serious or even permanent sequelae; one or more episodes satisfying this definition will lead to an additional set of responses. These are noted below.

3. Study Response to a First Event Requiring Medical or Paramedical Attention

a) An automated system notifies the site PI and coordinator, CCN PI and coordinator, and CCN Glycemia Working Group representative of the event. (Appendix 1).
b) The site PI completes an SAE form within 24 hours on the website.
c) The CCN PI/Glycemia Working Group representative reviews the data entered into the Severe Hypoglycemia Action Form and the Serious Adverse Experience Form on the ACCORD website for this event.
d) The CCN PI/Glycemia Working Group representative determines if the data entered and response to the event require direct contact with the site; if it does, he/she initiates that contact to review the case.

e) The CCN PI/Glycemia Working Group representative completes the First Review Event Form on the ACCORD web site (Appendix 1) documenting the fact that the case review occurred. After the Coordinating Center reviews for appropriateness, the event is coded as closed on the website.

4. Study Response to a Repeat Event Requiring Medical or Paramedical Attention

a) An automated system notifies the site PI and coordinator, CCN PI and coordinator, and CCN Glycemia Working Group representative of the event; this message includes a request to the site PI to provide a narrative report of the case to the CCN PI/Glycemia Working Group Representative within 72 hours along with directions for the website and what to include in the narrative (Appendix 2).
b) The site PI completes an SAE form within 24 hours and data enters on the website.
c) The CCN PI/Glycemia Working Group representative reviews the data entered into the Severe Hypoglycemia Action Form and Serious Adverse Experience Form on the ACCORD website for this event as well as the narrative report provided by the site PI.
d) The CCN PI/Glycemia Working Group representative contacts the site. During the contact, he/she determines if the data entered, narrative report and direct interaction may require further scrutiny of the case. If both the Glycemia Working Group representative and the CCN PI agree that it does, he/she (or a delegate) reviews the case with the site (including the site PI and coordinators) in even more detail; this may include a review of documentation, medical notes, or any discharge summaries.
e) The CCN PI/Glycemia Working Group representative completes and enters the Event Review Form (Appendix 2) on ACCORD website documenting the fact that the case review occurred and describes further action if required.

5. Response to a Third or More Event Requiring Medical or Paramedical Attention

In addition to an automated email for the 3rd or higher event (Appendix 3) and the steps outlined under second event response, the following steps will occur:

a) The documentation collected above will be reviewed by a Glycemia Working Group representative who is not part of that CCN. He/she will prepare a brief narrative report and action plan for the Coordinating Center that may include any or all of the following components:
    - relaxation of individual glycemia goals for that participant, instead of the previously assigned ACCORD titration algorithm, in such a way as to minimize the risk of any further events;
    - revision of the pharmacotherapeutic regimen;
    - structured behavioral intervention, such as additional visits to the site, supplementary nutritional education, or glucose testing instruction;
    - mobilization of community resources to assist management, such as interaction with the primary (community) physician, local community health nurses, or family members;
    - involvement of an ACCORD or non-ACCORD endocrinologist in the community;
    - Structured ongoing review of this subject's management by a member of the Glycemia Working Group.

b) Once the out of network Glycemia Working Group Representative finishes his/her review, the narrative is emailed to (Coordinating Center,) who enters the review into the Other CCN Glycemia Working Group Representative Narrative Form.

c) ACCORD follow-up visits will continue to occur for data collection, no matter what alteration of the originally assigned treatment algorithm has been made.

Appendix 1
Notification of a 1st Severe Hypoglycemia Event Needing Medical /Paramedical Help

The following message is automatically generated to the CCN PI, CCN Coordinator, and CCN Glycemia Working group Representative and copied to the site PI, Site Coordinator and Coordinating Center:

FROM:
TO: [CCN PI, CCN Coordinator, CCN Glycemia Working Group Representative]
CC: [Site PI, Site Coordinator, Coordinating Center]
SUBJECT: First Severe Hypoglycemic Event #form.patid#

Memo to CCN PI and CCN Glycemia Working Group Representative

A severe hypoglycemia event requiring medical and/or paramedical assistance has just been reported for participant (patID) in your CCN.

If you are unable to review this case within 3 days, please reply to this email so another GWG representative can be contacted for the review.

Please complete the following tasks:

a) Review details of this case as soon as possible on the website;
Please refer to www.accordtrial.org > reports >severe hypoglycemia > event status > section A to review the SHAF and SAE details next to the participant's ID.

b) Once reviewed, determine if the site needs to be contacted for additional information.

c) Click on "incomplete" in respective column to add your name, date, and comments. Once you have entered your comments and your review is complete, click yes for "review is complete". If you have not finished your review click no for "review is complete".

First Event Review Form [patID] on website

Answer all parts that apply.
Reviewer: [select CCN PI or CCN Glycemia Working Group Representative]

1. Data on website was reviewed and response deemed appropriate on: [MM/DD/YYYY]

2. Site PI/Site Co-PI contacted and case reviewed if needed:[select Site PI/ Site Co-PI]
   Date Site PI/Site Co-PI contacted: [MM/DD/YYYY]
   Additional information obtained and/or advice provided: [additional information]

3. A more detailed note is being prepared: [no/yes]

Person preparing more detailed note: [select name]
Date when more detailed note will be forwarded: [MM/DD/YYYY]

This review is complete: [yes/no]

Appendix 2
Notification of Second Severe Hypoglycemia Event Needing Med/Paramedical Help

The following message is automatically generated to the site PI, Site Coordinator, CCN PI, CCN Coordinator, and CCN Glycemia Working group Representative:

From:
TO: [Site PI, Site Coordinator]
CC: [CCN PI, CCN Coordinator, CCN Glycemia Working Group Representative, Coordinating Center]
SUBJECT: Second Event Email [pat ID]

Memo to Site PI

A repeat severe hypoglycemia event requiring medical and/or paramedical assistance has just been reported for participant (patID) at your site. Since this is the second event, this participant appears to be at high risk for severe hypoglycemia. ACCORD is carefully monitoring all such episodes to preserve the safety of its participants, and in doing so require the site investigator to provide a narrative **within 72 hours**. Once completed, your CCN PI or CCN Glycemia Working Group Representative will contact you to review the case.

Please complete the following tasks **within 72 hours**:

a) Refer to www.accordtrial.org > log in > click "Reports" > click "Severe Hypoglycemia" > click "Submit" beside "Event Status" > click on "incomplete" under the column "Second Event Site PI Narrative" corresponding to the participant in "Section B".

b) Review the pre-populated data that has been taken from the SHAF and SAE data entered by your staff. If you agree with the data, proceed to the next task. If not, your staff should correct and data enter the changes to the SHAF, SAE, or both before you proceed.

c) Enter your name, review date, and other event information in the text boxes provided (section #12, 13, 19, and 22) Click "Save My Answers" every time you exit the site to save the information you have added.

d) Once completed, click "Yes" for completing your narrative and click "Save My Answers".

This process is designed to minimize patient risk of participating in ACCORD and to identify potential problem participants early on.
Moreover, the information that you are providing will allow ACCORD to clearly report and measure the risks and benefits of targeting glycemic control in individuals with diabetes at high risk for cardiovascular disease.

Thank you for your prompt attention to this issue.

Event Review Form for Participant [pat ID] -Event [event_number] on website

Answer all parts that apply.
Reviewer: [select CCN PI or CCN Glycemia Working Group Representative]

1. Data on Website was reviewed on [MM/DD/YYYY]

2. Site's narrative report was reviewed on [MM/DD/YYYY]

3. Site PI or Co-PI was contacted [name of Site PI/ Site Co-PI]
   Date site was contacted [MM/DD/YYYY]
   Additional information was obtained and/or advice provided [enter additional information/advice]

4. Actions taken to prevent another severe hypoglycemic event: [actions taken]

5. Further suggestions made: [further suggestions]

6. Further scrutiny was indicated: [specify action- e.g. review of sent documentation, site visit, etc.]

7. Conclusions and CCN actions taken: [e.g. glycemia goals indefinitely modified, removal of specified medications, etc.]

This review is complete: [yes/no]

Appendix 3
Notification of Third + Severe Hypoglycemia Event Needing Med/Paramedical Help

The following message is automatically generated to the site PI, Site Coordinator, CCN PI, CCN Coordinator, and CCN Glycemia Working group Representative:

FROM:
TO: [Site PI, Site Coordinator]
CC: [CCN PI, CCN Coordinator, CCN Glycemia Working Group Representative, Coordinating Center]
SUBJECT: Third Plus Severe Hypoglycemic Event #form.patid#

Memo to Site PI

A repeat severe hypoglycemia event requiring medical and/or paramedical assistance has just been reported for participant (patID) at your site. Since this was the third or more severe hypoglycemic event, this participant appears to be at high risk for severe hypoglycemia. ACCORD is carefully monitoring all such episodes to preserve the safety of its participants, and in doing so require the site investigator to provide a narrative within 72 hours. Once completed, your CCN PI or CCN Glycemia Working Group Representative will contact you to review the case. A GWG representative from another network may also contact you regarding this event.

Please complete the following tasks within 72 hours:

a) Refer to www.accordtrial.org > log in > click "Reports" > click "Severe Hypoglycemia" > click "Submit" beside "Event Status" > click on "incomplete" under the column "Third Plus Event Site PI Narrative" corresponding to the participant in "Section C".

b) Review the pre-populated data that has been taken from the SHAF and SAE data entered by your staff. If you agree with the data, proceed to the next task. If not, your staff should correct and data enter the changes to the SHAF, SAE, or both before you proceed.

c) Enter your name, review date, and other event information in the text boxes provided (section #12, 13, 19, and 22). Click on "Save My Answers" every time you exit the site to save the information you have added.

d) Note the new HbA1c goal, which is required for third events, in the text box provided in section #21.

e) Once complete, click "Yes" for completing your narrative and click "Save My Answers".

This process is designed to minimize patient risk of participating in ACCORD and to identify potential problem participants.
Moreover, the information that you are providing will allow ACCORD to clearly report and measure the risks and benefits of targeting glycemic control in individuals with diabetes at high risk for cardiovascular disease.

Thank you for your prompt attention to this issue.

Event Review Form for Participant [pat ID] -Event [event_number] on website

Answer all parts that apply.
Reviewer: [select CCN PI or CCN Glycemia Working Group Representative]

1. Data on Website was reviewed on [MM/DD/YYYY]

2. Site's narrative report was reviewed on [MM/DD/YYYY]

3. Site PI or Co-PI was contacted [name of Site PI/ Site Co-PI]
   Date site was contacted [MM/DD/YYYY]
   Additional information was obtained and/or advice provided [enter additional information/advice]

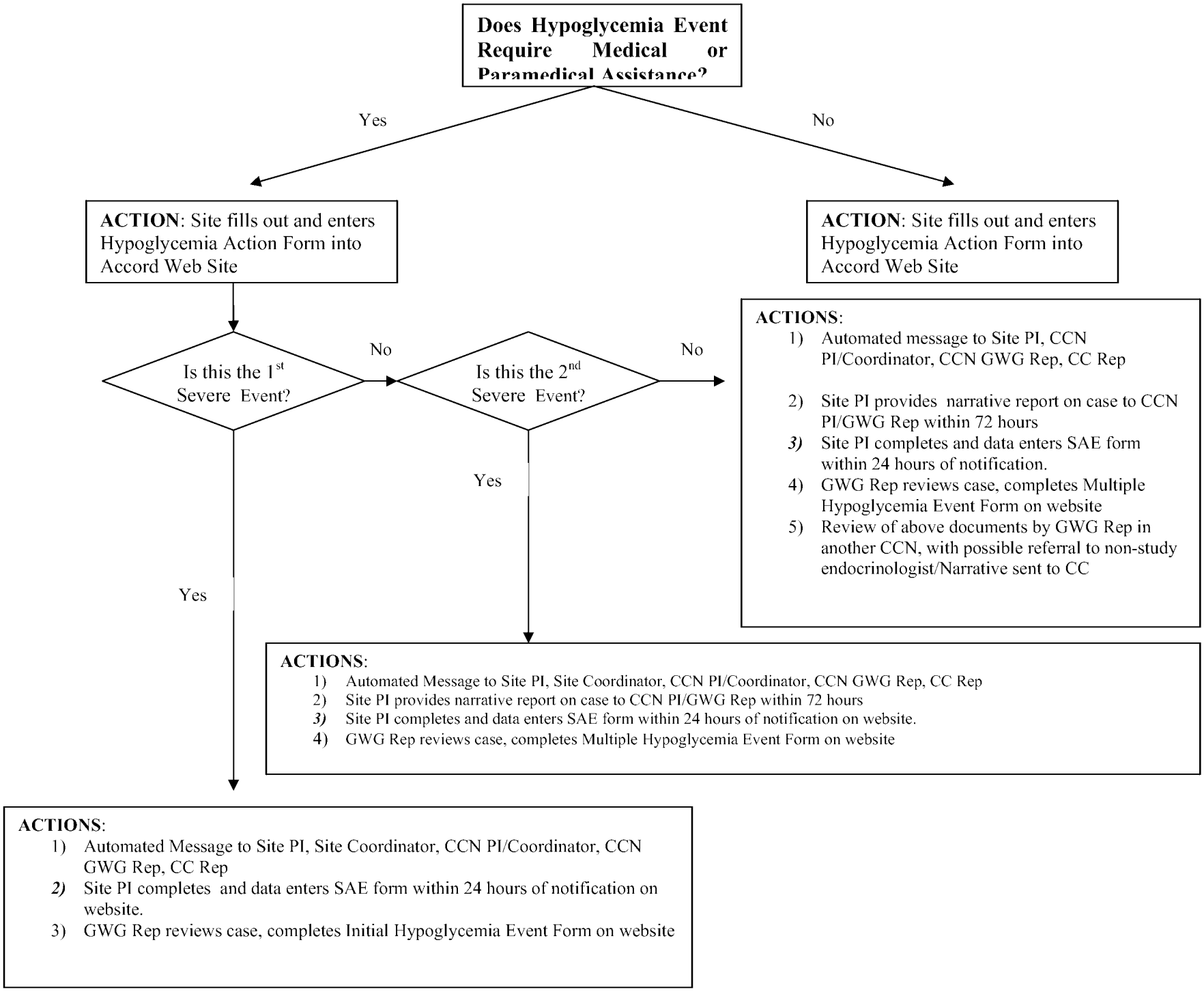
4. Actions taken to prevent another severe hypoglycemic event: [actions taken]

5. Further suggestions made: [further suggestions]

6. Further scrutiny was indicated: [specify action- e.g. review of sent documentation, site visit, etc.]

7. Conclusions and CCN actions taken: [e.g. glycemia goals indefinitely modified, removal of specified medications, etc.]

This review is complete: [yes/no]


Does Hypoglycemia Event Require Medical or Paramedical Assistance?
Yes
No
ACTION: Site fills out and enters Hypoglycemia Action Form into Accord Web Site
ACTION: Site fills out and enters Hypoglycemia Action Form into Accord Web Site
Is this the 1st Severe Event?
No
Is this the 2nd Severe Event?
No
Yes
Yes
ACTIONS:
1) Automated message to Site PI, CCN PI/Coordinator, CCN GWG Rep, CC Rep
2) Site PI provides narrative report on case to CCN PI/GWG Rep within 72 hours
3) Site PI completes and data enters SAE form within 24 hours of notification.
4) GWG Rep reviews case, completes Multiple Hypoglycemia Event Form on website
5) Review of above documents by GWG Rep in another CCN, with possible referral to non-study endocrinologist/Narrative sent to CC
ACTIONS:
1) Automated Message to Site PI, Site Coordinator, CCN PI/Coordinator, CCN GWG Rep, CC Rep
2) Site PI provides narrative report on case to CCN PI/GWG Rep within 72 hours
3) Site PI completes and data enters SAE form within 24 hours of notification on website.
4) GWG Rep reviews case, completes Multiple Hypoglycemia Event Form on website
ACTIONS:
1) Automated Message to Site PI, Site Coordinator, CCN PI/Coordinator, CCN GWG Rep, CC Rep
2) Site PI completes and data enters SAE form within 24 hours of notification on website.
3) GWG Rep reviews case, completes Initial Hypoglycemia Event Form on website

9. Measurement and Interview Procedures

9.1 Anthropometry

9.1.1 Background and Rationale

Body fat, both the amount and distribution in the body, is a significant predictor for the onset of diabetes and sub-clinical and clinically manifested cardiovascular disease. Excessive body and abdominal obesity also hinders diabetes control and increases the likelihood of the development of cardiovascular disease in this patient population. Successful management of Type 2 diabetes includes exercise and dietary modification with the goal of reducing total body fat, particularly abdominal fat. It is the intent of this study to gather data that will elucidate the impact of body fat and body composition on the course of cardiovascular disease among patients with diabetes without extreme burden to study participants and clinical investigators.

Body mass index (BMI), measured as weight (kg)/height $(m)^2$, is commonly used in clinical trials and population-based epidemiologic studies as an estimate of total body fat independent of height. Guidelines are currently available for the determination of overweight and obesity based on BMI values. BMI correlates well with adipose tissue composition measured by more burdensome procedures such as CT scan, underwater weighing and bioelectrical impedance. Similarly, abdominal obesity, as assessed by a measurement of waist circumference, is an easily measured indicator, which has been shown to be predictive of both of diabetes and cardiovascular disease risk.

9.1.2 Methods

Anthropometric measures that will be gathered for this study include (1) standing height, (2) weight and (3) waist circumference. Measured values should be recorded immediately by the technician to ensure accuracy. Calculations of BMI in the clinic are not necessary.

9.1.3 Height

Equipment:

1. Steel tape measure, marked in centimeters to the nearest 0.1 cm, hung vertically on the wall (with the tape at a right angle to the floor and installed accurately to zero at the base board – a floor and back board unit attached together is recommended). Commercial stadiometers are also acceptable.
2. Headboard – a right triangle with an angle brace.

Procedure:

1. Bare feet are preferred. Nylons or thin socks are acceptable. Thick socks must be removed.
2. The study participant should back up to the wall until their heels, buttocks, and/or shoulder blades touch the board (tape), with their eyes straight ahead. The subject's

head should be in the Frankfort (horizontal) plane. Feet should be together with ankles touching or as close as possible.
3. Place the headboard over the crown of the head with the headboard forming a right angle with the tape measure. The headboard should touch the scalp lightly. Have the subject take a full inspiration.
4. Ask the subject to step out from under the headboard.
5. Read the height to the nearest 0.5 cm or the nearest 0.25 inch.

9.1.4 Weight

Equipment: High-quality scales that are currently used in clinical practice (clinical staff should ensure that the scales used for this study are in good working order).

Procedure:
1. Scales should be placed on a firm, flat surface.
2. Perform necessary calibration based on the specifications of the scale being used.
3. Confirm that the scale is balanced (set on zero without a person or thing on the scales). Balance scales if necessary.
4. Subjects should wear as little clothing as possible, removing shoes, outerwear, items in pockets, etc.
5. Have subject stand on scales with weight distributed equally on both feet.
6. Record weight to nearest 0.1 kilogram or 0.25 pound.

Special circumstances:
1. Subjects with prosthetic limbs and breast prosthesis should be weighed with prosthesis in place.
2. For frail and unsteady subjects, weight should be taken by allowing subjects to be lightly steadied. Wheelchair bound subjects should not be measured and weight fields should be coded with -5.
3. For subjects weighing over 150 kg, an attempt should be made to obtain a weight on a scale that exceeds the 150-kg maximum. If not possible, weight should be recorded on the form as -5 kg and entered into the computer as -5.

9.1.5 Waist Circumference (WC)

Equipment: A steel tape is preferred, but non-stretching plastic is acceptable.

Procedure:
1. The waist circumference is taken with the subject standing and recorded to the nearest 0.1 centimeter.
2. Measure the waist circumference (WC) once. To the extent possible WC should be taken with the help of an assistant.
3. Waist (minimum) circumference should be measured at the smallest point between the 10^{th} rib and the iliac crest over bare skin. Check to see that the tape is level front and back and record the value in the source documentation and on the annual physical exam form.

9.2 Blood Pressure/Pulse

9.2.1 Background and Rationale

A standard automated blood pressure measurement device and a specific protocol in ACCORD for the measurement of BP and pulse will be utilized.

9.2.2 Definition

Seated BP and pulse are measured three times at each clinic visit. The seated BP and pulse readings for ACCORD are the averages of the three systolic and diastolic BPs and pulse rates measured by the OMRON HEM-907 automated blood pressure and pulse measurement device. In addition, 3 standing BP and pulse measurements will be made after the seated BP readings on the baseline, 1 year and 4 year visits. Standing systolic and diastolic BP and pulse are also measured three times using the OMRON HEM-907 device. Standing measurements should be collected while the participant is fasting (at least 90 minutes since the last meal).

9.2.3 Methods

This protocol is written for use with the OMRON HEM-907 automated blood pressure and pulse measurement device. Special attention must be placed on assessment and maintenance of the instrument's accuracy as per the manual that accompanies the instrument.

The design and operation of the OMRON HEM-907 automated blood pressure measurement device are based upon the combined principles of compression of the brachial artery under an elastic, inflatable cuff and estimation of the systolic and diastolic blood pressure levels by oscillimetric methods. The observer places the correct size cuff on the participant's arm, pushes the button on the device and waits for the output.

All readings will be recorded to the nearest digit.

Required Equipment

- One OMRON HEM-907 automated blood pressure measurement device.
- BP cuffs in three sizes:
  Large: 32-42 cm (13-17")
  Medium: 22-32 cm (9-13")
  Small: 17-22 cm (7-9")
- Metric tape
- Black pen
- Preferably, chair with arm support for blood pressure measurement, or chair and table (table must provide for a comfortable resting posture of the arm with mid-cuff at heart level). Chair must have a back for participant's back to be supported during rest and BP determinations.
- Data collection form

Cuff Size Determination

BP measurements should usually be taken in the right arm. The left arm may be used if the BP is known to be higher in that arm or in the presence of an anomaly or other circumstance prohibiting use of the right arm.

Proper cuff size must be used to avoid under or over-estimation of blood pressure. Cuff size refers to the cuff's bladder, not the cloth. A copy of the chart below should be attached to the sphygmomanometer for easy reference.

Cuff Size Indicated by Measured Arm Circumference

Arm Circumference	Cuff
32-42 cm (13-17")	Large
22-32 cm (9-13")	Medium
17-22 cm (7-9")	Small
>42 cm (>17")	Extra large or thigh (not available for Omron)

If the participant's arm circumference is > 42 cm, the Omron will not be used for BP and pulse measurements. In these participants, a manual (preferably mercury) manometer will need to be used with an extra large or thigh sized cuff.

- Have the participant remove his/her upper garment (bare arm).
- Have the participant stand, holding forearm horizontal (parallel) to the floor.
- Measure arm length from the acromion (bony protuberance at the shoulder) to the olecranon (tip of the elbow), using a metric tape.
- Mark the midpoint on the dorsal surface of the arm.
- Have participant relax arm along side of the body.
- Draw the tape snugly around the arm at the midpoint mark. NOTE: Keep the tape horizontal. Tape should not indent the skin.
- Use the criteria in the Table (above) for determining cuff size.

Wrapping the Blood Pressure Cuff Around the Arm

The participant should then be seated with back supported, legs uncrossed, in a quiet room, with the elbow and forearm resting comfortably on the armrest of the blood pressure measurement chair (or the table) with the palm of the hand turned upward. The area to which the cuff is to be applied must be bare.

Locate the brachial artery by palpation and mark the skin with a little dot. (The brachial artery is usually found at the crease of the arm, under the muscle and slightly towards the body).

Place the appropriate cuff around the upper right arm so that:

a) The midpoint of the length of the bladder lies over the brachial artery, and
b) The mid-height of the cuff is at heart level.

NOTE: Confirm for yourself where the midpoint of the length of the bladder is by folding the bladder in two. Do not trust the marking on the cuff.

Place the lower edge of the cuff, with its tubing connections, ½ to 1 inch above the natural crease across the inner aspect of the elbow.

Wrap the cuff snugly about the arm, with the palm of the participant's hand turned upward. Make sure that the long edges of the cuff lie on top of each other as you wrap the cuff around.

Secure the wrapped cuff firmly by applying pressure to the locking fabric fastener over the area where it is applied to the cuff.

Do not wrap the cuff too tightly around the arm, but so that you can insert only one finger between the cuff and arm.

Taking the Seated Blood Pressure and Pulse Measurements

The participant should sit quietly for a period of 5 minutes before the first blood pressure is taken. They should be seated comfortably, feet flat on the floor with their back supported. Ideally they should not have smoked or had any caffeine within the last 30 minutes prior to the BP determinations. For the baseline, 12 month and 48 month exams when standing BP is measured, the participant also should be fasting (at least 90 minutes since last meal).

The Omron may be preset (function F2) to wait 5 minutes before starting measurements after the start button is pushed so the 5-minute rest is automatically included. Also set the Omron (F1) to take an average of 3 measurements and set the interval between measurements (F3) for 60 seconds.

Push the button on the machine and wait for the output.

Record the average of the 3 systolic and diastolic blood pressure and pulse readings, from the OMRON BP device in the spaces provided on the physical exam or the Hypertension Medications form.

Taking Standing Blood Pressure and Pulse Measurements at Baseline, F12.0 and F48.0
Immediately after the seated BP and pulse measurements have been obtained and recorded, ask the participant to stand. Once his (her) feet touch the ground, press the start button on the Omron device to initiate a new set of BP and pulse measurements.

After 60 seconds, press the start button on the Omron again to take the first standing BP and Pulse measurement (this bypasses the 5 minute rest period programmed into the machine). The Omron device will then automatically record the 2nd and 3rd BP and pulse measurements at 1 minute intervals.

For standing BP measurement, the arm should be bent slightly and the hand of the cuffed arm supported at heart level (a Mayo stand is acceptable for support).

After the third and final standing BP and pulse reading, ask the participant "While you were standing, did you experience any dizziness or lightheadedness or feel faint?"

Record the 3 standing BP and pulse readings (not the mean) and the answer to the question regarding symptoms on the case report form.

9.2.3.1 Principles of proper technique for participants with arms too large for the Omron (> 42 cm circumference) or in other situations where the Omron cannot be used

The steps described below are in the usual order performed when approaching a participant for blood pressure and pulse measurements when the Omron device is not used. In these cases a mercury manometer is preferred. If a mercury manometer is unable to be used, another properly calibrated sphygmomanometer may be used. An alternative to the Omron device will be necessary in the situation where the arm circumference is >42 cm, since the Omron does not have that size cuff available. There may be other rare situations where the Omron is not accurate, such as in some participants with atrial fibrillation (See Section 9.3.2)

Arm measurement:
The proper size cuff must be used to obtain accurate blood pressure (BP) readings. See the table above (9.2.3) for determination of proper cuff size.

Applying the BP Cuff
1) Place the midpoint of the length of the bladder over the brachial artery and the midheight of the cuff at heart level.
2) The lower edge of the cuff should be about 1 inch above the natural crease of the inner aspect of the elbow.
3) Wrap the cuff snugly and secure firmly.
4) The participant should rest with their palm turned upward.

***The participant should be allowed to sit quietly for 5 minutes. They should be seated comfortably, feet flat on the floor with their back supported. Ideally they should not have smoked or had any caffeine within the last 30 minutes prior to the BP determinations.

Determination of Peak Inflation Level

The peak inflation level (pressure) should be determined to assure accurate measurement of the systolic blood pressure. This pressure is determined by:

1) Inflating the BP cuff while palpating the radial pulse and watching the mercury column.
2) When sufficient pressure has been applied, the pulse is no longer felt. When the pulse disappearance is detected, note the level and continue to inflate the cuff another 20 mm Hg.
3) Slowly deflate the cuff while watching the mercury column. Note the level where the pulse reappears, then quickly and completely deflate the cuff.
4) Peak Inflation Level (PIL) = Pulse Obliteration Pressure (POP) + 20 mm Hg.
5) All readings are made at the top of the meniscus. Readings are made to the nearest even digit. Readings that fall exactly between markings should be read to the next marking immediately above.

Pulse Measurement

Pulse measurements are obtained after the participant has rested 5 minutes and before the blood pressure is measured.

1) Palpate the radial pulse for 30 seconds and multiply by 2. The product is recorded as the heart rate.

Blood Pressure Readings

Blood Pressure Sounds

Systolic blood pressure (SBP) is the first of at least two regular tapping sounds heard when deflating the cuff.

Diastolic blood pressure (DBP) is the level at which the last of the rhythmic sounds are heard.

A single sound heard in isolation either before the SBP or after the DBP does not meet the BP criteria.

Obtaining the BP Readings

1. Following determination of the peak inflation level or any other BP measurement, wait 60 seconds after complete deflation of the cuff before re-inflating for the next reading.
2. Place the diaphragm of the stethoscope over the brachial artery.
3. Inflate the cuff at a rapid, smooth, continuous rate to the peak inflation level.
4. At a slow and constant rate of 2 mm Hg/second deflate the cuff listening throughout the entire range of deflation to 10 mm Hg below the DBP (last regular sound heard).
5. Quickly and completely deflate the cuff.
6. Record the reading.
7. Wait at least 60 seconds between readings and repeat steps 2-6 two more times.
8. Record the 3 readings in the source note and the average of the 3 on the case report form.
9. Standing BP and pulse measurements should not be collected in situations where the Omron cannot be used to obtain seated measurements.

All study personnel responsible for obtaining blood pressure readings must review and be familiar with the blood pressure measurement protocol. Blood pressure techniques will be reviewed periodically by the network project coordinators during site visits.

9.3 Guidelines for Proper Use and Maintenance of Equipment

9.3.1 Omron Calibration

The Omron unit has been validated to remain in calibration for up to 100,000 measurements. The units do not have to be calibrated before their first use. The CCNs will not have to perform the CHECK MODE function during the first year of ACCORD.

9.3.2 Atrial Fibrillation

Atrial fibrillation (AF) is not necessarily problematic with oscillometric devices. However, the presence of AF suggests that multiple measurements (three) be taken and averaged to provide a more accurate reading. Functionally, the OMRON IntelliSense unit is designed to take up to three measurements and average them automatically (in AVE Mode). An atrial fibrillation however, could cause the OMRON IntelliSense unit to error and restart the measurement. If this is the case, the three readings should be taken in the SINGLE Mode and manually averaged. If there is still a problem in obtaining the readings, they should be taken manually with a mercury or other properly calibrated manometer.

9.3.3 Troubleshooting

Refer to the OMRON HEM-907 IntelliSense Digital Blood Pressure Monitor Manual, given out at the ACCORD Study Training Program for a list of error codes and how to correct them.

9.3.4 Edema Exam

Perform pretibial edema exam. To perform the pretibial edema exam, place your index finger over the participant's tibia, 10 cm above the lateral malleolus. Exert pressure for 5 seconds. Any depression that does not resume its original contour almost immediately is a sign of pitting edema. The following scale should be used to grade any edema that is observed. Check the corresponding box on the form (**Interval History and Follow-up Form and Annual Follow-up and Physical Exam Form**).

Grade	Physical Characteristics
1+	No visible change in shape of the extremity, Pitting depth of 2 mm or less, pit disappears rapidly
2+	No marked change in shape of the extremity, 2-5 mm pitting depth, pit usually disappears in 10-15 seconds

3+ Noticeably swollen extremity, 5-10 mm pitting depth, pit may persist for about a minute

4+ Very swollen and distorted extremity, very deep pit (>10 mm), pit may persist 2-5 minutes

9.4 Eye Exam

9.4.1 Visual Acuity Measurements in ACCORD

9.4.1.1 Introduction:

The measurement of visual acuity is an important endpoint in the ACCORD Study. The visual acuity will be performed at baseline and all annual visits for all patients in the study. Since changes in visual acuity are important endpoints, it is essential for the visual acuities to be measured using the following standard protocol.

9.4.2 Measurement of visual acuity:

This technique should be used at baseline and all annual visits by the ACCORD clinical coordinator at each clinical site. Training for the protocol procedure for measuring visual acuity will be conducted at the group meeting as well as through a teaching video.

Patients should be instructed to bring their current glasses with them for their baseline and annual visits. All patients will be assessed for their "habitual vision" with their usual correction for the distance. Visual acuity will be assessed utilizing the patient's current distance glasses, which may be bifocals, trifocals, or variable lens but not reading glasses. Patients presently wearing contact lens will be assessed with their contact lens on. Patients will be asked to read the letters on the Visual Acuity Chart. They will be tested first for the right eye and then the left eye. A visual acuity score will be calculated using a worksheet. The visual acuity score can be recorded on the vision questionnaire.

9.4.2.1 Introduction

The visual acuity of patients will be measured using the R chart of the Lighthouse Distance Visual Acuity Test charts (second edition), which are modified ETDRS charts.[1] The charts are manufactured by:

Lighthouse Low Vision Products
36-02 Northern Boulevard
Long Island, New York 11101

Visual acuity testing is required at a distance of 4 meters and, for patients with sufficiently reduced vision, at 1 meter. This can be done in the hallway, if necessary. The

4-meter distance and 1-meter distance should be marked clearly and permanently; the participant may sit or stand for the 4-meter test, but should sit for the 1-meter test.

9.4.2.2 Visual acuity charts

The chart must be mounted at a height such that the top of the third row of letters is 49 $\pm$ 2 inches from the floor.

9.4.2.3 Illumination

Room illumination should be between 50 and 125-foot candles as measured with a photometer held four feet from the floor and directed to the ceiling. The chart should be evenly illuminated either in a visual acuity box or mounted on an evenly illuminated wall at the specified lighting levels.

9.4.2.4 4- and 1-meter visual acuity lanes

A distance of exactly 4 meters (13 feet and 1.5 inches, or 157.5 inches) is required between the patient's eyes and the visual acuity chart for the 4-meter test, and a distance of exactly 1-meter (39 and 3/8 inches) is required for the 1-meter test.

9.5 Testing of "Habitual" Visual Acuity

9.5.1 4-meter test

TESTING OF ALL EYES BEGINS AT 4 METERS.

First, the right eye is tested and then the left. The distance from the patient's eyes to the visual acuity chart must be exactly 4.0 meters (13 feet and 1.5 inches, or 157.5 inches). The patient may stand or sit for the 4-meter visual acuity test. If the patient is seated, his or her back should fit firmly touching the back of the chair. The examiner should ensure that the patient is standing or sitting comfortably, that the head does not move forward or backward during the test, and that the patient's eyes remain at the 4-meter distance.

The testing procedure for visual acuity is based on the principle that the objective is to test visual acuity and not intelligence or the ability to concentrate or follow or remember instructions (although all of these factors are involved). The patient should be told that the chart has letters only and no numbers. If the patient forgets this instruction and reads a number, he or she should be reminded that the chart contains no numbers and the examiner should request a letter in lieu of the number.

The patient should be asked to read slowly (at a rate not faster than about one letter per second) in order to achieve the best identification of each letter and to not proceed until the patient has given a definite response. It may be useful for the examiner to demonstrate the letter-a-second pace by reciting "A, B, C, ..." If, at any point, the

patient reads quickly, he or she should be asked to stop and read slowly. If the patient loses his or her place in reading or the examiner loses his or her place (possibly because the letters are read too quickly), the examiner should ask the patient to go back to where the place was lost. Examiners should never point to the chart or to specific letters on the chart or read any of the letters during the test.

Each letter is scored as right or wrong. Once a patient has identified a letter with a definite single-letter response and has read the next letter, a correction of the previous letter cannot be accepted. If the patient changes a response aloud (e.g., "That was a 'C,' not an 'O'") before he or she has read aloud the next letter, then the change should be accepted. If the patient changes a response after beginning to read the next letter, the change is not accepted.

When the patient says he or she cannot read a letter, he or she should be encouraged to guess. If the patient identifies a letter as one of two or more letters, he or she should be asked to choose one letter and, if necessary, to guess even if the next letter has already been read. The examiner may suggest that the patient turn or shake his or her head in any manner if this improves visual acuity. If the patient does this, care must be taken to ensure that the fellow eye remains covered. When it becomes evident that no further meaningful readings can be made, despite urgings to read or guess, the examiner should stop the test for that eye.

9.5.2 1-meter test

Eyes reading 19 or fewer letters correctly at 4 meters should be tested at 1 meter. The patient may stand or sit for the 4-meter test, but should sit for the 1-meter test. The avoidance of any head movement forward or backward is particularly important during the 1-meter test. The patient should be asked to read only the first six lines at 1 meter, making 30 the maximum score attainable at that distance.

9.5.3. Scoring best-corrected visual acuity

The examiner records each letter identified correctly by making a slash ("/") through the corresponding letter on the Visual Acuity Worksheet. Letters read incorrectly and letters for which no guesses are made are not marked on the form. Each letter read correctly is scored as one point. The score for each line (which is zero if no letters are read correctly) and the total score for each eye are recorded on the Visual Acuity Worksheet after testing is completed. The test should continue and *each line scored until the participant reaches a point where no letters are read correctly.* If testing at 1 meter is not required, 30 points are automatically scored for the 1-meter test. The total combined score (i.e., the sum of the 4- and 1-meter scores) and the approximate Snellen fraction, which is determined based on the lowest line read with one or fewer mistakes, are recorded on the Visual Acuity Worksheet.

9.5.4 Referral of patient with visual acuity score 70 or less

For the patient whose visual acuity score is 70 or less (less than 20/40), the patient is referred to an ophthalmologist (his or her own or the study ophthalmologist) to fill in the ACCORD Ophthalmologist Examination Form. This form will be faxed back to the coordinator who can edit and enter it into the ACCORD web database.

Consent for release of information to the ACCORD Study

Name: _____ Date: _____/_____/_____
Mo. Day
Year

Dear Doctor:

The above patient is enrolled in the ACCORD Study, which is designed to research ways of preventing cardiovascular disease in patients with diabetes. This is a randomized trial of glycemic, blood pressure and serum lipid control. He or she has recently been tested at our clinical center to have visual acuity of 20/40 or worse in his or her better eye. Please examine the patient, check off the appropriate responses, and fax the 1-page clinical exam form back to the clinical center.

Consent to release information to the study:

I, (patient's name)_____, consent to have this information released to the ACCORD Study Coordinating Center.

_____ _____
Signature Date Witness's signature Date

9.6 ACCORD Neuropathy Examination Form (Foot Exam)

As part of the physical examination at baseline and follow-up, a specialized foot examination will be used to identify the presence and/or development of diabetic peripheral neuropathy. This examination has been adopted from the Michigan Neuropathy Screening Instrument.

The examination has 5 parts: appearance of foot, ulceration, ankle reflexes, and vibration perception at great toe and 10-gram filament. Each foot is examined and scored separately. Note: if a participant has had an amputation, indicate this on the form and skip the examination.

9.6.1 The Clinical Examination

APPEARANCE OF FOOT (Foot Inspection) The feet are inspected for evidence of excessively dry skin, callus formation, fissures, frank ulceration, or deformities. Deformities would include flat feet, hammertoes, overlapping toes, hallux valgus, joint subluxation, prominent metatarsal head, medial convexity (Charcot foot), and amputation. Indicate on the form whether the foot appears abnormal or normal.

ULCERATION On the form, indicate whether ulcers were absent or present on the clinical examination.

ANKLE REFLEXES (Muscle Stretch Reflexes) The ankle reflexes will be examined using an appropriate reflex hammer (e.g., Tromner or Babinski (European), or Queen's Square or almost anything except a very light Taylor's (tomahawk) because the ankle jerk is difficult to elicit with them). The ankle reflexes should be elicited in the sitting position, with the foot dependent and patient relaxed. For the reflex, the foot should be passively positioned and the foot dorsiflexed slightly to obtain optimal stretch of the muscle. The Achilles Tendon should be percussed directly. If the reflex is obtained, it is graded as present. If the reflex is absent, the participant is asked to perform the Jendrassic Maneuver (i.e., locking the fingers together and pulling). Reflexes elicited with the Jendrassic Maneuver alone are designated as present with reinforcement. If the reflex is absent, even with Jendrassic Maneuver, the reflex is designated as absent.

VIBRATION PERCEPTION AT GREAT TOE (Vibration Sensation) Vibration sensation should be performed with the great toe unsupported. Vibration sensation will be tested bilaterally using a 128 Hz tuning fork place over the dorsum of the great toe on the bony prominent of the DIP joint. The participant (with eyes closed) is asked to indicate when he/she can no longer sense the vibration from the vibrating tuning fork.

In general, the examiner should be able to feel vibration from the hand-held tuning fork for 5 seconds longer on his/her distal forefinger than a normal participant can at the great toe (i.e., examiner's DIP joint of the first finger versus the participant's toe). If the examiner feels vibration for 10 or more seconds on her/her finger, then vibration is considered decreased. The test should be given when the tuning fork is not vibrating to be certain the participant is responding to vibration and not to pressure or some other

clue. Vibration is scored: present if the examiner senses the vibration on his/her finger for < 10 seconds; reduced if sensed for 10 or more seconds, and absent if no vibration is detected.

10 GRAM FILAMENT (Semmes-Weinstein Monofilament Examination) For this examination, the foot should not be supported (no standing). The filament must be 5.07 and should be initially pre-stressed (4-6 perpendicular applications to the dorsum of the examiner's first finger). The filament is then applied to the dorsum of the great toe midway between the nail fold and the DIP joint. Do not hold the toe directly. The filament is applied perpendicularly and briefly (for < 1 second) with an even pressure. When the filament bends the force of 10 grams has been applied. The patient, whose eyes are closed, is asked to respond 'yes' if he or shoe feels the filament. This is done ten times on each big toe. If there are 8 or more correct responses (out of 10 applications), this is considered present; 1-7 correct responses is considered reduced sensation; no correct responses is considered absent.

9.6.2 Recommended Instruments

Reflex Hammers:
Tromner Hammers $62.20

SSR Inc.
PO Box 537
Oyster Bay, NY 11711

Other Hammers:
Babinski (Euopean), Queen's Square

Tuning forks (128 Hz.) $11.40

Monofilament:
The monofilament must be 5.07 (eliciting 10 grams of pressure)
Center for Specialized Diabetic Foot Care
405 Hayden Street
PO Box 373
Belzoni, MS 39038

$10.00 each

Connecticut Bioinstruments Inc.
39-B Mill Plain Road
Danbury, CT 06811

$10.00 each

Smith & Nephew, Inc.
PO Box 1005
Germantown, WI 53022

$19.99 each

9.6.3 Scoring the ACCORD Neuropathy Screening Instrument.

For each foot separately, scores would be as follow:

Appearance of Foot:	Normal=0	Abnormal=1	
Ulceration:	Absent=0	Present=1	
Ankle Reflexes:	Present=0	Present with Reinforcement=0.5	Absent=1
Vibration Perception:	Present=0	Reduced=0.5	Absent=1
10-gram Filament:	8-10 Correct=0	1-7 Correct=0.5	None Correct=1

Calculate scores for each foot separately. There are a possible 5 points per foot.

Interpretation of Scores (Cross-sectionally and Longitudinally)
The following scores (out of a possible 10) from the clinical examination would denote presence/absence of neuropathy:

0 to 2	No Neuropathy
2.5 to 10	Neuropathic

Every increase over time of at least 1 point denotes progression of neuropathy.

9.7 Instructions for "Holding" Glycemia Management Forms

Below are instructions regarding completion of the Glycemia Management Form in instances where the clinical site would like to wait until receiving results of the central lab HbA1c at the current visit before documenting therapy changes and data entering the form. We refer to such instances as "holding" the Glycemia Management Form for the Central Lab HbA1c result.

At a regularly scheduled clinic visit where a Central Lab HbA1c is measured, site personnel have been given the option to "hold" a Glycemia Management Form and accompanying Glycemia Medications Log until the HbA1c result is known so that therapy adjustments can be made without documenting a PRN contact on a separate Management Form and Med Log pair.

Holding the Glycemia Management Form for the current Central Lab HbA1c should only be done for participants assigned to the *intensive* glycemia arm, and then only under specific circumstances (see below). It is imperative that all prescribed medication changes be documented on case report forms and in study data bases. Such documentation can always be accomplished by completing the Glycemia Management Form and Med Log at the current visit (regardless of therapy adjustments) then completing a PRN pair should the Central Lab HbA1c indicate the need for a therapy change that wasn't otherwise made at the visit.

Below are instructions regarding when and how a Glycemia Management Form and Medication Log may be held for a Central Lab HbA1c result.

1. Standard Glycemia Participants: do not hold the forms. Use the previous visit HbA1c result (it may be as much as four months old), the current SMBG logs, and self-reported symptom data to make therapy adjustments at the current visit. In the rare circumstance where a Central Lab HbA1c result requires action before the next scheduled follow-up visit, a PRN contact (either on phone or in the clinic) should be performed with Standard Glycemia Management Form and Glycemia Medication Log completed to document therapy changes.

2. Intensive Glycemia Participants

    a. **Situation 1**: a change in therapy (including intensification, reduction or therapeutic equivalent) is made at the clinic visit for any reason. Do not hold the forms. Therapy changes should be documented on the forms and, if warranted, a Severe Hypoglycemia Action Form should be completed, and all forms data entered. When the Central Lab HbA1c result is received, if further action is required a PRN contact (either on phone or in the clinic) should be performed with Intensive Glycemia Management Form and Glycemia Medication Log completed to document therapy changes. If no further therapy change is required, document the Central Lab HbA1c value in source notes with a remark that therapy changes were made at the visit.

    b. **Situation 2**: No change to the participant's therapy is made at the scheduled visit (i.e., the current POC HbA1c result and SMBG logs do not indicate need for therapy change, and no severe hypoglycemic events nor side effects warranting adjustments have been reported). The Glycemia Management Form and Medication log may be held while waiting for the Central Lab HbA1c result.
        i. At the time of the visit the Intensive Glycemia Management Form should be partially completed to document SMBG results, hypoglycemia information and compliance with insulin regimen. Partially complete the Med Log to document compliance with prescribed oral medication use.

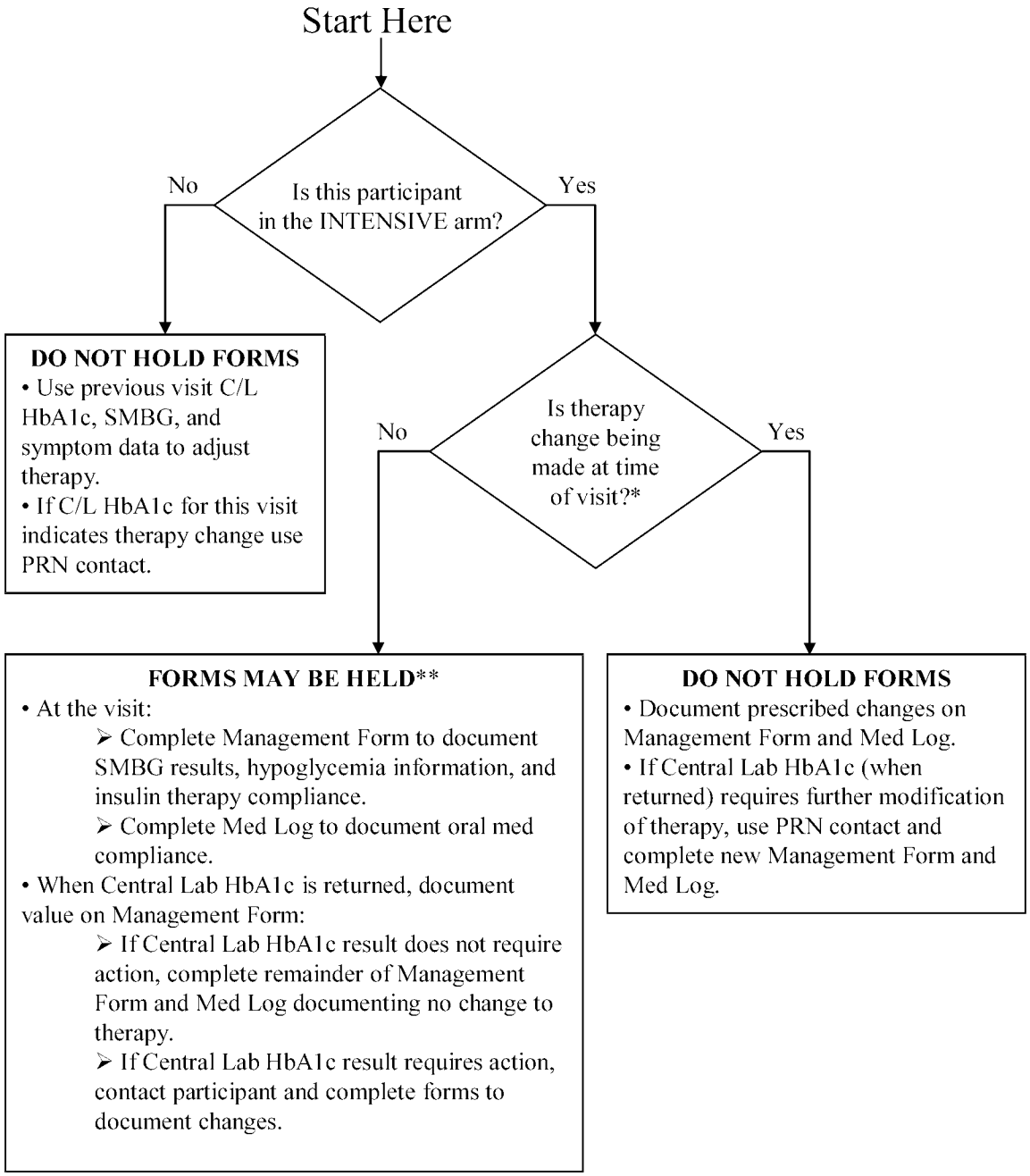
ii. When the Central Lab HbA1c result is returned, it should be documented on the held Glycemia Management Form.
iii. If the Central Lab HbA1c result does not require action, the remainder of the forms should be completed. Document therapy decisions based on all results (POC HbA1c, Central Lab HbA1c, SMBG values, and self-reported side effects) and no change in insulin regimen on the Glycemia Management Form. Document no change in oral medications at exit on the Med Log. Use the date of the clinic visit for the "visit date" on both the Management Form and the Med Log.
iv. If the Central Lab HbA1c result does require action, the participant should be contacted and directed to change prescribed therapy. Document the therapy decisions and insulin regimen changes on the Management Form. Document oral medication changes on the Med Log. ***Be sure to repeat and update hypoglycemia questions in Part II of the Glycemia Management Form and use the current date (the date of follow-up contact) as the "visit date" on both the Management Form and Med Log.***

Instances where the Management Form and Med Log are held should be relatively infrequent since most intensive arm participants are currently not at goal. At the time of clinic visit the (adjusted) POC HbA1c and/or SMBG results will usually indicate that intensification should be made.

Finally, a form should only be held up to seven days while waiting for a Central Lab HbA1c result. Unless there are problems with the sample or delays in shipping, results should be received within a week. If a Central Lab HbA1c result is not available at one week after the visit, complete the forms based on POC and SMBG data and use your best judgment as to whether a PRN blood draw (with accompanying glycemia forms) should be made.

Below is a flow chart illustrating the algorithm for holding Glycemia Management Forms and Medication Logs.

"Holding" Glycemia Management Forms and Medication Logs



*"Therapy change" refers to any modification in medical therapy (oral anti-hyperglycemics or insulin) including intensification, reduction or substitution resulting in therapeutic equivalence.

**Forms may be held for up to 7 days. See above for instructions if there are delays in receiving Central Lab result.

10. DATA Management

10.1 Overview

The data management system used for the collection of data during the ACCORD trial utilizes a Web browser-based interface, with electronic data being stored and managed centrally at the coordinating center. This model was chosen both for the rapid, efficient collection of clinical information using the existing technology of the Internet as well as the ease of use and familiarity of Web browsers. User-friendly screens, which match the case report forms (CRFs) have been developed using hypertext mark-up language (HTML). Participant data entered by clinic staff will reside on an NT server at the Coordinating Center, with *Cold Fusion* software enabling connectivity to the back-end database.

Standardized PC's and other hardware (printer, barcode reader, etc) were sent to each clinic to be used for the ACCORD project. While the web-based data management system can be used from any PC with a compatible browser (Internet Explorer 5.x), we have tailored the site layout to the capabilities of the PC shipped and therefore if the site is accessed on another PC, the screen layout may appear differently. We do request that the Internet Explorer 5.5 browser be used for data entry as the web-based forms are dynamically generated in some cases and using a non-compliant browser may result in certain functionality being hindered.

The **ACCORD Data Base Management System** allows the user to interact with all phases of the clinical data. Patient initialization, eligibility, randomization and entry of each of the study forms are available in this application. Users will be allowed, depending on their security access, to enter and edit data, view reports, print visit schedules; assign study drugs and more.

10.2 ACCORD Data Base Management System

10.2.1 Log on

Once Internet Explorer 5.5 (or a compatible browser) browser is invoked on the client computer, the following URL should be entered:

https://www.ACCORDtrial.org/

Clicking on the ACCORD logo in the middle of the screen will cause the ACCORD login screen to appear. The user can then enter his/her username and password into the appropriate fields. The system is password-protected in order to prevent unauthorized access. Once a valid username and password combination have been entered and verified, the user can click on the **login** button and proceed to the main screen. A username and password is provided for each person in the study by the Coordinating Center to each site at the start of the study and as new staff is hired. Passwords may be changed at any time throughout the study by simply clicking on Directory then the first letter of the last name. Click on the appropriate name on the list

then select Change Password. To further enhance security, data encryption techniques during transmission have been employed throughout the web application.

10.2.2 Data Management Organization

Once the user has successfully authenticated into the system, a series of menu options will direct them to the Clinical Data Management portion of the web site. Once they have accessed this portion of the site, they will be able to perform the following functions:

Data Entry: Allows the user to save, recall and edit data forms, organized by participant, by visit.

Tickler: The tickler is a tool that helps the sites manage upcoming participant visits. By providing the tool with a range of dates, the system will report which participant visits are due within that window, which ones are overdue and which ones have been scheduled.

Reporting: A variety of reports are available under the Report section of the Data Management system. Access to reports is controlled by the role of the user within the ACCORD study. Some study members therefore will not be able to access certain reports.

Other functions that are available in the Data Management portion of the site include clinic staff code lists, and data edit/query resolution reports.

10.2.3 Guidelines for Data Entry

As you work with the database management system, you should be familiar with the following operations:

1. Each screen will display a certain number of fields or slots where data from ACCORD forms are to be entered. These fields may appear on the screen as boxes of a different color from the screen background. Other fields are called "radio buttons", "list boxes", and "check boxes" and they allow the user to select from several choices. If information has been omitted from the forms, it may need to be shown as "missing". For more on missing data see #7 below.
2. You can move from field to field by using the *Tab* key, or by clicking on another field with the mouse.
3. If you make a mistake entering data while you are in a specific field, you can backspace over your error and retype it. If you notice your mistake after you have moved to a new field, you can use the mouse, Shift-Tab or Tab keys to move to the needed field.
4. In some cases the system will perform necessary calculations already performed by clinic staff. The cursor will not move to those fields. You should check the system's calculations against those made by hand. If any discrepancies appear, check first to make sure data have been entered correctly, and report any unresolved problems to the Clinic Coordinator.

5. When you reach the end of a screen, check your entries to make sure they are correct. You must save each form after you enter it. To save, click on the *Save Data* button at the bottom of the screen.
6. Each time you enter a participant ID and acrostic the system will check that the ID is valid. If not, access will be denied to the forms. You will be notified of the conflict and prompted to enter an Initial Screening form for that participant ID and acrostic.
7. The database system sets all data items to missing by default. If a data item is permanently missing (i.e. was not collected at that visit) enter a -5 to indicate that the item was not collected.
8. If there is invalid data on the paper form record it as missing on the computer screen and then consult the Clinic Coordinator. Be sure to log these discrepancies on paper, recording the participant ID, acrostic, visit form, date on the form, today's date and where the problem occurred.
9. A closely related issue is data out of "expected" ranges and "valid" ranges. For example, the expected range for systolic blood pressure is 50-250, and for diastolic it is 20-150. You may encounter valid values outside the expected range (i.e., a systolic blood pressure of 260 mmHg). In such cases the system will notify you, but entry **is** allowed. Data values that are outside the valid range **will not** be allowed. In such cases, leave the value missing and save the other information on the form. Next record the participant ID, acrostic, form, visit, data item, data value, today's date and the nature of the problem. These exceptions must be reported to the Coordinating Center for further action.

10.2.4 Participant and Form Selection

Once the user has accessed the Data Management system, they will be able to access participants by either scanning the barcode label into the appropriate box on the screen or by clicking on the participant's ID in the onscreen listing of clinic participant ID's. After a participant has been selected and the acrostic confirmed, the user will be able to see a detailed view of the current status of that participant and from there select any form or visit specific information. After selecting an individual form, the system will display that form, along with any previous data that would have been previously entered for that form on that visit.

10.2.5 Participant Initialization

Given that the ID and acrostic on the Initial Screening Form is the point of reference for data access, *great care should be given to the entry of these data items in that form.* Procedures for obtaining participant IDs are contained in Section 3.3 of the ACCORD MOP. Clinic staff will assign IDs by placing Participant Initiation Labels on the Inclusion/Exclusion Summary Form.

10.2.6 Randomization

Once the participant is determined eligible and data entry has occurred for the Inclusion/Exclusion Summary Form, the Blood Pressure Trial Screening Form, and the Lipid Trial Screening Form, he/she may be randomized into the study. At this time the participant will be assigned a treatment regimen. The randomization screen will display this information and allow the user to return to the main participant background screen. From there, the user can view or print a participant visit schedule, which can be filed in the participant's chart. A confirmation email message is then generated and sent to that clinic's principal investigator as well as the Coordinating Center's project manager. Any discrepancies should be reported to the Coordinating Center immediately.

10.2.7 Flow of Forms/Sequence of Entry

Once a participant has been initialized into the database, only the Screening Forms can be entered. These forms can be entered in any order but they must be entered completely and accurately before randomization can occur. If these forms are entered correctly and the participant is eligible for the study, randomization can be completed, at which time a visit schedule will be created tailored to their study assignments.

At each visit, forms should be gathered, labeled, completed, checked for accuracy and missing values. Any corrections that are needed should be made and noted in any clinic logs and then the forms should be turned over for data entry. It does not matter in which order the forms are data entered within a visit, but once a visit is complete, the Visit Disposition Form must be entered, accurately depicting the status of the visit.

Each visit should be completed and closed prior to entering any data for a future visit.

Some forms have been designated as PRN forms and can be used as needed. Use of these forms will be restricted to use for data that are collected outside the normal visit schedule.

10.2.8 LIPID Drug Assignment

Participants who were on a lipid- lowering agent at screening must agree to stop treatment no later than the day of randomization and be changed to simvastatin. The starting dose of simvastatin is 20 mg/day, administered once daily after the evening meal or at bedtime.

One month after randomization, the study fibrate/placebo will be started. It is recommended that simvastatin be taken in the evening and the masked fibrate/placebo be taken in the morning. If however, you feel compliance would be improved if both were taken together, that would be acceptable.

The starting dose of masked fenofibrate/placebo medication will be determined by the calculated glomerular filtration rate (GFR) using the baseline serum creatinine level and the abbreviated MDRD equation (Levey 2003). Those participants with a baseline GFR $\geq$50 ml/min/1.73m^2 will begin at a starting dose of 160 mg of fenofibrate or

identical placebo tablet. Those with a calculated GFR between 30 and <50 will start at the reduced dose of 54 mg/day fenofibrate or placebo.

Implementation of baseline assignment of blinded study medication dose:

- The Coordinating Center (CC) will determine the starting dose of the blinded study medication based on calculated GFR from the MDRD equation, using Central Lab values at baseline.
- The recommended dose will appear on the participant main page below "Lipid Bottle ID" (e.g., FULL, REDUCED, or NONE).
- The CC will communicate the starting dose to the Drug Distribution Center (DDC).
- DDC will send the appropriate dose to the clinical site labeled for the specific participant.
- One-month follow-up visits for Lipid Trial participants should be scheduled at least 3 weeks after the baseline visit to allow for arrival of blinded study medication.

10.2.9 Labels

A label-generating program (called the Label Program) is contained on the Clinical Site computer and generates participant ID labels. This program is the only way that IDs can be obtained for participants in ACCORD. General descriptions of the capabilities of this program are contained in MOP Chapter 3, Sections 3.3.2 and 3.11.1. Section 3.11.3 contains specific details on how to use the ACCORD Label Program and figures containing examples.

Participant ID's take the form ABBC#####, where A is a number that references the Clinical Center Network (CCN) number, BB is a number that references Clinical Site (CS) number within CCN, and C##### is a 5-digit number preceded by an alphabetical character that references the participant within the study. A participant's ID follows the participant throughout ACCORD screening and follow-up visits. If a participant changes CCN or CS, then the first two prefixes (A and BB) will change to reflect the new status. Specifically, the last 6 digits of an ID will follow a participant throughout the study.

Clinical Site's are assigned a unique block of screening IDs used by the Label Program to generate labels. When using the Label Program, ID's for use in initializing participants into the study will be obtained from pages of labels containing 30 unique participant IDs (screening labels). An example of a valid ACCORD ID is 101A00001. This number would reference a participant screened in CS #01 within CCN #1.

An identifying acrostic will also be used within clinics to aid in situations where pages of forms become detached from the remainder of forms. The acrostic will consist of the first three letters of the last name, plus the first two of the first name, plus the middle initial. It should be hand written on the top of every form. If there is no middle initial, then the acrostic should be filled with a dash "-". An example of a valid acrostic

for John S. Smith would be "smijos". If Mr. Smith did not have a middle initial, then the acrostic would be "smijo-".

You will be able to print additional labels containing a participant's ID. These can also be placed on each page of multi-page forms if placement of the labels does not interfere with data that has been written on the form.

The first step in assigning participant IDs requires you to print screening label batches or pages. The thirty sequential screening labels specific to each CS is printed per page. Each label contains a unique participant ID and a barcode that can be scanned. Each participant that is screened is given a screening label to be placed on the participant's Inclusion/Exclusion Summary Form.

When printing these labels you must identify the number of batches (pages) of 30 labels that should be generated. Once a page of unique IDs has been printed, you will be unable to reprint this group of unique participant IDs.

10.2.10 Data Validation Procedures

The database management system performs several validation checks during the entry process. Data must 1) match the correct type (numeric data in numeric fields), 2) be in the correct range of valid responses, and 3) be appropriately marked when missing. Data that fail the established validation checks generate messages or prompts that describe the problem and required actions. The data validation checks always suspend cursor movement until acceptable data are entered.

All questions will be pre-assigned missing values for the purpose of data entry. The data entry screens will require a set degree of completeness before a form can be accepted. Should the forms be incomplete, the missing value would be entered into the database. Validation checks will be applied during the data entry process. Insofar as possible, checks will be programmed using JavaScript routines and made as the clinic staff enter data from each CRF. At certain intervals, the clinics will be mailed reports showing the current status of missing data within the database.

10.2.11 Reporting

Monitoring of study data will take place at both the Coordinating Center and the CCN in order to achieve and maintain a high level of quality. Some of the monitoring and quality control reports will be transmitted to the Clinical Centers for immediate action and attention; other quality control and monitoring reports will be generated for the Project Office/Steering Committee and Data and Safety Monitoring Committee

10.3 DBMS Software Updates

Periodically, throughout the ACCORD study, the Coordinating Center will update the database management system. If significant changes are made to the system, clinic staff will be informed via the Main page of the web site in order to note the new changes.

10.4 Electronic Transfer of Central Laboratory Data

The clinics will log each shipment of specimens sent to central laboratories. Data from the core lab is delivered to the Coordinating Center via email and uploaded to a repository on the server. Specific import routines will be developed to verify and merge these data with the main database.

10.5 Data Conversion and Extraction

SAS analysis files can be extracted from the database using SAS/Access. Programmers, at the Coordinating Center will develop routines to create other specialized analysis files from the SQL Server database or the SAS database. Prior to merging or extracting any data into or from the database, merge/extraction routines will be developed and thoroughly tested. Since data will be arriving from differing locations, verification will include consistency checks across all platforms as well as any other routine checks. All routines will be properly documented and changes and updates to the code will be noted.

10.6 Database Closure and Documentation

Upon study completion, after all clinic and laboratory data have been collected and filtered through various quality control routines, the resulting SQL Server database will be converted to SAS and ASCII data sets and certified. The database will be taken offline and archived on magnetic tape and/or CDROM. The final data sets will be certified and issued version numbers to synchronize analytic efforts and will be distributed in accordance with steering committee and institutional policy. The choice of media on which to copy and distribute copies of the database to the investigators will depend upon the systems and the media available at that point in time.

Documentation will be prepared that contains a brief overview of the project, the goals, and the type of data collected. This will be followed by a list of variable names, date format, their positions, and short descriptions of each variable contained on the media.

10.7 Security

Normally, data are transmitted across the Internet as plain text. It is possible, though highly unlikely, for someone to monitor this traffic and, using the proper equipment, reconstruct the individual pieces into the original data. Because of this threat, we employ a digital server certificate from Verisign Inc. This certificate allows the communications between the web server and the client system to be encrypted. This encryption is as advanced as is now allowable by the United States Government. This mechanism is the same as is used by the banking industry and for electronic commerce.

We feel strongly that this system will provide more than adequate security against unauthorized use.

Restricted areas of the web site are protected by user login. Prior to gaining access to the restricted area, the user is required to enter a username and password that will be checked against a database. If the combination is correct, a "flag" will be set to allow the user to enter certain areas of the web site. For security purposes, once a user has successfully logged into the system, inactivity for a period of 60 minutes will automatically force the user to re-authenticate prior to using the system again. We strongly recommend that users log out of the system before leaving their work area for any extended period.

WFUSM is protected by a Cisco firewall that limits the source and type of traffic coming into the institution. This product remains under constant monitoring and control.

10.8 Disaster Recovery

Each night, all data, programs, code, documents, etc. associated with the ACCORD project will be backed up to a DLT tape library. These tapes are kept indefinitely and are located in a fireproof cabinet that remains locked at all times. Periodically, copies of tapes are moved to an off-site location for storage. In the event that there is any loss of data, the information can be restored from tape in a matter of hours. The entire PHS computer facility is provided with conditioned power, UPS capability and environmental sensors with notification protocols.

11. Termination/Discontinuation

11.1 Overview

This section provides guidelines for termination/discontinuation policies for study participants using the **ACCORD Study Status Form.** The clinical centers must **follow** every randomized participant until the end of the study unless death or a refusal precedes the study duration first. Other trials have described the effect of participant losses, which adversely affected the power of their studies. For ACCORD to validate the primary outcomes, diligence in participant adherence is essential to the success of the trial. The primary reasons for using this form are:

- Problem or discontinuation of study medications
- Adverse events and safety considerations
- Refusals and losses to follow-up

If all of the participant adherence recommendations found in MOP Chapter 18 have been addressed, **contact your CCN Coordinator** and complete the **ACCORD Study Status Form.** This form will be used to document a participant's status as either a "true refusal" (e.g. desires no further contact of any kind with the ACCORD Trial) or a participant that becomes lost to follow-up and/or to document a participant's return to active status or follow-up if they were previously refusing participation or had been lost to follow-up. **Data entry of the Study Status Form is not allowed without prior approval from your CCN Coordinator.**

Completion of this form will negate the need to complete any study visit forms for missed clinic or phone visits for participants identified as refusing or lost to follow-up.

11.2 Discontinuation of Study Medications

Discontinuation of study medications may be necessary because of side effects, serious adverse events or other safety considerations. It is also common for study medications to be discontinued in the setting of serious medical illness. Patients may also refuse to continue their study medications for any of the above reasons or for non-medical reasons.

Management of side effects is based on the philosophy of protecting the safety of the participant while at the same time making every effort to adhere to the study protocol. In those instances where deviations from the study protocol are necessary in the judgement of the treating clinician, these deviations should be as minimal as possible. In many cases, reassurance and watchful waiting are effective strategies for managing all but the most troublesome side effects. For persistent or intolerable side effects, the dosage of the study medication may need to be decreased or the medication may need to be discontinued temporarily. If the perceived side effect does not resolve, the medication may be restarted after careful negotiations with the participant. If the side effect symptoms do resolve, it is also nearly always desirable to re-challenge the participant with the medication suspected of causing side effects. If the side effects recur, and are

not tolerable at the lowest dose of the study medication, it is then reasonable to discontinue the medication and seek alternative choices allowed by the protocol. Common and unusual side effects of the ACCORD study medications are enumerated in MOP Chapter 8.

Serious adverse events attributable to study medication warrant discontinuation of the study medication suspected of causing them. Any serious adverse events that are deemed by the investigator to be caused by study medication must be reported to the Coordinating Center via the **ACCORD Serious Adverse Experience Form**. If the event is a death or life-threatening event, the Coordinating Center should be notified by telephone, email or fax within one working day of discovery. Please refer to MOP Chapter 8 for instructions relating to the **Serious Adverse Experience Form**.

Abnormal values for safety laboratory tests may also warrant temporary or permanent discontinuation of study medication. It may also be necessary to discontinue study medications because of the potential for adverse interactions with other non-study medications. Whenever possible, participants and their physicians should be discouraged from starting non-study medications that pose safety concerns when used in combination with study medication. (See Table 11.1)

When participants are hospitalized or develop serious acute illness, the treating physician may discontinue study medication. In some cases, the event may warrant permanent discontinuation of study medication, e.g. metformin in a patient with the new onset of congestive heart failure [Refer to Table 11.1]. However, in most cases, study medication can safely be resumed when the patient has recovered. Patients should be reminded to inform non-study caregivers that they are participating in ACCORD, and should provide them with appropriate contact information for the study team, Coordinating Center and Drug Distribution Center. Good communication between the study team and the treating physician can minimize unnecessary disruptions in ACCORD treatments. Please refer to MOP Chapter 17, Section 17.10 for description of unblinding procedures.

11.3 Termination of Follow-up

The **ACCORD Study Status Form** is also used to document participant refusals and losses to follow-up.

Refusals. Refusals are classified as a denial for any personal future contact or data retrieval to ACCORD administration and staff. All efforts should be made by the investigator and staff to negotiate a final clinic visit for the purpose of data collection, event ascertainment and medication adherence. If the participant refuses to come for a clinic visit, request some acceptable minimum adherence that provides approval until the end of the study. This minimum acceptance is the review of medical records, documentation of vital status and primary outcomes. If these negotiations are acceptable to the participant, DO NOT complete this form at this time. ACCORD is different from other studies because participants are:

- followed even off study medications

- followed after study events
- followed after a serious adverse event

However, if the participant is adamant about discontinuing any further involvement in ACCORD, complete item #1 in the Refusal section.

Lost to Follow-Up. Use the **ACCORD Study Status Form** for participants who have missed his/her last two consecutive visits **And** cannot be contacted at last known phone number or address, or through relatives, neighbors, or other contacts. Check item # 1 in the Lost to Follow-Up section on the form and complete the appropriate information. If the participant does contact the ACCORD clinic again, and wishes to return to active status, check the box in the Return to Active Status section and data enter the date.

Table 11.1
Non-Study Medications that Pose Safety Concerns When Used in Combination With Study Medications

A general caution is issued regarding the use of the following classes of drugs because of concurrent hyperglycemia:

- **High dose thiazide or other diuretics; e.g. hydrochlorothiazide, chlorthalidone, furosemide**
- **Corticosteroides**
- **Phenothiazines**
- **Thyroid Products**
- **Estrogens**
- **Phenytoin**
- **Nicotinic acid**
- **Sympathomimetics**
- **Isoniazid**

A general caution is issued regarding the use of sulfonylureas (e.g. glimepiride) with other highly protein bound agents because the action of the sulfonylurea will be enhanced:

- **Non-steroidal anti-inflammatory agents**
- **Salicylates**
- **Sulfonamides**
- **Chloramphenicol**
- **Coumarins**
- **Probenicid**
- **Beta-adrenerigic blocking agents**

Metformin is contraindicated in the following conditions:

- **Acute MI**
- **Breast Feeding**
- **Cardiogenic shock**

- **Acute or chronic metabolic acidosis**
- **Hypoxemia**
- **Lactic acidosis**
- **Sepsis**
- **Severe dehydration**
- **Heart failure requiring pharmacologic treatment**
- **Serum creatinine greater than or equal to 1.5 mg/dl**
- **Excessive use of ethanol**
- **Increased ALT levels (3x uln, my level)**

Thiazolidinediones (e.g. rosiglitazone) are contraindicated in the following:

- **Diabetic Ketoacidosis**
- **Jaundice**
- **Heart-failure - there is a general caution about the use of these agents in Class 3 or Class 4 heart failure patients, but it appears that no study has ever been done in those patients. There is only concern about what may happen because of increased fluid retention observed in others.**
- **Liver function abnormalities - these agents should not be initiated in patients with ALT levels greater than 2.5 x uln and should be discontinued in participants with ALT levels greater than 3x uln.**

Cautions regarding Statin (e.g. simvastatin) use are urged in:

- **Conditions resulting in CPK levels greater than 3X uln (contraindicated)**
- **Conditions that result in ALT levels greater than 3X uln (contraindicated).**
- **Caution is urged when used at the same time as any other medication(s) or substance(s) is used requiring the 3A4 isoform of the cytochrome P450 liver metabolism mechanism.**

Cautions regarding the use of fibrates (e.g. fenofibrate) is urged in:

- **Conditions that result in ALT levels greater than 3X uln (contraindicated).**
- **Concomitant treatment with oral anticoagulants, statins, bile acid resins (separate resins and fibrates 4-6 hours)**

Cautions regarding thiazide diuretic (e.g. HCTZ) use is urged in:

- **Conditions resulting in hypokalemia and inability to use potassium supplements.**

Cautions regarding Angiotensin Converting Enzyme Inhibitor (e.g. benazepril, lisinopril, ramipril) use is urged in:

- **Conditions resulting in angioedemia. (contraindicated)**
- **Conditions resulting in hyperkalermia**

Cautions regarding Angiotensin II Receptor Blocker (e.g. candesartan, valsartan) use is urged in:

- **Conditions that result in salt depletion.**
- **Heart Failure**

Cautions regarding Dyhydropyridine Calcium Channel Blocker (e.g. amlodipine) use is urged in:

- **Participants with Class 4 heart Failure.**
- **Conditions that result in ALT levels 3X uln**

Cautions regarding Non-dyhydropyridine Calcium Channel Blocker (e.g. diltiazem) use is urged in :

- **Participants with Class 3 or 4 Heart Failure**
- **Sinoatrial nodal dysfunction (sick sinus syndrome)**
- **Hypotention**
- **Bradycardia**
- **Asystole**

Cautions regarding Beta Adrenergic Blocker (e.g. metoprolol, carvediloluse is urged in:

- **Patients using insulin who have had recurrent episodes of hypoglycemia (prolonged recovery).**
- **Conditions associated with bronchospasm in patients with asthma.**
- **Concomitant use in patients using phenytoin or phenobarbital or in those who smoke may result in lesser effect of the agent.**
- **Heart failure**
- **Heart block**

1. Clinical Events

12.1 Introduction

After randomization, an ACCORD participant may be hospitalized, experience a new or recurrent myocardial infarction or stroke, develop congestive heart failure (with subsequent hospitalization) or unstable angina, or undergo a cardiovascular procedure. These events require the completion of special forms that are explained in this chapter of the MOP. In addition, we will conduct foot and eye examinations annually in the ACCORD participants to detect development or progression of neurological and ocular conditions. A description of these examinations and instructions for completing the appropriate sections of the forms are in MOP Chapter 9.

Since completion of most forms requires obtaining information from medical records, each ACCORD Clinical Site should have the participant sign a "Release of Medical Information" form at the time that the participant notifies the site of the event. This form should be developed by the Clinical Site in keeping with local institutional policies.

If a hospitalization or non-fatal event occurs, the ACCORD investigator should contact the patient's private physician to discuss the current and future status of the ACCORD medications, as well as the patient's overall medical condition.

12.2 ACCORD Outcomes of Interest

The primary (macrovascular) endpoint for ACCORD is the composite outcome of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. Cardiovascular deaths, myocardial infarctions, and strokes are defined in Chapter 5 of the Protocol. Details for completing the **Death Report Form, Myocardial Infarction Report Form, Unstable Angina Report Form, Stroke Report Form, Miscellaneous Cardiovascular Outcomes Report Form,** and **Preliminary Event Notification Form** are given below.

The **Preliminary Event Notification Form** is completed at the clinical site and must be submitted to the Coordinating Center (through the ACCORD web data entry system) **within 7 days** of discovering the event. The other five forms (**Death Report Form, Myocardial Infarction Report Form, Unstable Angina Report Form, Stroke Report Form, Miscellaneous Cardiovascular Outcomes Report Form**) are completed at the clinical site, but data entered at the Coordinating Center. Upon completion of any of these forms, the clinical site is to mail them (along with all supporting documentation) to the Coordinating Center for data entry (as described below).

To document the occurrence of an outcome event, you should download and print the needed forms from the ACCORD web site (www.accordtrial.org). For the five event forms, the completed original and any supporting documentation (as described below) are to be mailed to the Coordinating Center **within 90 days** of the date that the clinic discovered the event. Before sending these materials to the Coordinating Center, the clinical site should

photocopy the completed form and all supporting materials, and store the copy in the participant's study chart at the clinical site.

It is recommended that you use the CCN PI and Coordinator as resources to answer questions and to review summaries.

It is extremely important that Clinical Site personnel be diligent in identifying events and in collecting all relevant and requested data (including hospital data and information from the participant and/or friends or family of the participant). Note that you will be asking the participant about events every 4 months through the completion of the **Interval History and Follow-up Forms** and the **Annual Follow-up and Physical Exam Forms**.

Using data and materials collected by the ACCORD Clinical Sites and applying the event definitions presented in the protocol, the Morbidity and Mortality Subcommittee (composed of ACCORD physician investigators) will review and classify each death and each suspected MI and stroke. This committee will also review reports of unstable anginal events for the purpose of determining whether the event actually fulfills the ACCORD definition of MI (primarily through the elevation of cardiac enzymes).

12.3 ACCORD Preliminary Event Notification Form

It is extremely important that the Coordinating Center be notified quickly that an ACCORD participant has died or has had an MI, stroke, unstable anginal event, or miscellaneous cardiovascular event (specifically, a cardiovascular procedure or hospitalized for CHF). This is accomplished by completing the **ACCORD Preliminary Event Notification Form.**

Indicate on this form which event (or events) the participant has experienced and indicate the date of the event(s) on the form. Even if the events are related (e.g., if the participant died of an MI), check all relevant boxes (e.g., both the death and the MI fields) and indicate the dates of the events (even if they are the same date). If the participant has had more than one cardiovascular procedure, you should enter the date of the earliest on the **Preliminary Event Notification Form**.

Enter the **Preliminary Event Notification Form** into the ACCORD database within 7 days of discovering that the event has occurred. Then complete the appropriate event-specific form(s) (i.e., the **Death, Myocardial Infarction, Stroke, Unstable Angina, or Miscellaneous Cardiovascular Outcomes Report Forms**), collect any necessary supporting documentation for the event(s), and mail these materials to the Coordinating Center within 90 days of the date that the clinic discovered the event . Note: supporting documentation (described below) is required for:

Any death
Any MI
Any Unstable Anginal Event
Any Stroke

Supporting documentation is not required for cardiovascular procedures or hospitalizations for CHF, unless the procedure/failure is associated with an MI, stroke, unstable anginal event, or death (in which case you would have had to collect this information anyway).

12.4 ACCORD Death Report Form

12.4.1 General Instructions

An **ACCORD Death Report Form** (form DTHR) must be completed whenever any randomized ACCORD participant dies. Unlike most ACCORD forms, this form is not data entered at the clinical site. The completed original and its supporting documentation are to be mailed to the Coordinating Center for data entry within 90 days of the date that the clinic discovers the event. The clinical sites should photocopy the completed form and all supporting documentation and retain them in the participant's chart at the clinical site.

In addition to this form, the clinical site is required to send to the Coordinating Center copies of supporting clinical documentation, with participant identifying information deleted by heavy black magic marker (to maintain confidentiality). Do not forget to put the ACCORD Participant ID Number and Acrostic on each page of the documents. The reports that should be included in this documentation are:

- Death Certificate
- Hospitals discharge summary (if the participant was hospitalized at the time of death)
- Admission history and physical (if the participant was hospitalized at the time of death)
- Emergency room notes (if the participant was seen in the emergency room at the time of death)
- All relevant ECGs and rhythm strips
- Cardiac enzyme data (send any available lab reports; indicate normal troponin and/or CKMB values)
- The autopsy report, if autopsy was performed

If the participant dies outside the hospital and there are available medical records that would assist the M and M committee members in classifying the cause of death, these records should be sent with the death form. For example, if the participant is known to have cancer and then dies at home, documentation of the cancer diagnosis should be sent. This documentation could include previous hospital discharge summaries, progress notes of pathology notes.

12.4.2 Definitions for Death

Fatal myocardial infarction (MI): death within 7 days of the onset of documented MI (see next Section of MOP [and Protocol Chapter 5] for the ACCORD definition of MI).

Stroke death: Death due to stroke occurring within 7 days of the signs and symptoms of a stroke. (Strokes are defined below and in Chapter 5 of the Protocol).

Unexpected death (within 24 hours of symptom onset): Unexpected death presumed to be due to ischemic cardiovascular disease, occurring within 24 hours of the onset of symptoms without confirmation of cardiovascular disease, and without clinical or post mortem evidence of other etiology.

Congestive heart failure (CHF) Death: Death due to clinical, radiological or postmortem evidence of CHF without clinical or postmortem evidence of an acute ischemic event. (Cardiogenic shock is included.) If the deceased was hospitalized for CHF, a **Miscellaneous Cardiovascular Outcomes Report Form** should be completed as well.

Death after invasive cardiovascular interventions: Death associated with the intervention, i.e., within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterization, arrhythmia ablation, angioplasty, atherectomy, stent deployment, or other invasive coronary or peripheral vascular intervention. A corresponding **Miscellaneous Cardiovascular Outcomes Report Form** should be completed as well.

Documented arrhythmia: Death due to bradyarrhythmias or tachyarrhythmias not associated with an acute cardiac ischemic event.

Death after non-cardiovascular surgery: death due to cardiovascular causes within 30 days of surgery. The specific cardiovascular causes for this outcome are:

- Unexpected cardiovascular death (as defined above)
- Fatal Myocardial Infarction (MI) (as defined above)
- Congestive Heart Failure Death (as defined above)
- Documented arrhythmia (as defined above)
- Stroke (as defined above)
- Other cardiovascular disease death (as defined below)

Presumed cardiovascular death: Suspicion of cardiovascular death with supporting clinical evidence that may not fulfill criteria otherwise stated. Example: Patient admitted with typical chest pain of 3 hours duration and treated as an MI, but without ECG and enzymatic documentation to meet usual criteria.

Other cardiovascular disease death: Death due to other vascular diseases including pulmonary emboli and abdominal aortic aneurysm rupture. Suspected cause should be specified in the fields provided.

Hepatic failure: Death primarily due to liver disease of any kind.

Renal Failure: Death primarily due to renal failure or end stage renal disease.

Cancer: Death primarily due to cancer. Specify the primary site and type of cancer in the fields provided.

Other (specify): Death primarily due to any of the causes not listed above, including accident, trauma, suicide, and violence, as well as any acute or chronic illnesses not specified previously. Specify the cause in the field provided.

12.4.3 Specific Instructions Regarding Form Completion

Date of Death. Double check to be sure the date is correct, especially the year. Enter date of death in MM/DD/YY format.

Time of Death. Use a 24-hour clock to give the most specific time available. Round to nearest hour (e.g., enter 23 if death occurred at 11:14 p.m., or enter 08 if death occurred at 7:50 a.m.). If death occurred at 30 minutes past hour, round down (e.g., enter 17 if death occurred at 5:30 p.m.).

Death Witnessed? A death is considered witnessed if the deceased was actually in visual or voice contact with an observer at the time of death (e.g., if a death occurs while someone is talking with the participant in another room, but not actually able to see the participant). Similarly, if the participant dies while talking to someone on a phone, the event is considered witnessed. If the participant was seen to be alive by an observer within 5 minutes of a cardiac arrest, the event is considered witnessed, with the relevant observations occurring at the last time the participant was seen or the last time anyone talked to the participant. There is a significant difference between an unwitnessed death and a death in which there is no information available to determine whether it was witnessed or not. In the latter case, the answer should be marked 'unknown'.

Location of Death. 'Out of Hospital' death refers to deaths outside of an acute care hospital or to participants who are dead on arrival (DOA) at an Emergency Room. Participants dying in a nursing home are considered out of hospital deaths. 'In Hospital' death refers to deaths that occur at any time after admission to a hospital, whether a transfer from the Emergency Room or an elective admission that was not necessarily related to the terminal event. An 'Emergency Room' death is one in which the participant arrives with potential for resuscitation (spontaneous and/or cardiac electrical activity) or is otherwise alive, but resuscitation fails and the patient dies in the Emergency Room. 'Unknown' should be used when the location of death is completely unknown and the information is irretrievable.

Primary Cause of Death. Using the definitions presented above in Section 12.4.2, check one box indicating the primary cause of death. If this is a myocardial infarction death you will need to also complete an **ACCORD Myocardial Infarction Report**. If this is a stroke death, you will need to complete an **ACCORD Stroke Report Form**. If this is a cancer death, indicate the primary site and type.

Narrative Summary The narrative summary provides essential information when reviewing the fatal event for final classification. Be as complete and as specific as possible. Describe the circumstances surrounding the terminal event, including the source of information, time of day, symptoms, location, social setting, type and duration

of symptoms. Be as specific as possible when reporting information such as exact location of death, when and by whom participant was last seen alive, and location of those in the same house when the participant died. Also comment on the underlying causes of death and the suspected mechanism of death.

The narrative summary must be written and signed by the Principal Investigator at the ACCORD Clinical Site. Use as many continuation sheets as necessary to describe the terminal event.

Indicate the total number of pages that should be attached: Enter the total number of pages used to document this event, including the **ACCORD Death Report Form**, the narrative summary, and all supporting documentation. Make sure that the participant's ID and acrostic are on every page.

INVESTIGATOR Signature: The clinical site PI should review the completed form and all supporting documentation, and then sign in the area provided. Mark the "Reviewed" box at the time that the form is signed. This field will be keyed as confirmation of review and signature.

12.5 ACCORD Myocardial Infarction Report Form

12.5.1 General Instructions

An **ACCORD Myocardial Infarction Report Form** (Form MIRF) must be completed whenever any randomized ACCORD participant has a myocardial infarction (heart attack). Unlike most ACCORD forms, this form is not data entered by the clinical site. The completed original and its supporting documentation are to be mailed to the Coordinating Center for data entry within 90 days of the date that the clinic discovers the event. The clinical sites should photocopy the completed form and all supporting documentation and retain them in the participant's chart at the clinical site.

In addition to this form, the clinical site is required to send to the Coordinating Center copies of supporting clinical documentation, with participant identifying information deleted by heavy black magic marker (to maintain confidentiality). Do not forget to put the ACCORD Participant ID Number and Acrostic on each page of the documents. The reports that should be included in this documentation are:

- Emergency room notes
- Admission history and physical (if hospitalized)
- All relevant ECGs and rhythm strips
- Cardiac enzyme data (send any available lab reports; indicate normal troponin and/or CKMB values)
- Cardiac procedure reports
- Cardiology consults
- The hospital discharge summary (if hospitalized)

12.5.2 Definition of Myocardial Infarction

For event classification purposes, myocardial infarction (MI) in ACCORD will be defined as either: Q-wave MI, non-Q-wave MI, probable non-Q-wave MI, MI after invasive cardiovascular intervention(s) or MI after coronary bypass graft surgery (CABG).

The definitions of an ACCORD MI may include the presence of:

> Prolonged ischemic symptoms (i.e. lasting at least 20 minutes), and/or
>
> Significant elevation of cardiac enzymes, including either troponin T or I and/or serum CKMB.

The clinical site Principal Investigator is asked to provide supporting evidence for, and his/her assessment of the type of MI sustained by ACCORD subjects, according to the following criteria. (Note that more than one classification is possible, such as a probable non-Q-wave MI following invasive cardiovascular intervention).

1. Q-wave MI: Diagnosis based on the occurrence of a compatible clinical syndrome with prolonged ischemic symptoms associated with the development of new Q waves in $\geq$2 contiguous leads, with elevation of serum enzymes (if obtained). For diagnostic purposes a new Q wave shall be considered significant if it is: any Q wave in leads V1 through V3, or Q wave $\geq$0.03 seconds or 30 ms in leads I, II, aVL, aVF, V4 through V6. Contiguity will be defined by the sequence V1 through V6 in the precordial leads, and in the frontal plane by the sequence aVL, I, inverted aVR, II, aVF and III. Diagnostic elevation of cardiac enzymes will include increase in troponin T or I to a level that indicates myonecrosis in the laboratory performing the study and/or an increase in CKMB to a level greater than twice the upper limit of normal.

2. Definite Non-Q-wave MI: Diagnosis based on the occurrence of a compatible clinical syndrome with prolonged ischemic symptoms, associated with elevation of serum enzymes, as for Q-wave MI. Only in the case that both troponin and CKMB measurements are unavailable would the elevation of total CK to $\geq$ twice the upper limit of normal qualify for diagnosis.

3. Probable non-Q-wave MI: Diagnosis based on the occurrence of a compatible clinical syndrome with prolonged ischemic symptoms, without documentation of cardiac enzyme elevation, but associated with the development of new and persistent ST-T changes (>24 hr in duration): a) Persistent ST-segment depression $\geq$ 0.05 mV (0.08 seconds after the J-point) in at least two leads, not known to be old and not in the setting of LVH, or b) Persistent T wave inversion $\geq$ 0.03 mV (or pseudonormalization

$\geq$ 0.1 mV above the isoelectric baseline) in at least three leads, not known to be old and not in the setting of LVH.

4. MI after invasive cardiovascular intervention: Diagnosis based upon the occurrence of abnormal levels of troponin or CKMB increased 3-5 times normal for the laboratory performing the studies, occurring within 7 days of cardiac catheterization, arrhythmia ablation, angioplasty, atherectomy, stent deployment or other invasive coronary, carotid or peripheral vascular intervention.

5. MI after coronary bypass graft surgery: Diagnosis based upon the occurrence of CKMB or troponin elevations to a level increased $\geq$ 5-10 times normal for the laboratory performing the studies, occurring within 30 days of cardiac surgery.

12.5.3 Specific Instructions Regarding Form Completion

Date of onset of symptoms. Record the date of the onset of symptoms. Double check to be sure the date is correct, especially the year. Enter date in MM/DD/YY format.

Time of Onset of MI. Use a 24-hour clock to give the most specific time available. Round to nearest hour (e.g., enter 23 if MI occurred at 11:14 p.m., or enter 08 if MI occurred at 7:50 a.m.). If MI occurred at 30 minutes past hour, round down (e.g., enter 17 if MI occurred at 5:30 p.m.).

Did the participant have characteristic symptoms for $\geq$ 20 minutes? Indicate 'Yes' or 'No.'

Were ECGs Done? Indicate 'Yes' or 'No.' If 'No,' indicate why not. If 'Yes' send all 12-lead ECGs to the ACCORD Coordinating Center with the other documentation. Make sure that the participant's ID number and ACROSTIC are on the ECGs. When copying the ECGS, do not obscure the time or date of the ECG.

Were cardiac enzymes/biomarkers measured? Indicate 'Yes' or 'No.' If 'No,' skip to Question 4. If 'Yes,' indicate whether troponin T or I was elevated. Then enter the peak enzyme values, the threshold values used by the local lab indicating an acute MI, and units in the appropriate spaces. Send actual lab reports with cardiac enzyme values and normal lab values. If Troponin was measured but elevation undetermined due to lack of threshold values or other reasons, mark N/A.

Please be aware that mention of cardiac enzymes in the discharge summary is not adequate and you will receive a request for additional information from the coordinating center- the actual lab reports are needed.

Was an assessment of LV function done? Indicate 'No' or 'Yes.' If 'Yes,' record the left ventricular ejection fraction (LVEF). If LVEF assessment was qualitative (i.e., no estimation of ejection fraction is available), mark N/A.

Was a coronary arteriogram done? Indicate 'Yes' or 'No.' If 'Yes,' indicate whether there was a narrowed coronary artery serving the region of the MI (and send the cath report to the Coordinating Center along with the supporting documentation).

Did the participant die? Indicate 'Yes' or 'No.' If 'Yes,' complete the **ACCORD Death Report Form**.

Was there percutaneous intervention within the last 7 days prior to the event? Indicate 'Yes' or 'No.' If 'Yes' then specify type.

Was there cardiac surgery within the last 30 days prior to the event? Indicate 'Yes' or 'No.' If 'Yes' then specify type.

Was there non-cardiovascular surgery within the last 30 days prior to the event? Indicate 'Yes' or 'No.' If 'Yes' then specify type.

Using the definitions presented above in Section 12.5.2, indicate below the MI diagnoses best supported by the clinical evidence. Again note that you can select more than one. Sufficient data should be provided to justify the conclusion reached. The choices are:

1. Q-wave MI
2. Definite Non-Q-wave MI
3. Probable non-Q-wave MI
4. MI after invasive cardiovascular intervention
5. MI after coronary artery bypass (CABG) surgery

Please provide additional clinical details. In the space provided, write any additional clinical details that you think are important for the classification of this event. Please print or type the information.

Indicate the total number of pages that should be attached: Enter the total number of pages used to document this event, including the **ACCORD Myocardial Infarction Report Form** and all supporting documentation. Make sure that the participant's ID and acrostic are on every page.

INVESTIGATOR Signature: The clinical site PI should review the completed form and all supporting documentation, and then sign in the area provided. Mark the "Reviewed" box at the time that the form is signed. This field will be keyed as confirmation of review and signature.

12.6 ACCORD Unstable Angina Report Form

12.6.1 General Instructions

An **ACCORD Unstable Angina Report Form** (Form USAN) must be completed whenever an unstable anginal event occurs in any randomized ACCORD participant. Unlike most ACCORD forms, this form is not data entered by the clinical site. The

completed original and its supporting documentation are to be mailed to the Coordinating Center for data entry within 90 days of the date that the clinic discovers the event. The clinical sites should photocopy the completed form and all supporting documentation and retain them in the participant's chart.

In addition to this form, the clinical site is required to send to the Coordinating Center copies of supporting clinical documentation, with participant identifying information deleted by heavy black magic marker (to maintain confidentiality). Do not forget to put the ACCORD Participant ID Number and Acrostic on each page of the documents. The reports that should be included in this documentation are:

- Emergency room notes
- Admission history and physical (if hospitalized)
- All relevant ECGs and rhythm strips
- Cardiac enzyme data (send any available lab reports; indicate normal troponin and/or CKMB values)
- Cardiac procedure reports, if applicable
- Cardiology consult, if applicable
- The hospital discharge summary

12.6.2 Definition of Unstable Angina

Unstable angina in ACCORD is defined as new onset exertional angina, accelerated or rest angina, and at least one of the following indicators of myocardial ischemia:

a) At least 1 mm ST segment depression occurring spontaneously or with stress testing in subjects with normal baseline ST and T waves, or
b) Angiographic findings of at least 90% epicardial coronary artery or at least 50% stenosis of the left main coronary artery, or
c) At least 1 mm ST depression or transient ST elevation with pain occurring spontaneously or on ECG stress testing, with evidence of at least 50% stenosis of a major epicardial coronary artery

12.6.3 Specific Instructions Regarding Form Completion

Date of Onset of Symptoms. Record the date of the onset of symptoms. Double check to be sure the date is correct, especially the year. Enter date in MM/DD/YY format.

Were ECGs Done? Indicate 'Yes' or 'No.' If 'No,' indicate why not. If 'Yes' send all 12-lead ECGs to the ACCORD Coordinating Center with the other documentation. Make sure that the participant's ID number and ACROSTIC are on the ECGs.

Were cardiac enzymes/biomarkers measured? Indicate 'Yes' or 'No.' If 'No,' skip to Question 3. If 'Yes,' indicate whether troponin T or I was elevated. Then enter the peak enzyme values, the threshold values used by the local lab indicating an acute MI, and units in the appropriate spaces. Send all lab reports with cardiac enzyme values and normal lab values.

Please be aware that mention of cardiac enzymes in the discharge summary is not adequate and you will receive a request for additional information from the coordinating center- the actual lab reports are needed.

Was an assessment of LV function done? Indicate 'Yes' or 'No.' If 'Yes,' record the left ventricular ejection fraction (LVEF).

Was a coronary arteriogram done? Indicate 'Yes' or 'No.' If 'Yes,' indicate whether there was a narrowed coronary artery serving the region of the MI (and send the catheterization report to the Coordinating Center along with the supporting documentation).

Which of the following best describes this episode? Check all that apply: new onset exertional angina, accelerated angina, or rest angina.

Did the ischemic symptoms last for $\geq$ 20 minutes? Indicate 'Yes' or 'No.'

Evidence for Angina: Using the definitions presented above in Section 12.6.2, indicate what evidence you have for the myocardial ischemia (and choose all that apply).

Please provide additional clinical details. In the space provided, write any additional clinical details that you think are important for the classification of this event. Please print or type the information.

Indicate the total number of pages that should be attached: Enter the total number of pages used to document this event, including the **ACCORD Unstable Angina Report Form** and all supporting documentation. Make sure that the participant's ID and acrostic are on every page.

INVESTIGATOR Signature: The clinical site PI should review the completed form and all supporting documentation, and then sign in the area provided. Mark the "Reviewed" box at the time that the form is signed. This field will be keyed as confirmation of review and signature.

12.7 ACCORD Stroke Report Form

12.7.1 General Instructions

An **ACCORD Stroke Report Form** (Form STRF) must be completed whenever any randomized ACCORD participant experiences a fatal or non-fatal stroke. Unlike most ACCORD forms, this form is not data entered by the clinical site. The completed original and its supporting documentation are to be mailed to the Coordinating Center within 90 days of the date that the clinic discovers the event. The clinical sites should photocopy the completed form and all supporting documentation and retain them in the participant's chart.

In addition to this form, the clinical site is required to send to the Coordinating Center copies of supporting clinical documentation, with participant identifying information deleted by heavy black magic marker (to maintain confidentiality). Do not forget to put the ACCORD Participant ID Number and Acrostic on each page of the documents. The reports that should be included in this documentation are:

- Emergency room notes
- Admission history and physician (if hospitalized)
- Neurology consult notes
- The hospital discharge summary
- CT scan reports
- MRI reports

In the clinic situation, vascular strokes are defined as definite ischemic stroke, definite primary intracerebral hemorrhage, subarachnoid hemorrhage, and stroke of unknown etiology and non-fatal stroke after cardiovascular invasive interventions or after non-cardiovascular surgery.

In addition, this form is to be completed if the participant has experienced a stroke that was not primarily due to a vascular cause (e.g., a tumor).

12.7.2 Definitions of Stroke

1. Definite ischemic stroke: CT or MRI scan within 14 days of onset of a focal neurological deficit lasting more than 24 hours with evidence of brain infarction (mottled cerebral pattern or decreased density in a compatible location), no intraparenchymal hemorrhage by CT/MRI, no significant blood in the subarachnoid space by CT/MRI or by lumbar puncture, or autopsy confirmation. A nonvascular etiology must be absent.

2. Definite primary intracerebral hemorrhage: Focal neurological deficit lasting more than 24 hours. Confirmation of intraparenchymal hemorrhage in a compatible location with CT/MRI scan within 14 days of the deficit onset, or at autopsy, or by lumbar puncture.

3. Subarachnoid hemorrhage: Sudden onset of a headache, neck stiffness, loss of consciousness. There may be a focal neurological deficit, but neck stiffness is more prominent. Blood in the subarachnoid space by CT/MRI or lumbar puncture or intraventricular by CT/MRI.

4. Non-fatal stroke after cardiovascular invasive interventions: Stroke (as defined in 1 through 3 above and 7 below) associated to the intervention within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterization, arrhythmia ablation, angioplasty, atherectomy, stent deployment or other invasive coronary or peripheral vascular interventions.

5. Non-fatal stroke post non-cardiovascular surgery: Stroke (as defined in 1 through 3 above and 7 below) occurring within 30 days of non-cardiovascular surgery.

6. Stroke not primarily due to vascular causes (e.g., due to a tumor)

7. Stroke of unknown etiology: Definite stroke of unknown etiology when CT, MRI, or autopsy are not done. Information is inadequate to diagnose ischemic (infarction), intracerebral hemorrhage, or subarachnoid hemorrhage.

12.7.3 Specific Instructions Regarding Form Completion

Date of Onset of Stroke Symptoms. Record the date of the onset of symptoms. Double check to be sure the date is correct, especially the year. Enter date in MM/DD/YY format.

Symptoms (At Onset and **At 24 Hours):** Put a check mark next to each symptom that is present at each time point. You can select more that one symptom.

Status: Indicate the single best description at either 7 days after onset or at discharge (whichever is earlier). Select only one box. If the participant died during this period, you must also complete an **ACCORD Death Report Form.**

Body Side/Visual Field: Put a check mark next to all applicable areas.

Was CT scan done to confirm diagnosis? Indicate 'Yes' or 'No.' If 'Yes' then send report to Coordinating Center along with other supporting documentation.

Was MRI done to confirm diagnosis? Indicate 'Yes' or 'No.' If 'Yes' then send report to Coordinating Center along with other supporting documentation.

Was autopsy done to confirm diagnosis? Indicate 'Yes' or 'No.' If 'Yes' then send report to Coordinating Center along with other supporting documentation.

STROKE TYPE: Using the definitions above, check the one box that best describes the final diagnosis for this event. Note, if this is a stroke not primarily due to a vascular cause (e.g., a tumor or trauma), specify the cause in the space provided.

Was there percutaneous intervention within the last 7 days prior to the event? Indicate 'Yes' or 'No.' If 'Yes' then specify type.

Was there cardiac surgery within the last 30 days prior to the event? Indicate 'Yes' or 'No.' If 'Yes' then specify type.

Was there non-cardiovascular surgery within the last 30 days prior to the event? Indicate 'Yes' or 'No.' If 'Yes' then specify type.

Indicate the total number of pages that should be attached: Enter the total number of pages used to document this event, including the **ACCORD Stroke Report Form** and all supporting documentation. Make sure that the participant's ID and acrostic are on every page.

INVESTIGATOR Signature: The clinical site PI should review the completed form and all supporting documentation, and then sign in the area provided. Mark the "Reviewed" box at the time that the form is signed. This field will be keyed as confirmation of review and signature.

12.8 ACCORD Miscellaneous Cardiovascular Outcomes Report Form

12.8.1 General Instructions

The **ACCORD Miscellaneous Cardiovascular Outcomes Report Form** (Form MCVE) must be completed whenever any randomized ACCORD participant experiences:

- A Therapeutic Cardiovascular Procedure, or
- A Hospitalized Congestive Failure Event

12.8.2 Specific Instructions Regarding Form Completion

Did the participant have a cardiovascular procedure? If the participant had a cardiovascular procedure, complete this section. Please note that these include therapeutic procedures, NOT diagnostic ones (such as nuclear procedures or cardiac catheterization without intervention). Specifically indicate if the participant had any of the following:

- PTCA (balloon)
- PTCA (with stent only)
- CABG Surgery
- Carotid angioplasty with stent
- Carotid endarterectomy
- Peripheral angioplasty with or without stent
- Peripheral vascular surgery, including aortic aneurysm repair
- Limb amputation: including partial or digit amputation due to vascular disease

For each procedure marked, indicate the date it was performed. Double check to be sure the date is correct, especially the year. Enter date in MM/DD/YY format.

Was this procedure associated with any of the following events? If this procedure was associated with unstable angina, myocardial infarction, stroke, or death, indicate 'Yes' and complete the appropriate event form.

Was the participant hospitalized for congestive heart failure? Indicate 'Yes' or 'No.' If yes, specify: admission diagnosis (including ICD-9 code), date of hospitalization, and lowest ejection fraction for this admission.

INVESTIGATOR Signature: The clinical site PI should review the completed form and all supporting documentation, then sign in the area provided. Mark the "Reviewed" box at the time that the form is signed. This field will be keyed as confirmation of review and signature.

1.0 Adjudication of Events by The ACCORD Morbidity and Mortality Subcommittee

The following describes the procedures that will be followed in ACCORD to classify the events (**Death, MI, Stroke**) that constitute the primary ACCORD outcome. Note that **unstable anginal events** with supporting cardiac enzyme lab data will be reviewed by the ACCORD Morbidity and Mortality Subcommittee for the purpose of determining whether there is evidence that the event actually fulfilled the ACCORD definition for myocardial infarction.

At the Clinical Site:

1. A coordinator or investigator at the clinical site who follows the participant will complete the appropriate endpoint form(s) (**Death Report Form, Myocardial Infarction Report Form, Unstable Angina Report Form, Stroke Report Form)** and assemble supporting documentation.

2. Participant identifiers and indicators of treatment assignment will be removed from supporting documents by a heavy black magic marker.

3. The principal investigator at the clinical site will review the form, narrative and supporting documentation. Any questions or disagreements will be reconciled before the forms and supporting documents are sent to the Coordinating Center. The CCN PI or Coordinator can be consulted.

4. The forms and supporting documents will be sent to the Coordinating Center.

At the Coordinating Center:

1. The forms and supporting documents are received by the Coordinating Center where a physician at the Coordinating Center will review the forms and documentation for completeness and to ensure that all participant identifiers are removed from the documents.

2. Missing information will be requested by the Coordinating Center.

3. For each cardiovascular death, MI, and unstable anginal event, the ACCORD ECG Reading Center will be asked to supply the Coordinating Center all available ECGs that were read centrally, including the baseline and biannual ECGs.

4. Once the Coordinating Center is satisfied that all available information for each death, MI, unstable anginal event, and stroke has been obtained, a master "Events Packet" will be created for the event. From this packet, a secondary

"Review Packet' will be created by the physician at the Coordinating Center from which all non-relevant materials will be removed before distribution to subcommittee members.

1. For deaths, and myocardial infarctions, copies of the "Review Packet' will be sent to two members of the Morbidity and Mortality (M&M) Subcommittee along with the appropriate classification form(s). The Coordinating Center will select the pairs of reviewers, with the guiding principles that (a) subcommittee members will not review events in participants from their own clinical center and (b) the work is evenly spread among members of the subcommittee. Unstable angina events will be reviewed by the physician at the Coordinating Center for potential events fitting the ACCORD definition of a myocardial infarction. If cases fitting these criteria are found, they will be prepared in the above manner for full adjudication by the ACCORD M and M committee. Clinical sites will be asked at that time to enter an ACCORD myocardial infarction form.

2. Strokes will be assigned to two members of the M&M subcommittee and an independent neurologist for review.

The Review of an Event by the Morbidity and Mortality Subcommittee

1. Using the definitions in Chapter 5 of the ***August 31, 2004 ACCORD Protocol***, each subcommittee member will classify the endpoint event and return the classification form by FAX to the Coordinating Center.

2. Special Rules Regarding Presumed CVD Death vs Unexpected Death:
   a) For Presumed Cardiovascular Death, there must be prior evidence of cardiovascular disease.
   b) Unexpected Death has priority over Presumed Cardiovascular Death
   c) Use Presumed Cardiovascular Death when none of the first eight protocol criteria (5.1.a.1 through 5.1.a.8 of ***November 14, 2002 Protocol***) are satisfied.

3. Special Rule Regarding Date of Event:
   If the date of an event is known, then that will be used as the 'Date of Event,' otherwise the date of hospitalization will be used.

4. If the two reviewers agree on the classification of the event, the classification will be considered final and will not be scheduled for review at a meeting or conference call of the M&M Subcommittee.

5. If the two reviewers do not agree, the event will be scheduled for review by the fuller M&M Subcommittee (either by conference call or at a face-to-face Steering Committee meeting).

6. For those events that need to be re-reviewed by the fuller M&M Subcommittee, the events will be classified by consensus or vote (or will be returned to the clinical site for additional information).

7. If there is ever a disagreement between the M&M and clinical site classifications of an event, the Coordinating Center will notify the clinical site and CCN PIs of the disagreement. If they wish, the investigators at the clinical site can provide additional information to support their classification. If the clinical site challenges the M&M Subcommittee review, the challenge will be reviewed at the next meeting of the Subcommittee.

12.9 Adjudication of Involvement of Hypoglycemia in Death Cases by the ACCORD Morbidity and Mortality Subcommittee

Hypoglycemia is a major risk of the ACCORD trial. As such awareness of the involvement of hypoglycemia in death cases is needed. All death cases will be adjudicated for involvement of hypoglycemia. The adjudication for hypoglycemia involvement will occur after primary adjudication for cause of death is complete. The following procedures will be followed

At the Coordinating Center:

1. The Coordinating Center will prepare a list of the participant's last known glycemia medication, and previously reported hypoglycemia episodes.

2. A review packet will be created with the above information and the relevant medical records and other available documentation.

3. The Cases will be assigned to 2 members of the M and M committee. At least one of the two must be a diabetologist. Neither member can be from the CCN in which the participant was located.

The Review of an Event by the Morbidity and Mortality Subcommittee

1. A case will be considered closed after the initial review if both members agree on the outcome and the agreed outcome is unlikely or possibly (for example, both independently adjudicate involvement of hypoglycemia was unlikely)

2. If one member adjudicates unlikely while the other member adjudicates possibly the case will be sent to a third member for review. The final adjudication will be a determined by the majority (i.e. if 2 of the 3 reviewing members state that hypoglycemia was unlikely, while the other stated that it was probably, the final adjudication will be unlikely).

3. Any case that receives an adjudication of either probably or definitely from any member of the initial adjudication team will be reviewed by the entire M and M committee.

4. Cases brought before the entire committee that do not have a unanimous opinion after discussion will be determine by majority rules. For example, if a case has 8 member who vote that hypoglycemia was possibly involved in the death and 6 who believe it was probably involved, the final adjudication will be possibly.

12.10 Tracking of completeness of clinical events by Clinical Sites and Clinical Coordinating Networks

Clinical sites are required to provide essential documentation within 90 of their becoming aware of the event. Two reports are available on the ACCORD website to assist with management of clinical events. Located under Reports: Clinic Management, they are titled: "Outstanding Event Documentation, CCN-level" and "Outstanding Event Documentation, site-level". These rports indicate the documentation required, the documentation received, the days since the clinic became aware of the event. Those events that are more than 90 days old are marked with yellow. Clinics will receive automated email notification each month if they have an outcome event with outstanding documentation over 90 days. If required documentation is not available, the clinic must send written explanation to the Coordinating Center and the CCN Coordinator that includes an explanation of why the information will not be sent.

13. Assessment of Health Related Quality of Life (HRQL) in ACCORD

13.1 Introduction

The goal of the ACCORD HRQL investigation is to assess the impact of the ACCORD interventions on well being in a sub sample of the total group randomized. This assessment will address both:

1. Short-term symptoms and side-effects mediated largely through level/intensity of glycemic, hypertension, and lipid control treatment; and possible interactions among the glycemic and lipid control treatments; and
2. Long-term affects on general health and well being mediated through potential differences in effectiveness of risk factor reduction among the ACCORD treatment strategies.

The HRQL measures will be administered to a sub sample of 250 participants in each cell of the 8 ACCORD treatment groups (2000 participants total) at baseline, 12, 36 months and study exit. The randomization screen will display whether or not a participant has been selected for this sub study (See MOP Chapter 10, Section 10.2.6).

13.1.1 Short-Term

Medication-related effects on HRQL are assessed primarily with a symptom inventory developed and refined empirically from a database of multiple previous diabetes, lipid and hypertension treatment trials. Participant ratings of overall well-being will be assessed with a single-item "feeling thermometer" at each clinic visit. A brief treatment satisfaction instrument is included to assess the level of acceptability and satisfaction within each ACCORD treatment group.

13.1.2 Long-Term

These HRQL outcomes largely involve general health states known to be influenced by macrovascular and microvascular disease processes and events. Participant ratings will be assessed for general health (e.g., physical, social and psychological wellbeing) using the SF-36v2; depressive symptoms with Patient Health Questionnaire, and health state utilities with the Health Utilities Index-III. Potential substudies external to the main HRQL study of cognitive function and visual function, which would collect more detailed data, are under consideration.

13.2 The HRQL Instruments

Selection of the ACCORD HRQL instruments was made based upon the following criteria:

1. Must be relatively brief,
2. Include the major dimensions shown in the literature to be effected by diabetes and/or its treatment,

3. Proven to be responsive to treatment-related changes in previous clinical trials of conventional diabetes agents,
4. Appropriate for diverse ages, ethnicity groups, and
5. Have been tested in diverse populations for ease of self-administration and measurement validity.

13.2.1 Symptoms Inventory

The Symptom Testing In Diabetes Questionnaire includes 60 items developed by Testa and colleagues (1993, 1994 Phase V Technologies). Scales were selected from original, more lengthy instruments shown to be responsive to glucose, blood pressure and lipid control in previous randomized, double blind placebo-controlled clinical trials. Items assess presence of symptom and degree of distress. The symptom scale is scored by summing the items, each weighted by severity of impact (scored as 0 ="not at all" to 4= "extremely").

13.2.2 General Health Status

The SF-36v2 contains 36 items assessing general health status along 8 distinct health concepts: physical, social and role (emotional and physical) functioning, emotional wellbeing (fatigue and affect), bodily pain, and general health. In tests of older adults with chronic illnesses, the SF-36 (V2) has taken approximately 10 minutes to complete. SF-36 scale scores are obtained using algorithms published in the literature (see Ware, et al, 1991) and are reported in terms of a percentage of perfect general health (range 0 to 100). Norm based scoring is available for version 2.0 from Q-metric which allows a given score to be calculated as a percentage of a norm, representing an age-relevant general population sample.

13.2.3 Feeling Thermometer

This visual analog scale from the EQ5D (Euroqol instrument) rates how well the patient feels along a continuum of 'worst imaginable health state' to 'best imaginable health state'. Recording the value marked along the 100-mm thermometer by the subject scores this single item. The feeling thermometer takes less than 1 minute to complete.

13.2.4 Depression Assessment and Alerts

The Patient Health Questionnaire (PHQ) is a brief instrument designed to assess the presence and frequency of depression symptoms. The PHQ assesses the frequency of 9 symptoms over the previous two weeks as "not at all", "several days", "more than half the days", or "nearly every day", and takes approximately 1-2 minutes to complete. The PHQ is scored by counting as a positive symptom any item rated "more than half the days" or "nearly every day." Five symptoms or more scored in this way yields a sensitivity of 73% and a specificity of 98% for the diagnosis of major depression in primary care populations.

13.2.4.1 Assessment of Depression-related Alerts

Scoring the PHQ questionnaire will result in classification of the participant into one of three risk levels: (1) none—not currently at risk for depression or suicide; (2) non-emergent—at risk for depression but not suicide; or (3) emergent—depressed or at risk for depression and possibly suicidal. Classification into the first level requires no further follow-up. Classification into either second ("non-emergent") or third level ("emergent") requires follow-up by clinical staff.

To assess participant risk of depression or suicide, the following procedure should be followed:

- After the HRQL Questionnaire is completed (and before the participant leaves the clinic) it should be reviewed for completeness. If any items are left blank, ask the participant to re-read the item and mark a response. Though designed as a self-administered instrument, the questionnaire can be completed in an interview format for participants with physical, visual, or literacy problems (see section titled "Guidelines for Use as an Interviewer Administered Questionnaire" in MOP Appendix A.3).
- Once the questionnaire has been reviewed for completeness, go back to the PHQ portion (questions 9-17 on page 3). Calculate the depression risk score by summing the coded responses (0 for "Not at all", 1 for "Several days", 2 for "More than half the days", and 3 for "Nearly every day").
- If the response to question 17 ("Thoughts that you would be better off dead or of hurting yourself in some way") is scored 2 or 3 (i.e., "More than half the days" or "Nearly every day") an emergent action is required (see below for instructions).
- If the response to question 17 is scored 0 or 1, but the sum of all scores is greater than or equal to 15 then non-emergent action is required (see below for instructions).

13.2.4.2 Taking *Emergent* or *Non-emergent* Action

After determining that action is required, discuss questionnaire responses with participant to make sure he/she understood the questions and to verify that the intended responses were marked. If it is determined that the participant is truly at risk for major depression or suicide (i.e., a response of 2 or 3 for question 17 accurately reflects the participant's mental health state) promptly take whatever action is consistent with your clinic's standard practice regarding urgent or emergency mental health concerns. This action may include one or more of the following:

- Notifying the participant's physician (if the participant has given permission to do so);
- Making an appointment for the participant with an appropriate provider (e.g., a psychiatrist);

- Electing to evaluate and treat the participant at the clinical site.

In cases of emergent alert, this action should be taken with 24 hours.

If the participant is determined to be depressed or at risk of depression (but not at risk of suicide), then any of the actions listed above (or other actions in keeping with your clinic's usual practices upon determining a patient is depressed) should be taken within one week. In both emergent and non-emergent cases, notification in the form of a letter should be sent to the participant's PCP (if the participant has given permission to contact his/her PCP). A copy of the letter and any other documentation of actions taken should be placed in the participant's ACCORD study binder.

13.2.4.3 Automated Email Notification

An email notification system has been set up to send notification of emergent and non-emergent alerts to clinical site PIs and coordinators, with copies to the CCN coordinator and Coordinating Center. Such emails will be sent automatically upon saving HRQL questionnaire data in the ACCORD web data base. This system serves as a failsafe reminder that action is required; however, since data entry is delayed in many instances for several days after completion of a clinic visit, review of the completed HRQL instrument and calculation of the PHQ risk score must be performed at the time of visit.

13.3 Data Collection

There are several protocol concerns that must be taken into account when including HRQL measures in clinical trials, including: the time course of the trial, frequency of contact with the study population, timing of clinical assessments, the complexity of the trial design, the number of patients enrolled in the study, and the patient and staff burden. Therefore the HRQL assessment component has been designed to rely upon brief, self-administered instruments, which require less than 20 minutes to complete. All of the ACCORD HRQL instruments have been widely used in clinical studies involving patients with illnesses, and have been shown to be easy to administer and adequately understood by the participant.

The collection time points are designed to capture both near-term medication mediated effects on well being, and longer-term effects on well being mediated by potential variations in the progression of micro and macro-vascular disease processes produced by the ACCORD interventions. While it is anticipated that most participants recruited in the study will be able to provide valid self-report information on HRQL, a few individuals may require assistance completing the forms. Please see Appendix A.3 for methods to conduct the interviewer administered HRQL form.

ACCORD participants will complete the full HRQL battery during the scheduled randomization (baseline), 12 month, 36 month and study termination visits. The feeling thermometer only will be completed every four months at the regular study clinic visits.

13.3.1 Methods

At baseline, the ACCORD HRQL instrument will be completed on location, after eligibility has been confirmed and consent taken, but before medical testing has begun. Clinic staff will administer the baseline patient self-report questionnaires following guidelines described in Appendix A.3 *Methods for Collecting HRQL Data.* All questionnaires will be returned to the study coordinator by the patient following completion, and reviewed for data quality. Follow-up HRQL data collection will take place during the clinic visit during a convenient time, such as waiting periods prior to other testing. The HRQL assessments should be completed prior to all ACCORD medical or clinical exams as these have the potential to influence how a participant reports feeling physically or emotionally.

13.3.2 Training

Careful attention must be paid to the training of staff in order to ensure the collection of quality data from the study participants. To ensure high quality data collection, the lead study coordinator responsible for data collection at each clinical center will be trained in HRQL data collection and processing by the Coordinating Center as outlined in the data collection manual.

13.3.3 Population Issues

In ACCORD it is necessary to have Spanish and French language translations of the HRQL instruments. Most of the instruments have already been translated. Reading level of the HRQL instruments have been generally reported to be no higher than 8th grade level.

13.4 Data storage and entry

After the HRQL battery has been completed and reviewed by the clinic coordinator, the completed form should be data entered. The copy must be filed in a locked and secure file cabinet, designated for ACCORD data forms.

13.5 Safety Issues

Symptom data will be reported to the DSMB at regular intervals, as determined by the Steering Committee, for review of medication safety. Depression symptoms, if severe, will be reported back to the subject's primary care physician. None of the other HRQL data has common use for clinical and safety purposes.

14. Cost Effectiveness

14.1 Cost Substudy Form

The **Cost Substudy Form** is a brief (1 page) questionnaire that updates information on out patient procedures and health provider contacts. This form should be administered every 4 months for ACCORD participants in the Cost Substudy.

14.2 Health Utilities Index (HUI)

The HUI is a generic, preference-based measure of health-related quality of life, producing utility scores for economic evaluation. The HUI-Self -Administered (HUI-SA) questionnaire consists of 15 items, that convert into eight attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain), each containing five or six levels. The HUI-SA takes approximately 5-10 minutes to complete.

14.2 HUI Self-Administered Form

This form is designed to capture changes in the participant's health-related quality of life. It is administered to all participants at randomization, 1 year, 3 year and study termination visit. Below is an overview with directions for completing the form.

Page 1. Complete header information.

Questions 1 through 15 ask the participant to answer his/her level of ability or disability in domains of vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain during the past 4 weeks.

The participant should focus his/her answer on his/her overall abilities and how he/she/felt during the past 4 weeks.

The participant should answer all 15 questions.

The participant should answer each question independently.

For each question, the participant should select only one answer that best describes his/her condition.

The participant should indicate the selected answer by marking the appropriate box beside his/her answer.

14.3 Hospital Discharge Summary

Hospital discharge summaries are to be obtained for a subsample of participants selected for inclusion in the Cost Substudy . The purpose of collecting a hospital discharge summary for each hospitalization of patients who participate in the Cost Substudy is to

examine use of inpatient resource and cost. The basic design is for staff at each clinic to obtain a copy of the hospital discharge summary for each hospital admission and send it to the Coordinating Center. A specially trained medical coder at the Coordinating Center will map diagnoses and procedures into a unique DRG code for each hospital admission.

Instruction:

1. Staff at each clinical site are to obtain a copy of the hospital discharge summary for **EACH** hospital admission from any hospitals where the participant was hospitalized when a substudy participant answers "Yes" on Question 5 on **the Interval History/Follow-up Form**.

2. Make a photocopy of the discharge summary. Place one copy in the participant's ACCORD Study File, and send the other to the Coordinating Center via registered mail to the following address:

   ACCORD Coordinating Center

   Wake Forest University School of Medicine
   Medical Center Blvd.
   Winston-Salem, NC 27157-1063

Action to Control Cardiovascular Risk in Diabetes

ACCORD

Central Chemistry Laboratory

Manual of Procedures

Specimen Collection
Processing
Shipment

NORTHWEST LIPID METABOLISM AND DIABETES RESEARCH LABORATORIES
University of Washington School of Medicine

September 2007

ACCORD

TABLE of CONTENTS

ABOUT THE LABORATORY

A History

The Northwest Lipid Metabolism and Diabetes Research Laboratories (NWRL) was established in 1971 as one of twelve laboratories involved in the Lipid Research Clinics Program, and subsequent Coronary Primary Prevention Study, funded by the National Heart, Lung, and Blood Institute. During the program, this laboratory participated in the development and standardization of methods for the separation of lipoproteins and for the chemical quantification of their components, and performance was monitored continually through the Lipoprotein Standardization Program of the Centers for Disease Control. The laboratory is directed by

Research Professor of Medicine, Division of Metabolism, Endocrinology, & Nutrition, Department of Medicine, University of Washington.

The laboratory is an Abell Kendall reference network laboratory of the National Reference System for Cholesterol, and participates in the lipid standardization programs offered by the National Heart, Lung, and Blood Institute, Centers for Disease Control, and the College of American Pathologists. In addition, the laboratory serves as the reference laboratory for the International Standardization of Apolipoproteins AI, B, and Lp(a) and monitors the stability of the World Health Organization International Reference Materials for Apo AI, B and Lp(a).

For more than 25 years, the laboratory has participated in studies to identify the prevalence of hyperlipidemia in the population and to evaluate the efficacy of intervention. Reported in 1983, results of the Coronary Primary Prevention Study demonstrated that lowering cholesterol was effective in reducing the risk of premature heart disease; this information was key in the development of treatment recommendations issued by the National Cholesterol Education Program. To maintain a high level of accuracy and consistency in results, we continue to perform the Beta Quantification procedure as outlined in the Manual of Laboratory Operations for the Lipid Research Clinics Program without introducing any technical change to the laborious and time-consuming technique. The NWRL continues to provide analyses for the lipoprotein and apolipoprotein research performed at the University of Washington, and has been involved in numerous and varied multi-center investigations throughout the United States and internationally. We currently serve as the Central Laboratory for the following NIH-sponsored studies:

ACCORD – Action to Control Cardiovascular Risk in Diabetes
CARDIA - Coronary Artery Risk Development in Young Adults
DPPOS – Diabetes Prevention Program Outcomes Study
Look AHEAD – Action for Health in Diabetes
SEARCH – Search for Diabetes in Youth
STOPP-T2D – Studies to Treat or Prevent Pediatric Type 2 Diabetes
TrialNet - Anti-CD, Exenatide, MMF-DZZB, MMTT-GST, Natural History, NIP and Thymoglobulin Protocols

Vision Statement

To be a model organization, thriving in a dynamic environment and respected as a leader in quality laboratory services with a strong commitment to continuous quality improvement.

Mission Statement

The mission of the Northwest Lipid Metabolism and Diabetes Research Laboratories is to continuously provide the highest standards of professional and technical expertise and organizational support. Our commitment is to not only provide the utmost in quality analytical, interpretative, advisory and consultation services, but is to offer comprehensive support as a central biochemistry laboratory for research and clinical trial studies. Our pledge is to take the steps necessary, whatever they may be, to ensure the greatest success of the studies in which we are involved.

Introduction to the CCL Laboratory Manual

This manual provides basic overviews in the areas of which you have already had training, such as Universal Precautions and Phlebotomy Procedures, but these are provided only as reminders and should be treated as such. If you feel you need additional training in these areas, we have provided some resources for you. The sections covering specimen collection, processing and shipping that are directly related to the ACCORD trial, however, are provided in detailed form. This detail is provided for a reason: submission of proper specimens under optimum conditions is very important. *Accurate analyses can seldom be performed on poor specimens.* Once you have familiarized yourself with this manual and have repeatedly performed these procedures, it will not be necessary for you to refer to the manual each time you collect and process blood. However, we ask that when in doubt, please do refer to the manual or contact the CCL for problem resolution.

WE ARE HAPPY TO ASSIST!

Should question arise, we are happy to answer them or to assist you at any time. Please feel free to contact any one of the following people. We are committed to you and to the study, and we will do what it takes to ensure our combined success!

LABORATORY DIRECTOR

Research Professor of Medicine
Director
Principal Investigator, CBL
Phone:
Cell:

Operations Personnel:

SITE LIAISON

Phone:

SUPPLY COORDINATION and SHIPPING

Phone:

DATA MANAGEMENT

Phone:
Cell:

SUPPLIES PROVIDED BY THE CCL

Specimen collection materials are provided in "visit packs" for all per protocol scheduled visits, with one pack per participant per visit. However, for those visits where only one collection tube is required, multiple tubes will be provided in each visit pack for use with 10 participants. Bulk supplies may be ordered to have on-hand for those visits not specifically pre-determined in the protocol (PRN visits). Specimen tube and shipment form labels are provided in sheets covering multiple visits for a single participant per sheet, and can therefore be placed in the chart for safekeeping. Labels for the Baseline visit are provided in the visit packs. Supplies provided by the CCL are as follows:

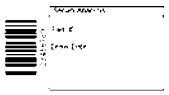
For Blood Collection:

- Vacutainers:
  - 9.5 mL tiger-top SST (with inert gel separator)
  - 2.0 mL purple-top (EDTA anticoagulant)
  - 10 mL purple-top (EDTA anticoagulant)
  - 8.5 mL yellow-top (ACD solution)

For Urine Collection:

- Antiseptic towelettes
- Sterile urine collection cups
- Disposable plastic transfer pipettes
- Screw-cap sample vials: 10 mL polypropylene

For Specimen Identification:



- Bar-coded labels for specimen tubes and shipment forms

For Specimen Shipping:

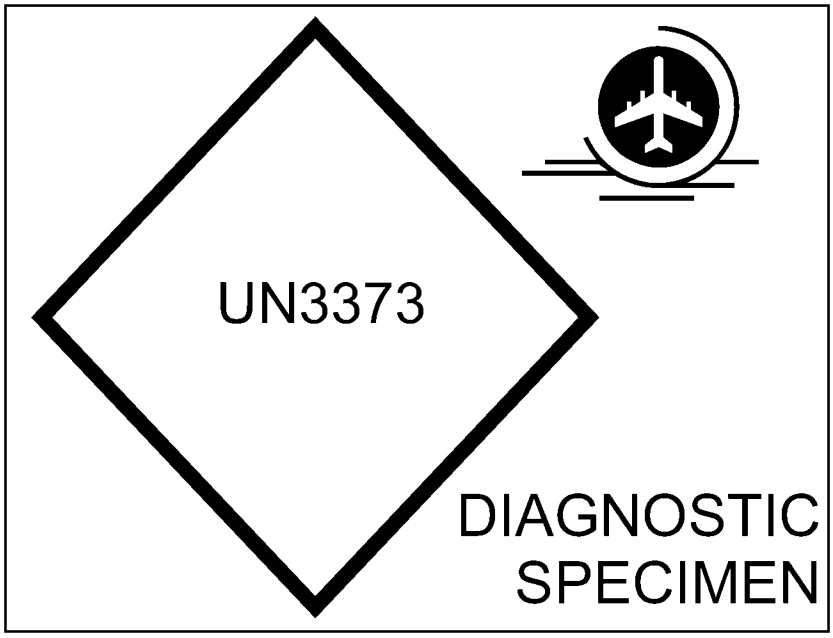
- Biohazard bags
- Ziploc bags
- Cold packs
- Polyfoam tube holders with absorbent pad and outer sleeve
- Polyfoam shipping containers with cardboard outer box
- FedEx air waybills
- "EXEMPT HUMAN SPECIMEN" labels for shipping boxes

Supplies provided by the NWRL (continued)

Exempt Human Specimen label to affix on the shipping box when no known pathogens exist:

EXEMPT
HUMAN
SPECIMEN

Sticker UN3373 to affix on the shipping box ONLY when you are sending specimens with KNOWN Pathogens:



Use the *Supply Request Form* to order extra supplies, allowing two weeks lead time for receipt. Visit packs and labels (which are pre-printed with participant ID after Baseline) will be shipped automatically following the established visit scheme. Baseline visit packs will be replenished via returned shipping container each time one is used. We will start each clinic with 10 Baseline kits that will continue to be replenished until we are informed otherwise. However, if the need for additional kits is anticipated feel free to order more.

To order supplies, use the ***Supply Request Form*** (attachment B).
Follow the instructions on the form and, once completed, Fax to:
If you have questions, please call:

EQUIPMENT, SUPPLIES & FACILITIES PROVIDED BY CLINICAL SITES

These are suggested supplies only; clinics may use equivalent substitutions, if desired.

For Blood Collection:

- ✓ Alcohol wipes
- ✓ Ammonia spirits ampules
- ✓ Band-Aids
- ✓ Cold compresses
- ✓ Disposable gloves (powder-free, to avoid possible cross-contamination from powder)
- ✓ Needle (Vacutainer) holders
- ✓ Paper and/or other dermatological tape
- ✓ Sterile and non-sterile gauze pads
- ✓ Sterile, 21 gauge, 1" needles (multiple-sampling)
- ✓ Sterile, 21 gauge butterfly needles (multiple-sampling)
- ✓ Tourniquets

For Blood Processing/Shipping/Storage:

- ✓ Ice bucket
- ✓ Tube racks
- ✓ Plastic-backed table covers
- ✓ Waterproof pens (such as laundry markers, fine-point, for scribing on labels)
- ✓ Centrifuge: refrigerated (preferably), swinging-bucket type
- ✓ Refrigerator
- ✓ Freezer: -20°C, non-cycling, or -70°C freezer
- ✓ Dry Ice
- ✓ Wide (2") packing tape for sealing shipping containers

For Specimen Handling:

- ✓ Lab coat
- ✓ Goggles or face shield
- ✓ Paper towels
- ✓ Bleach decontaminant -1 part Clorox to 9 parts water, stored in a labeled bottle
- ✓ Biohazard waste containers with orange or red-plastic liners
- ✓ Sharps/biohazard containers - rigid red or orange plastic containers for sharps waste

The ***Phlebotomy Area*** should include a chair for the subject, a table for blood collection supplies, a bed, exam table, or treatment chair that flattens out, and phone/ intercom/physical access to emergency equipment. If possible, a sitting area should be provided so that the subject can sit quietly in a chair for 5 minutes prior to any lipid blood draw, as recommended by NCEP guidelines. Additionally, a conveniently located lavatory is required for urine specimen collection.

UNIVERSAL PRECAUTIONS

Universal Precautions were mandated into standards December 6, 1991, by the Occupational Safety and Health Administration (OSHA) in response to increasing public concern over possible transmission of the Acquired Immune Deficiency Syndrome (AIDS) virus and Hepatitis B virus. This standard states that any health care worker who might potentially come into contact with body fluids should be educated in infection control and treat all body fluids as though they are potentially infectious.

It is assumed that you have already had training in universal precautions. The following is a summary of the basic knowledge required by health care workers and is not intended to be a complete picture of universal precautions, but only the basics. For a more complete overview of universal precautions, you can visit the following web sites:

- http://www.osha.gov
- http://www.niehs.nih.gov

According to OSHA, the following is the recommended protective barrier - gloves, gown, mask and goggles, or face-shield, and they should be used when handling any body fluids.

A. Gloves

1. Wear gloves for all patient contact when body fluids are involved.
2. Change gloves between patients and when gloves are soiled or torn.
3. Wash hands thoroughly after removing gloves.
4. Remove gloves before touching telephones, charts, computers, monitors, doorknobs, refrigerator handles, food, pens/pencils, and elevator buttons. The only exception to this is telephones designated as contaminated.
5. Carry spare non-sterile vinyl exam gloves in uniform/lab coat pocket for use with unexpected contact with blood and body fluids.

B. Gowns

Wear water-repellent gowns, plastic disposable aprons, etc. when soiling with blood or body fluids is anticipated.

C. Face-Shields

Protect mucous membranes (eyes, nose, mouth) by wearing a mask and/or glasses/goggles, or use a counter-top splashguard, etc. when performing procedures where splashing of the face is likely to occur (uncapping, decanting, etc.).

COLLECTION PROCEDURES

Blood Collection

As with universal precautions, it is assumed that you have already had training in blood collection and completed a phlebotomy course. This section is designed as a brief review of the basics. For a more complete overview of blood collection procedures, you can visit a number of web sites. These sites are suggested only, and their usefulness must be determined individually. To choose from a list of sites, proceed to the following URL:

- http://phlebotomy.com/Links.htm

It is understood that universal precautions will be employed during any specimen collection. The following is a suggested method of performing blood specimen collection by venipuncture.

1. Make positive patient identification.
2. Gather necessary equipment.
3. Wash your hands.
4. Don non-sterile exam gloves.
5. Explain planned procedure to patient.
6. Position patient's arm in comfortable position.
7. Select appropriate collection site.
8. Place the tourniquet above the selected collection site. Do not leave tourniquet on for longer than one minute.
9. Clean site with alcohol using circular motion from center outward; allow to air dry (using a gauze pad may recontaminate the area).
10. Grasp arm 1-2 inches below the site to decrease vein rolling.
11. Enter the vein with the vacutainer needle bevel up at a 15 degree angle.
12. Fill necessary blood tubes.
13. Place sharps in puncture resistant sharps container.
14. Apply gauze and tape holding pressure for 2 to 3 minutes to minimize the formation of a hematoma.
15. Remove gloves and wash hands.

Urine Collection

Urine collection procedures should be posted in the lavatory and explained to the participant. The CCL provides these instructions in laminated form for this purpose.

Confirm that participants understand the following procedure:

Female: Holding the labial folds apart with one hand, wipe once with the first wipe from front to back down the left fold and discard wipe; wipe once with the second wipe from front to back down the right fold and discard wipe; wipe once down the center from front to back and discard wipe. Void a small amount of urine into the toilet. Void urine into the sample collection cup without allowing the cup to contact anything but the flow of urine. Cap quickly.

Male: Wipe the tip of the penis and discard wipe. Void a small amount of urine into the toilet. Void urine into sample collection cup without allowing the cup to contact anything but the flow of urine. Cap quickly.

Femmes: En tenant les grandes lèvres écartées d'une main, essuyer une fois le long de la lèvre gauche, d'avant en arrière, avec la première lingette, puis jeter la lingette; essuyer une fois le long de la lèvre droite, d'avant en arrière, avec la seconde lingette, puis jeter la lingette; essuyer une fois entre les deux, d'avant en arrière, puis jeter la lingette. Déverser une petite quantité d'urine dans les toilettes. Déverser de l'urine dans le récipient destiné à recevoir l'échantillon d'urine en veillant à ce que rien mis à part le flot d'urine n'entre en contact avec le recipient. Refermer rapidement.

Hommes: Essuyer le bout du pénis et jeter la lingette. Déverser une petite quantité d'urine dans les toilettes. Déverser de l'urine dans le récipient destiné à recevoir l'échantillon d'urine en veillant à ce que rien mis à part le flot d'urine n'entre en contact avec le récipient. Refermer rapidement.

Hembra: Sujetando el pliegue labial, apártelo con una mano, límpiese una vez con el primer paño desde la parte delantera hacia la parte trasera y hacia la izquierda del pliegue y deseche el paño, límpiese una vez con el segundo paño desde la parte de delante hacia la parte trasera y hacia la derecha del pliegue y deseche el paño, límpiese una vez hacia el centro desde la parte delantera y hacia la parte trasera y deseche el paño. Vacíe una cantidad pequeña de orina en el inodoro. Vacíe la orina en el vaso de recolección de muestras sin dejar el vaso en contacto con ningún objeto excepto el fluido de la orina. Tápelo rápidamente.

Macho: Límpiese la punta del pene y deseche el paño. Vacíe una cantidad pequeña de orina en el inodoro. Vacíe la orina en el vaso de recolección de muestras sin dejar el vaso en contacto con ningún objeto excepto el fluido de la orina. Tápelo rápidamente.

SPECIMEN COLLECTION

Blood specimens collected will be shipped fresh to the CCL on cold pack refrigerant in their collection Vacutainers, or in transfer tubes, via **Federal Express Overnight Courier Services**, within 24 hours of blood draw. When plasma for storage needs to be collected at the appropriate visits, use the following procedure:

- Collect blood in a 10 mL purple-top vacutainer. Use a **non-barcoded** label marked Plasma Storage for these tubes.
- Refrigerate until ready to centrifuge (no longer than 30 minutes in an ice bucket or refrigerator).
- Centrifuge with the other specimens.
- Using a plastic transfer pipette, aspirate the plasma from the vacutainer, paying careful attention not to disturb the red cell barrier.
- Transfer the plasma to a 10 mL plastic transfer tube. Use a **barcoded** label marked Plasma Storage for these tubes.

Urine specimens are shipped in transfer tubes along with the blood. Keep all specimens in a refrigerated state prior to shipment.

Briefly, the sequence is:

1. Verify that the participant has reported as fasting for at least **8 hours**.
2. Label specimen vacutainers and urine collection cups.
3. Collect specimens.
4. Centrifuge SST and 10 mL purple-top vacutainers
5. Transfer plasma and urine in appropriately labeled 10 mL plastic tubes.
6. Refrigerate specimens if not shipped immediately.
7. Complete shipment form and ship specimens to the CCL.

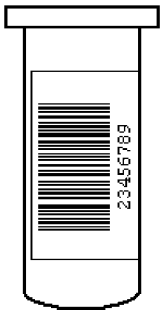
How should collection tubes be labeled?

The CCL provides labels. Participant ID and draw date information will need to be scribed on the labels, where indicated, for Baseline visits (do this before removing labels from their page, and use an indelible pen). These labels are provided in the Baseline visit pack. For all subsequent visits, participant ID information will be pre-printed on labels, which are shipped to clinics in the month prior to their anticipated need. Month 1 visit labels are shipped as soon as possible after Baseline.

Affix the appropriate label (as denoted by the label title) to each of the vacutainers and urine collection cups according to the visit tables on the following pages. *'PRN' (as needed) analysis tubes should have a 'Spare' label affixed with the requested analysis hand-written on both the label and the specimen shipment form for unscheduled analysis (when needed).*

Important: these labels utilize barcode technology and are linked to one another as visit sets. DO NOT mix visit/label sets. If, for some reason, a label becomes unusable, such as by an accidental breakage of a tube, use a provided 'Spare' label (which does not contain a barcode) and hand-write the analysis on the label. The CCL will manually enter that sample.

Label orientation is important for proper scanning of the end barcode. Please affix labels to tubes and vials as shown here, with the barcode form running <u>vertically</u>.



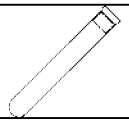
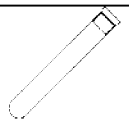
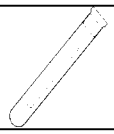
Hold the tube upright in your hand, with the stopper towards the ceiling. Place the label around the tube so that the analysis title is read vertically.

Which specimens need to be collected?

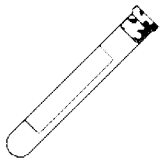
Schedule of Assessments

Follow the study protocol to determine which assessments must be made at each of the visits and use the tables below as reference guides for specimen collection. The specimen tube labels are encoded with the proper analyses to be performed for each of the study arms. ***Find the current visit on the tables below and make certain the labels for the correct visit are used.*** This will result in the proper analyses being performed.

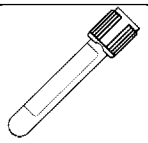
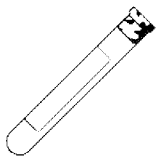
VISITS: Baseline, M24

Analyses	Label to Affix	Fasting Condition	Blood Collection Tube	Visual Reference	Processing
HbA1c	**HbA1c**	Non-fasting acceptable	2.0 mL Purple-top		• Refrigerate. • **Do Not** Centrifuge.
Glucose Chemistries Lipids	**Glu/Chem/DBQ**	Fasting	9.5 mL Tiger-top SST		• 20 - 30 Minutes at Room Temperature. • Centrifuge. • Refrigerate or ship.
Serum Storage	**Serum Storage**	Fasting	9.5 mL Tiger-top SST		• 20 - 30 Minutes at Room Temperature. • Centrifuge. • Refrigerate or ship.
Plasma Storage	**Plasma Storage** (placed on vacutainer) **Plasma Storage** (barcode on transfer tube)	Fasting	10.0 mL Purple-top		• Refrigerate. • Centrifuge. • Transfer to plastic tube • Refrigerate or ship
Urine Albumin, Creatinine, Storage	**Urine Cup** (placed on collection cup) **Urinalysis** (barcode on transfer tube) **Storage**	Non-fasting acceptable	Collection Cup & 10 mL poly-transfer tube (min vol. 5 mL urine)	 	• Refrigerate or ship immediately.
Collected at Baseline only—or subsequently, if missed prior (to be drawn only for participants who consent to genetic studies):					
White Cell Collection	**White Cells**	Non-fasting acceptable	8.5 mL Yellow-top		• Refrigerate. • **Do Not** Centrifuge.

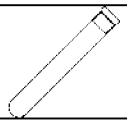
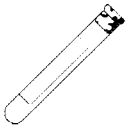
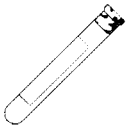
VISITS: M1 (Lipid Trial participants only)

Analyses	Label to Affix	Fasting Condition	Blood Collection Tube	Visual Reference	Processing
Chemistries (ALT/CPK)	**Chem**	Non-fasting acceptable	9.5 mL Tiger-top SST		• 20 - 30 Minutes at Room Temperature. • Centrifuge. • Refrigerate or ship.

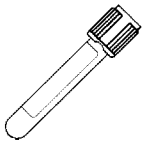
VISITS: M4, M8, M36, M60, M84, M96

Analyses	Label to Affix	Fasting Condition	Blood Collection Tube	Visual Reference	Processing
HbA1c	**HbA1c**	Non-fasting acceptable	2.0 mL Purple-top		• Refrigerate. • **Do Not** Centrifuge.
Glucose Chemistries Lipids	**Glu/Chem** (non-lipid: months 4 & 8) **or Glu/Chem/DBQ**	Fasting	9.5 mL Tiger-top SST		• 20 - 30 Minutes at Room Temperature. • Centrifuge. • Refrigerate or ship.

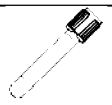
VISITS: M12

Analyses	Label to Affix	Fasting Condition	Blood Collection Tube	Visual Reference	Processing
HbA1c	**HbA1c**	Non-fasting acceptable	2.0 mL Purple-top		• Refrigerate. • **Do Not** Centrifuge.
Glucose Chemistries Lipids	**Glu/Chem/DBQ**	Fasting	9.5 mL Tiger-top SST		• 20 - 30 Minutes at Room Temperature. • Centrifuge. • Refrigerate or ship.
Serum Storage	**Serum Storage**	Fasting	9.5 mL Tiger-top SST		• 20 - 30 Minutes at Room Temperature. • Centrifuge. • Refrigerate or ship.

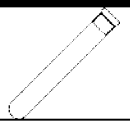
VISITS: M16, M20, M28, M32, M40, M44, M52, M56, M64, M68, M76, M80, M88, M92

Analyses	Label to Affix	Fasting Condition	Blood Collection Tube	Visual Reference	Processing
HbA1c	**HbA1c**	Non-fasting acceptable	2.0 mL Purple-top		• Refrigerate. • **Do Not** Centrifuge.
Creatinine (Lipid Trial Participants Only)	**Chem**	Non-fasting acceptable	9.5 mL Tiger-top SST		• 20 - 30 Minutes at Room Temperature. • Centrifuge. • Refrigerate or Ship.

VISITS: M72

Analyses	Label to Affix	Fasting Condition	Blood Collection Tube	Visual Reference	Processing
HbA1c	**HbA1c**	Non-fasting acceptable	2.0 mL Purple-top		• Refrigerate. • **Do Not** Centrifuge.
Glucose Chemistries Lipids	**Glu/Chem** (non-lipid: months 4 & 8) **or Glu/Chem/DBQ**	Fasting	9.5 mL Tiger-top SST		• 20 - 30 Minutes at Room Temperature. • Centrifuge. • Refrigerate or ship.
Urine Alb, Creat	**Urine Cup** (placed on collection cup) **Urinalysis** (barcode on transfer tube)	Non-fasting acceptable	Collection Cup & 10 mL transfer tube		• Refrigerate or ship immediately.

VISITS: M48, Exit

Analyses	Label to Affix	Fasting Condition	Blood Collection Tube	Visual Reference	Processing
HbA1c	**HbA1c**	Non-fasting acceptable	2.0 mL Purple-top		• Refrigerate. • **Do Not** Centrifuge.
Glucose Chemistries Lipids	**Glu/Chem/DBQ**	Fasting	9.5 mL Tiger-top SST		• 20 - 30 Minutes at Room Temperature. • Centrifuge. • Refrigerate or ship.
Urine Albumin, Creatinine	**Urine Cup** (placed on collection cup) **Urinalysis** (barcode on transfer tube)	Non-fasting acceptable	Collection Cup & 10 mL poly-transfer tube (min vol. 5 mL urine)		• Refrigerate or ship immediately.
Serum Storage	**Serum Storage**	Fasting	9.5 mL Tiger-top SST		• 20 - 30 Minutes at Room Temperature. • Centrifuge. • Refrigerate or ship.

ACCORD Central Laboratory Procedures Grid

	BLR	*M01*	*M04*	*M08*	*M12*	*M16*	*M20*	*M24*	*Q4*	*Q12*	*M48*	*M72*	*PRN*	*EXIT*
HbA1c (Central Lab)	A		A	A	A	A	A	A	A		A			A
FPG	A		A	A	A			A		A	A			A
Potassium	A		A	A	A			B		B	B		A	A
ALT	A	L	A	A	A			A		A	A		A	A
Creatinine	A		A	A	A	L	L	A	L	A	A		A	A
Lipid Profile	A		L	L	A			A		A	A		L	A
CPK	A	L	L	L	L			L		L	L		L	A
Urinalysis	A							A			A	A	A	A
Serum Storage[1]	A				A			A			A			A
EDTA Plasma Storage[1]	A							A						
White Cell Storage[1,2]	A													
Urine Storage[1]	A							A						

A - All participants (regardless of sub-trial)
L – Lipid Trial participants only
B - Blood Pressure Trial participants only
[1]No blood and/or urine storage performed at VA clinical sites
[1,2]White cell storage only performed for participants who grant consent

How should I collect and process specimens?

Collect Specimens

As stated earlier, we presume that all personnel performing this work have been trained in proper blood collection procedures, so listed below are just some important reminders.

As a general rule, tubes with anticoagulant should be drawn first. Additionally, the following rules should be adhered to when collecting specimens.

As you draw blood, remember to:

- Mix each plasma blood tube **8-10 times immediately** after collection by inverting the tube gently and evenly. This assures adequate mixing with the anticoagulant.

- The same needs to be performed with the tiger-top tubes to assure adequate mixing of silica particles with the blood, which is required to activate clot formation. Gently invert these tubes **5 times**.

- **Avoid under-filling** the collection tubes. Purple-top collection tubes containing EDTA must be filled to at least 30% of the fill volume of the tube. If the tube is not filled to at least 30% of fill volume, there will be a dilutional effect from the anticoagulant and the specimen will be unsatisfactory for testing.

Once blood has been collected and mixed:

- Transfer purple-top (for *HbA1c* analysis) and yellow-top (for *white cell* collection) tubes to a refrigerator set at 4°C. **Do not centrifuge these tubes**.

- To allow clot formation prior to their transfer to the centrifuge, tiger-top SST tubes must stand upright at **room temperature for at least 20 minutes, but no longer than 30 minutes**. Prolonged standing can have a compromising effect on analyte levels.

- Place the 10 mL purple-top vacutainers for plasma storage (when collected) in an ice bucket or in the refrigerator for 30 minutes prior to their transfer to the centrifuge.

Urine Specimen:

- Instruct the study participant in the proper procedure for urine collection, and provide him/her with the necessary collection materials. *PLEASE NOTE:* Due to the possibility of blood contamination during collection, participants who are menstruating or bleeding should not be asked to provide a urine sample.

- Transfer the filled urine collection cup to the refrigerator until later processing.

Process Blood

Centrifuge SST Vacutainers and 10 mL Purple-top Vacutainers, Refrigerate Others

- **Do NOT** centrifuge vacutainers for *HbA1c and White Cells:* refrigerate the whole blood at 4°C until shipment is made.

SST Tiger-tops: After a strict ***20 to 30 minutes*** from collection and standing at room temperature, transfer the vacutainers to the centrifuge, loading it according to the manufacturer's instructions.

10 mL Purple-tops: After collection, store on ice or in refrigerator for 30 minutes, transfer to the centrifuge.

Centrifuge at 1200 RCF(g) [~3000 RPM] for 10 minutes *
(if swinging bucket type)

Or for 15 minutes (if fixed angle type).

** This data pertains to general bench-top centrifuges, use of a larger centrifuge may require different RPM settings to produce 1200-1300 RCF.*

Refrigerated Centrifuge

If using a refrigerated centrifuge, set the temperature to 4°C. Following centrifugation, transfer the tubes to a refrigerator set at 4°C or prepare the tubes for shipment.

Non-refrigerated Centrifuge

If using a non-refrigerated centrifuge, it is *imperative* that blood tubes not be allowed to sit unattended after rotation has ceased. Because the process generates heat, tubes must be either immediately transferred to a refrigerator once spinning has stopped, or immediately prepared for shipment. It is recommended that a timer pinned to the labcoat be used to alert you when tubes will need to be removed from the centrifuge.

Leaving tubes in a non-refrigerated centrifuge or at room temperature will compromise the accuracy of the analyses.

Important Information

To insure that the gel barrier in the SST Tiger-tops is effective in separating serum from the red cells, please perform the following:

1. Check the centrifuge speed
2. Make sure that the samples in the centrifuge are well-balanced
3. Make sure that the samples are not centrifuged for too extended or too short a time period
4. Carefully, inspect all tubes after they are removed from the centrifuge.

The serum of well collected and well centrifuged blood samples should appear clear with no red cell layer between the gel and the specimen.

Invert the tubes gently several times, if the gel barrier is good, and the red cells are not contaminating the serum after the tubes are inverted, there will be no problem with the shipment. If the gel barrier appears to be compromised, transfer the serum or plasma to a transfer tube, centrifuge again, transfer to another tube, and ship to the laboratory.

Process Urine

1. Obtain the 10 mL screw-cap vial you have labeled ***Urinalysis*** and use a clean transfer pipette to transfer at least 5 mL urine from the collection cup into the vial labeled **Urinalysis** or **Urinalysis/Storage** when applicable. Screw the cap on tightly and refrigerate at 4°C until shipment to the CCL.

2. Any remaining urine in the collection cup should be discarded in the toilet and the collection cup and lid discarded into a biohazard waste container.

How do I prepare specimens for shipment?

Specimens collected for ACCORD will be shipped fresh to the CCL on cold pack refrigerant, via **Federal Express Overnight Courier**, within 24 hours of blood draw. Keep all specimens in a refrigerated state prior to shipment. If shipment cannot be made within 24 hours, ship as soon as possible or call the CCL for instructions.

Follow the instructions below for specimen shipment preparation. Department of Transportation (DOT CFR 49) guidelines stipulate that the minimum requirements listed under item #6 below be observed for all airfreight packages containing **diagnostic specimens.**

1. Obtain the participant's labels sheet used during specimen collection.

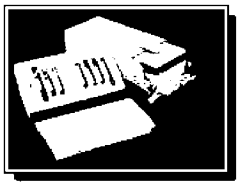
2. Obtain the *Specimen Shipment Form* (provided by the CoC).

3. Label the shipment form with the CCL bar-coded *Shipment Form* label. Neatly write in participant ID and visit information on the form or affix a study-provided ID label.

4. Obtain a polyfoam tube holder (with absorbent pad) and place it open on the work surface.

5. Obtain the specimen tubes from the refrigerator and place them on the work surface, preferably in a tube rack. Check the tube labels, inspect for hemolysis or red cells, and verify the draw date and ID information. Complete the shipment form, checking-off the spaces corresponding to the specimens.

6. Place the specimen tubes on their side in the open polyfoam tube holder (in the slots). Place the absorbent pad on top of the tubes(s), properly align the top-half and slide the holder into the cardboard sleeve. Insert into a Ziploc biohazard bag and seal. You may ship multiple vacutainers in a single holder.



Canadian Sites

Canadian sites must ship to the US following International Shipping Guidelines (IATA Packaging Instruction **602**). These guidelines stipulate that shipments of **diagnostic specimens** must be made in specially rated containers, with multiple layers of protection, and full declaration of contents and packaging codes. The CCL will provide these shipping materials to Canadian sites, but they must check with their own organizations for proper usage.

SHIPPING INSTRUCTIONS

New domestic shipping guidelines were implemented January 1, 2005. These regulations implemented by the International Air Transport Association are for the packaging and shipping of diagnostic specimens. IATA regulations stipulate that it is the responsibility of each facility or organization to properly train personnel who will package and ship diagnostic specimens, and to certify personnel who will be shipping infectious substances. Therefore, you must check with your institution concerning their policies and requirements and become trained/certified in the procedures for shipping these materials. The major effect of these new guidelines is changes required in the label affixed to the shipping box and the air waybills, both of which are provided to you by the CCL.

The CCL will provide you with shipping materials that meet these new regulations as interpreted by our institution. However, if your institution deems it necessary to use alternate supplies, you will be responsible for purchasing them independently.

As *attachment D* of this manual, we have included current shipping reference information for your use. These general directions cover shipping diagnostic specimens, dangerous goods and infectious substances. Please use these secondary to your own institutional guidelines and training.

Shipment Forms

The shipment form (provided by the CoC) is used to indicate the number and types of tubes included in the shipment, the identity of the samples, and pertinent clinic and visit information. The forms are organized so that one form must be filled out per subject per shipment. When a shipment is made, a photocopy of the form should be produced and retained at the clinic. The original is placed in a Ziploc bag and included with the specimens.

Shipping Containers and Coolant

Polyfoam shipping containers with cardboard outer shells are provided. Tube holders containing blood vacutainers and urine transfer tubes should be shipped on cold packs that have been frozen solidly at **-20°C, never at -70°C**, as this may cause freezing of the blood during transport. Also, *only use cold packs provided for this study as they are rated specifically for this use*.

Shipping Schedule

Shipments must be sent via *Federal Express* ***Priority Overnight*** *Service*, preferably **Monday through Thursday** of the week only. When blood is drawn on a Friday, however, specimens must be sent for Saturday delivery. If this is necessary, follow these procedures:

1. Only ship one participant sample set per shipping container.
2. Place as many frozen cold packs into the container as is possible.
3. Make sure to select **'Saturday Delivery'** on the airbill.
4. Make sure to alert the CCL of the shipment(s) and its tracking #.

Shipping to the CCL

Use the provided FedEx pre-printed shipping air waybills, or address your own to:

ACCORD-CCL
Northwest Lipid Metabolism and Diabetes Research Laboratories
401 Queen Anne Avenue North
Seattle, WA 98109-4517

FAX the CCL with the FedEx tracking number(s):

Any day a shipment is made, FAX the CCL, using a copy of the *Shipment Notification Fax* form (attachment A), to alert of a shipment's pending arrival. This will allow CCL personnel to investigate and track packages if there are delays or problems with the courier. Make multiple copies of this form for your use since one will be used each day a shipment is made.

REMEMBER: *When shipping on a Friday, it is imperative that you mark the air waybill for '****Saturday Delivery****' or FedEx will not deliver, and will hold the package until Monday.*

Holiday Schedule

The CCL is officially closed on all US federal holidays and, more importantly, **FedEx will NOT deliver on these days.** Therefore, avoid shipping on any day *preceding* a US federal holiday (see calendar below).

When a holiday falls on a Monday or Tuesday, the last day to ship samples is the Thursday of the preceding week. The samples are expected to be delivered on Friday, but if there is a FedEx delay we will have personnel in the laboratory to receive the samples on Saturday. **PLEASE NOTE:** The Christmas holiday falls on a Monday in 2005 and 2006. The week before Christmas is an especially busy week for FedEx, and delays are expected. Therefore, we strongly recommend that the last day to ship samples is the Tuesday preceding Christmas, i.e. Tuesday, December 20, 2005 or Tuesday, December 19, 2006.

When a holiday falls on a Friday, the last day to ship samples is the Wednesday of that week. The samples are expected to be delivered on Thursday, but this allows for receipt on Saturday if there are FedEx delays.

Due to the length of the **Thanksgiving holiday**, the last day to ship samples is the Monday of Thanksgiving week. The samples are expected to be delivered on Tuesday, but if there is a FedEx delay we will have personnel in the laboratory to receive the samples on Wednesday. **Remember, FedEx will NOT delivery on Thanksgiving.**

Federal Holiday	2007	2008
New Year's Day	Monday, January 1	Tuesday, January 1
MLK Jr's Birthday	Monday, January 15	Monday, January 21
President's Day	Monday, February 19	Monday, February 18
Memorial Day	Monday, May 28	Monday, May 26
Independence Day	Wednesday, July 4	Friday, July 4
Labor Day	Monday, September 3	Monday, September 1
Veterans Day	Monday, November 12	Tuesday, November 11
Thanksgiving	Thursday, November 22 Friday, November 23	Thursday, November 27 Friday, November 28
Christmas Day	Tuesday, December 25	Thursday, December 25

Federal Holiday	2009	2010
New Year's Day	Thursday, January 1	Friday, January 1
MLK Jr's Birthday	Monday, January 19	Monday, January 18
President's Day	Monday, February 16	Monday, February 15
Memorial Day	Monday, May 25	Monday, May 31
Independence Day	Friday, July 3	Monday, July 5
Labor Day	Monday, September 7	Monday, September 6
Veterans Day	Wednesday, Nov. 11	Thursday, Nov. 11
Thanksgiving	Thursday, November 27 Friday, November 28	Thursday, November 25 Friday, November 26
Christmas Day	Friday, December 25	Friday December 24

ATTACHMENTS - FORMS

A: Fax Notification
B: Supply Request
C: Sample Destruction Request
D: Shipping Guidelines (for reference only)

Action to Control Cardiovascular Risk in Diabetes

ACCORD

FAX

Northwest Lipid Metabolism & Diabetes Research Laboratories –
University of Washington

TO: **Specimen Processing**

FROM: _____

Phone: _____

FAX: _____

PLEASE BE ADVISED OF THE FOLLOWING SHIPMENT ARRIVAL:

Clinical Site: _____ Number of boxes shipped: _____

Date specimens shipped: _____

Fed Ex Tracking Numbers: _____

_____

_____

_____

Remarks:

SUPPLY REQUEST FORM

ALL REQUESTS FOR SUPPLIES SHOULD BE MADE AT LEAST *TWO WEEKS* PRIOR TO THEIR ANTICIPATED NEED

Action to Control Cardiovascular Risk in Diabetes
ACCORD

Clinic:_____ Order Completed by:_____ Phone:_____

Date Ordered: _____/_____/_____ (MM DD YY) Date Needed: _____/_____/_____ (MM DD YY)

Date Request Received by Lab: ___/___/___ (MM DD YY) Date Supplies Shipped from Lab: ___/___/___ (MM DD YY)

Questions? Please call:

SUPPLY	**QUANTITY DESIRED**	QUANTITY SHIPPED	QUANTITY PENDING
9.5mL Tiger-top SST			
2.0mL Purple-top			
10.0mL Purple-top			
8.5mL Yellow-top			
Visit Packs			
Baseline			
Other (specify):			
Urine Collection Cup			
Antiseptic Towlette			
Disposable Pipette			
10mL Transfer tube			
Polyfoam Tube Holder with cardboard sleeve			
Biohazard Bag			
Cold Pack			
Polyfoam Shipping Container			
Participant Tube Labels Pat. ID = _____			
Ziploc Bags			
FedEx Air Waybill			
Other (specify):			

-Fill in the amount of each item desired on the table to the left.

-Fax the completed form to the lab:

-Your order will be processed and shipped to you with a copy of this form enclosed.

-Upon receipt, verify that the contents exactly match the supplies specified on this form.

-If there are no discrepancies, sign the form and fax back to the lab.

If there are problems, please call:

Comments:_____
_____

I have reviewed the contents of my shipment and confirm that all supplies listed have been received.

Signed: _____ Date: _____

Request for Sample Destruction

At any time, participants who have given written consent for the collection and storage of white cells, serum, plasma and/or urine may decide to withdraw their consent. Participants have the right to request that their stored specimens be retrieved and destroyed. Participants are entitled to written confirmation that their stored specimens have been destroyed.

The Request for Sample Destruction is used to communicate the participant's request for their specimens to be destroyed. The clinical site is responsible for conveying this request to the Central Chemistry Laboratory (CCL) where the specimens are being stored.

The Request for Sample Destruction form is divided into three sections. Section 1 is the request for stored specimen destruction and is completed by the clinical site. Sections 2 and 3 are completed at the CCL verifying that stored specimens have been retrieved and destroyed.

Upon receipt of a Request for Sample Destruction form from the clinical site, the CCL will destroy all stored specimens specified by the request. Destruction of stored specimens will be done in accordance with standard procedures for decontamination and removal of human specimens.

Section1 must be completed by the clinical site identifying the study participant and type of stored specimens to be destroyed. It is required that this section be signed by the Principal Investigator or Study Coordinator. After completion, the Request for Sample Destruction form is transmitted via FAX or sent by regular mail to the CCL.

Section 2 and 3 are completed at the CCL. After receipt of the signed Request for Sample Destruction, the Database Administrator will identify the sample ids for the stored specimens involved. The sample id's along with the Request for Sample Destruction form will be forwarded to Specimen Management. Specimen Management will pull and deliver the identified samples to the Autoclave Technician. Specimen Management will sign their part of Section 2 after samples are retrieved from storage and delivered to autoclaving. Section 2 is also signed by the Autoclave Technician, who personally autoclaves and disposes of the samples, attesting that samples provided to him have been properly destroyed. Notation regarding storage status of the samples is then updated by the appropriate staff person at the CCL.

Section 3 is signed by the Laboratory Director as final confirmation that removal and destruction of the samples has been properly performed and documented.

The completed Request for Sample Destruction is then faxed to the clinical site to confirm that the destruction of stored specimens has been completed. The Request for Sample Destruction is then filed at the CCL as confirmation that the destruction has been completed.

Request for Sample Destruction

Action to Control Cardiovascular Risk in Diabetes

CCL - Northwest Lipid Metabolism & Diabetes Research Laboratories
University of Washington
401 Queen Anne Avenue North
Seattle, WA 98109-4517

Section 1

Clinical Site: _____ Participant ID: _____

I formally request that the vial(s) obtained from the above study participant containing the stored specimens checked below be disposed of and not retained for use in any research activities.

❑ White Cells ❑ Reserve Urine **(check which is applicable)**
❑ Reserve Serum ❑ All Reserves
❑ Reserve Plasma

Signature: _____ Date: _____
Principal Investigator or Study Coordinator

Section 2

I attest that the samples requested for disposal have been identified, retrieved, and provided to the autoclave technician for destruction, and status of these samples updated in the database.

Signature: _____ Date: _____
Specimen Management

I attest that the samples delivered to me by Specimen Management have been destroyed in accordance with standard procedures for decontamination and destruction of human specimens.

Signature: _____ Date: _____
Autoclave Technician

Section 3

As requested by the Clinical Site on behalf of the study participant listed above, I confirm that all samples requested for disposal have been completely and properly destroyed.

Signature: _____ Date: _____

Laboratory Director and PI

Section 1: To be filled out by the Clinical Site, then fax or mail to the CCL.

Section 2 & 3: to be completed by the CCL, then faxed or mailed back to the Clinical Site.

Guidelines FOR SHIPPING PATIENT SPECIMENS

GENERAL INFORMATION

Summary of Patient Specimen Exemptions: Under IATA DGR 2007, Section 3.6.2.2.3.6 permits certain types of patient specimens to be shipped with reduced documentation, labeling, and packaging if the specimens meet the standards for the exemption. Specimens that meet the following definitions and other criteria are qualified for the exemption; specimens that fail to meet the definition and other criteria must continue to be meet the 2007 rules:

1. Specimen must meet the following definition:

Specimens are those collected directly from humans or animals, including, but not limited to, excreta, secreta, blood and its components …being transported for purposes such as research, diagnosis, investigational activities, disease treatment, and prevention.

2. Minimal likelihood that the specimen contains a pathogen:

A patient …specimen is considered exempt if there is a minimal likelihood that pathogens are present. In determining whether a patient …specimen has a minimal likelihood that pathogens are present, an element of professional judgment is required to determine if a substance is exempt. This judgment should be based on the known medical history, symptoms, and individual circumstances of the source …and endemic local conditions.

Examples of specimens which MAY be transported under the exemption include the blood or urine tests to monitor cholesterol levels, glucose levels, or hormone levels, …tests required to monitor organ function such as heart, liver, or kidney function for humans…and antibody detection in humans…

Patient …specimens, for which there is minimal likelihood that pathogens are present may utilize the exemption, provided the specimen is in a packaging which will prevent any leakage. The packaging must meet the following conditions:

1. The packaging must consist of three components:

(a) a leak-proof primary receptacle (s);
(b) a leak-proof secondary packaging, and
(c) an outer packaging of adequate strength for its capacity, mass and intended use, and with at least one surface having minimum dimensions of 100 mm x 100 mm.

2. For liquids, absorbent material in sufficient quantity to absorb the entire contents must be placed between the primary receptacle(s) and the secondary packaging so that during transport, any release or leak of a liquid substance will

not reach the outer packaging and will not compromise the integrity of the cushioning material.

3. When multiple fragile primary receptacles are placed in a single secondary packaging, they must be individually wrapped or separated to prevent contact between them.

DOCUMENTATION

1. If dry ice is used as a refrigerant, mark "Dry ice, 9, UN1845, III on the air bill (check the dry ice checkbox on the FedEx air bill).

2. Check the "no" checkbox on the FedEx air bill in response to the question: "Does this shipment contain Dangerous Goods"

PACKAGING and LABELING

1. Place the “Exempt Human Specimen” label on the outside of the shipping box if the specimen contains no known pathogen.

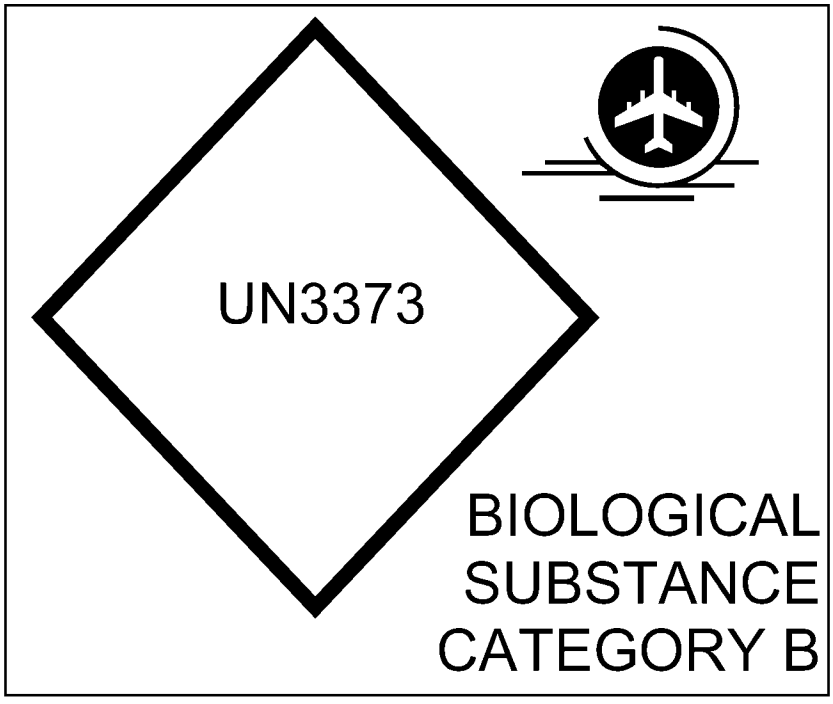
2. DO NOT use the "Biological Substance, Category B UN3373” label on the outer container unless you ARE aware the specimen contains a pathogen.

3. If dry ice is used as a refrigerant place the standard Dry Ice label on the outside of the shipping box and complete the required information on it.

Be certain to review these policies with your institution to assure compliance with your local policies or determinations. The information provided here is our recommendation for clinical sites to expedite shipments in the most efficient manner while maintaining compliance with IATA regulations.

Affix "Exempt Human Specimen" label on all shipments that have NO KNOWN PATHOGENS.

Affix this label to the outside box ONLY when you are AWARE you are sending specimens that contain **known** pathogens.



.

SHIPPING DRY ICE REFRIGERATING A NON-DANGEROUS COMMODITY[1]

Step 1 Understand that Dry ice is a listed Dangerous Good. "Dry Ice" appears in bold print and is therefore a Proper Shipping Name. ("Carbon dioxide, solid" may also be used.)

UN/ ID No.	Proper Shipping Name/Description	Class or Div.	Sub Risk	Hazard Label(s)	PG	Passenger and Cargo Aircraft				Cargo Aircraft Only		S.P. see 4.4	ERG Code
						Ltd Qty							
						Pkg Inst	Max Qty per Pkg	Pkg Inst	Max Qty per Pkg	Pkg Inst	Max Qty per Pkg		
A	B	C		E	F	G	H	I	J	K	L	M	N
1845	Dry Ice†	9		Miscel-laneous	III	—	—	904	200 kg	904	200 kg	A48	9L

Step 2 As a listed dangerous good packaging must conform to Packing Instruction #904. The Special Provision in Column M ("A48") states that packaging tests are not considered necessary. (No UN packaging is required.)

Step 3 The General Packing Requirements (See Below) must be followed, but we may use any good, strong non-spec outer packaging designed to allow the outflow of dry ice vapors. The Shipper's Declaration is not required for Dry ice and non-dangerous goods. Dry ice may be included in an overpack, provided the overpack meets the requirements of Packing Instruction 904.

IATA **Dangerous Goods Regulations**

PACKING INSTRUCTION 904

STATE VARIATIONS: USG-13

OPERATOR VARIATIONS: HP-02, IC-08, VN-11

This instruction applies to UN 1845 on passenger and cargo aircraft and CAO.

The General Packing Requirements of 5.0.2 must be met.

Carbon dioxide, solid (dry ice), when offered for transport by air, must be in packaging designed and constructed to permi the release of carbon dioxide gas and to prevent a build-up of pressure that could rupture the packaging.

Arrangements between shipper and operator(s) must be made for each shipment, to ensure ventilation safety procedures are followed.

The Shipper's Declaration requirements of Subsections 8.1 and 10.8.1 are only applicable when the Carbon dioxide, solic (dry ice) is used as a refrigerant for dangerous goods that require a Shipper's Declaration.

When a Shipper's Declaration is not required, the following information, as required by 8.2.3 for the Carbon dioxide, solic (dry ice), must be contained in the "Nature and Quantity of Goods" box on the air waybill:

- proper shipping name (**Dry Ice** or **Carbon dioxide, solid**);
- UN 1845;
- the number of packages; and
- the net quantity of dry ice in each package.

The net weight of the Carbon dioxide, solid (dry ice) must be marked on the outside of the package.

Note 1: Refer to the relevant airline's loading procedures for Carbon dioxide, solid (dry ice) limitations.

Note 2: For Air Waybill requirements see 8.2.3. For loading instructions see 9.3.12.

Note 3: For cooling purposes, an overpack may contain Carbon dioxide, solid (dry ice), provided that the overpack meets the requirements of Packing Instruction 904.

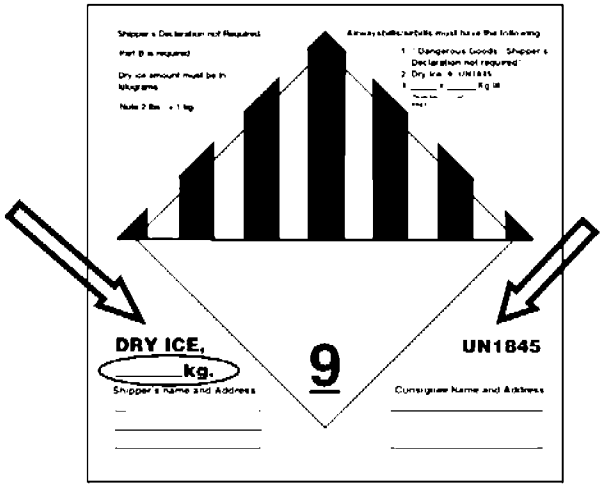
5

904

[1] This information is intended to promote safe shipping and handling by the University of Washington and those entities that conduct business with the University of Washington. It is not intended to meet any training requirements or to constitute a determination of compliance with the law. Any non-University of Washington entity must make an independent determination of compliance with the law.

Step 4 Mark and label the package. While you don't need a UN specification package or a DDG, the package must be marked and labeled. Mark the outside of the outer package with the gross weight of dry ice inside.

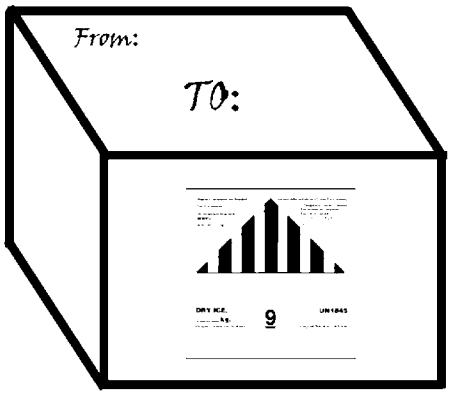
If you have one of these labels that has the proper shipping name and ID number pre-printed on it (See the arrows) then all you need to do is fill in the weight in Kg of the dry ice inside and list it in the encircled area.



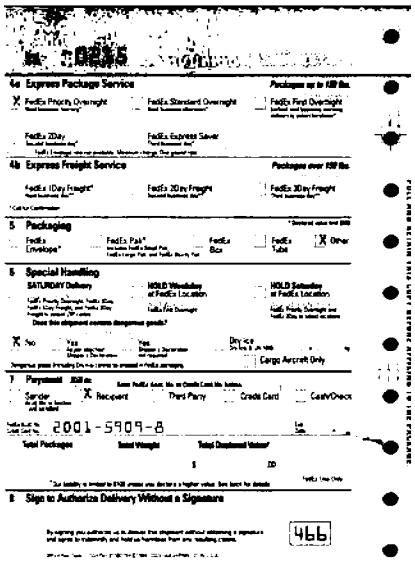
If you use a regular class 9 label you will need to mark the box with the proper shipping name, UN number and the weight of dry ice in kilograms.

"Dry Ice"
"UN1845"
"___ Kg"

The Finished box should look like this:



In the "Special Handling" area of the waybill, you need to check the "Dry Ice" box and list the number of packages and net quantity of dry ice per package.



CHAPTER 16

CENTRAL ECG READING CENTER (CERC) FOR THE ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES (ACCORD) TRIAL (For the Continuation)

Prepared by

November 2002

TABLE OF CONTENTS

Chapter 16.
Central ECG Reading Center for ACCORD

A. CERC Contact Personnel

The ACCORD Central ECG Reading Center (CERC) is located at Wake Forest University School of Medicine, Department of Public Health Sciences, EPICARE Section. The CERC personnel are listed on the previous page (List of CERC Personnel). The main contact numbers for ACCORD clinic personnel to contact CERC are:

Name	Telephone	Fax
Principal Investigator		
Senior Computer ECG Technician		
ECG Technician		
Data Coordinator		

and should be contacted for all matters pertaining to recording and transmission of ECGs and for ECG technician certification and recertification.

B. Background and Purpose

The ECG recordings in ACCORD will serve to establish the distribution of cardiac disease findings at baseline and the development of new disease, including silent myocardial infarction, left ventricular hypertrophy, ischemia, prolonged QT interval, and arrhythmias as well as the development of subclinical ECG findings that are determined to be associated with a poor prognosis and that will serve as descriptions of baseline equivalency of disease between treatment groups. The ECG is the only non-invasive cardiovascular function measure to be employed in ACCORD and will be used to detect new (incident) cardiac disease.

C. ECG Recording Schedule

C.1. Digital ECGs

1. ACCORD clinics will deal with three different ECG formats: a) Digitally recorded ECGs; b) Locally read baseline and follow-up scheduled ECGs and "alerts," and c) Hospital ECGs.

2. At each examination digital ECGs will be recorded electronically with a GE/Medical Systems Information Technology (GEMS/IT) MAC 1200 electrocardiograph. The software of each clinic site's electrocardiograph has been configured specifically for ACCORD for correct transmission of signals by modem and phone line to the CERC.

3. The CERC will process all baseline ECGs and ECGs recorded at four scheduled follow-up examinations in ACCORD.

4. At each visit the clinic ECG technicians will record the scheduled ECGs with the participant **fasting**. That is, the ECG must be recorded after an overnight fast (and checking this history in the clinic) **and before any snack** is given.

5. The clinic ECGs stored in the MAC1200s will be transmitted to the CERC as necessary.

6. ECGs will be processed (see below) and monthly transmissions of the reports made to the ACCORD CC.

C.2. **Locally Read ECGs**

C.2.1 "Alert" ECGs

The computer statements on the clinic ECGs are often overstated, that is, incorrect. Also, many minor, non-clinically significant ECG findings are found in a general population sample and most of these do not need immediate attention (of course, all ECG findings along with other clinic results will be passed along to participants and their physicians at a later date). However, certain ECG findings printed on the clinic ECGs need to be reviewed by the clinic physician **before the participant leaves the clinic.**

While the participant is in the clinic, the ECG technician prints out a paper copy of the ECG and computer interpretation. If the computer reading only has normal ECG, sinus arrhythmia, sinus bradycardia (rate >40), sinus tachycardia (<105), axis deviation, PACs, rare PVCs, incomplete BBB, first degree AV block, or perhaps a few other items (to be determined over time by the clinic physician), the technician can tell the participant that the ECG "appeared good, but it will be reviewed by a physician later." (Some examples of the above appear as Figures 1a-f.)

If the ECG says, "nonspecific ST-T abnormalities," "bundle branch block," "junctional rhythm," "low voltage QRS," or perhaps a few other items, the technician can say, "the ECG does not show any MAJOR abnormality, but it will be reviewed by a physician later."

However, clinic study physicians need to report on and technicians need to look out for "alert" ECGs at baseline or follow-up when the printout of a clinic recorded ECG on the MAC1200 electrocardiograph indicates one of the following conditions (examples are included as Figures 2a-i):

a) Atrial fibrillation
b) Atrial flutter
c) Ventricular tachycardia
d) Acute myocardial infarction
e) Ventricular preexcitation or Wolff-Parkinson-White (WPW) ECG pattern
f) Complete atrioventricular block
g) Left bundle branch block
h) Cardiac pacemaker
i) Any statement which includes a reference to **acute** injury or ischemia or pericarditis

In the case of any of these alert statements, take the tracing to the clinic physician who will decide if any further action is needed. It is not advisable to alarm the participant by revealing these unconfirmed interpretative statements. However, it is helpful to casually inquire if the person has recently had chest pain or discomfort. A negative answer does not mean that the alert can be ignored because heart attacks can be asymptomatic (silent). These "asymptomatic alerts" are most of the time not in the same category of possible urgency as alerts associated with recent chest pain or discomfort or fainting attacks.

C.3 **Hospital ECGs**

All participant hospital admissions for suspected cardiovascular disease will be abstracted by clinic personnel and **all hospital-recorded ECGs for each admission should be mailed directly to the ACCORD Coordinating Center (CC).** The ECGs accompanv the "ACCORD Myocardial Infarction Records Requested," and are sent to the attention of

A copy of all ECGs recorded for each hospital event should be sent to the ACCORD CC.

D. **ECG Acquisition Procedures**

D.1 **Electrocardiograph**

The electrocardiograph to be used for ECG recording and transmission for ACCORD is the GEMS/IT MAC 1200 portable electrocardiograph. Each clinic's machine was formatted with the ACCORD SETUP at the initial training session.

- It is intended that the MAC1200 be used for resting ECG recording and realtime ECG recording with or without arrhythmia detection.
- It is not intended for use as a vital signs physiological monitor.
- The MAC1200 offers no diagnostic opinion to the user. Instead, it provides analytical statements when configured with the appropriate options.
- It is intended to be used by trained operators under direct physician supervision when ECG records are required.
- It is designed for continuous operation.
- The MAC1200 is designed as a portable device and can easily be moved from one location to another. It must be transported and handled with extreme care.
- Equipped with the standard software, the MAC1200 supports the following operating modes:
    - 12 Lead Mode (acquisition of 12 leads of ECG for a period of 10 seconds)
    - 6 Lead Mode (real time recording of 6 ECG leads)

The MAC1200 has a liquid crystal display (LCD) which shows 3 leads at a time. The MAC1200s used in ACCORD have a customized menu specific to the ACCORD study. A complete guide and operations manual for the MAC1200 was provided with each machine. All ECG technicians for ACCORD must become familiar with this manual, and are urged to read the manual periodically. The manual outlines all steps for operation, loading chart paper, cleaning and disinfecting the recorder, and maintenance of the equipment. Troubleshooting and technical specifications are also described in detail.

The MAC1200 has five (5) components in SETUP. Access to all of these components is achieved by pressing the SETUP button.

1. 12-LEAD SETUP
2. SYSTEM SETUP
3. COMMUNICATION SETUP
4. PATIENT DATA SETUP
5. OPTION CODE SETUP (Do NOT change this component)

D.2 **Supplies**

1. GEMS/IT MAC1200 Electrocardiograph, 10 lead Acquisition Module, External Modem, telephone jack cable [all part numbers for supplies are provided in the MAC1200 Operations Manual
2. MAC1200 ECG paper, GE/Marquette disposable silver silver chloride electrodes

3. Isopropyl alcohol gauze pads and swabs
4. Scissors
5. Cotton surgical tape
6. Felt tip non-toxic washable markers
7. 1 HEARTSQUARE [Figure 3]
8. 4 strips of narrow velcro [helpful in stabilizing the limb lead wires during recording]
9. Examining table disposable paper
10. 2 manuals kept within easy reach: EPICARE ECG Acquisition Procedures Manual and GEMS/IT MAC1200 Operations Manual
11. Baby oil: used only after ECG recording if the participant's skin appears irritated or red

How to Order Supplies:

-Call GEMSIT at (800) 558-5102
-To Fax orders, fax # is (800) 232-2599
-Online web catelog: www.gemedicalsystems.com
-Have Part No. ready:

Paper for MAC1200:	Part No. E9004 FL @ $129/case; 16 pkg. paper/case (150 sheets/pkg)
Electrodes:	Part No. E9001 AC @ $37/case (1000 electrodes/case or 100 participants/case)

E. Recording ECGs

Standard 12-Lead ECGs are acquired from all study participants. ECGs are recorded after 12 hours of overnight fasting and ***before*** any snack or juice is given to the participant at the clinic.

ECGs are recorded in a supine or semi-recumbent position. ECGs will be recorded at:

- •baseline
- •scheduled follow-up visits (every two years)
- •close-out visit

All scheduled ECGs will be transmitted electronically to the ACCORD CERC at EPICARE.

E.1 Preparation of Participant for ECG Recording

-The Participant's safety and comfort are of utmost importance.
-Clean sheets /examination paper must be used at all times.
-The lead placement areas must be marked with non-toxic washable markers.
-The bed must be wide enough to avoid falls. A bed which is too narrow may also lead to poor quality recordings. The left arm must be properly supported. If the bed is too narrow, a portable ironing board can be attached to the left side of the bed so that the left arm may rest on it in order to provide less tension in the muscles.
- Introduce yourself. Ask the participant to relax and provide a brief explanation of the ACCORD study.
- Always ensure that all correct participant information is entered into your MAC1200 electrocardiograph before recording the ECG.

E.2 **Participant Data Entry into the MAC1200:**

***Category** [What shows on MAC1200 Screen]*	***Entry** [What you Enter]*
NEW PATIENT	YES
LAST NAME*	1st three digits of Last Name plus 1st two digits of First Name plus Middle Initial (as outlined by ACCORD MOP)*
FIRST NAME*	Enter Visit Code: **BLR** (Baseline); **F24** (2-yr follow-up; **F48** (4-yr follow-up); **Exit** (Exit visit)
DATE OF BIRTH	MM/DD/YYYY
PARTICIPANT ID	Assigned Clinic/Cart # plus Assigned Country/State # plus Assigned Suffix plus ID # (example: 112A12345 = Canada, Clinic No. 12, A group, 12345 ID No.)
SECONDARY ID	Same as Participant ID
PACEMAKER	NO [YES IF PACEMAKER]
GENDER	M OR F
HEIGHT **(Do NOT Enter Height)**	E Measurement of HeartSquare (e.g., if E=16.0, enter 160)
WEIGHT **(Do NOT Enter Weight)**	V6 Measurement of HeartSquare (e.g., if V6=12.0, enter 120)
RACE	Use Other and enter defined race codes
REFERRING PHYSICIAN	This should already be set up with Name/Cart and Station ID (e.g., Northeast 5-03)
TECHNICIAN	Use other and enter defined Tech. ID #
LOCATION	Cart ID as described in SETUP, Section D.2

*Do not enter participant's full name.

E.3 Electrode Lead Placement

-Stand on the left side of the participant at the level of the chest electrodes.
-Participant should be in a supine/semi recumbent position with chest bared. With female participants, cover the areas of the chest not used for ECG recording.
-Always follow the same procedure to ensure efficiency and quality of ECG.
-Attach a green ribbon on the Right Leg Electrode lead wire.
-Mark areas for electrode placement with non–toxic washable markers.
-Prepare the skin by rubbing areas marked (a gauze pad will abraid the skin best after using an alcohol wipe). (See Figure 4: Skin Preparation)
-Apply electrodes on the limbs as shown in Figure 5. Ensure that the Right Leg, Left Leg electrodes show the silver silver chloride end face upwards towards the torso. The arm electrodes may face either way depending on the height of the participant. The lead wires must show no tension or looping.

E.4 Chest Lead Electrode Placement and HEARTSQUARE Instructions

-V1 and V2:

First locate the sternal angle about the width of your 3 middle fingers below the sternal notch (See Figures 6 and 7).

Feel the sternal angle between the index and middle fingers of your right hand, keeping the fingers wide apart and moving your fingers firmly up and down. Feeling the sternal angle, move your fingers to the left side of the sternum and feel between your fingers the 2nd rib where it joins the sternal angle.

Move your middle finger to the interspace below the second rib and with your index finger locate the interspace below the next rib (3rd) and again below the next (4th) rib. This is the 4th intercostal space. Mark an **X** at this level at the midsternal line. **X** is your reference level for V1 and V2. Mark their locations at the right and left sternal border (see Figure 7).

E.5 Reference Point E for Locating V4, V5 and V6

From the location of **V2**, palpate with the middle finger of your right hand the 4th intercostal space and follow it laterally outside the sternal border and at a slight angle down.

Feel the 5th rib between your index and middle fingers and feel the 5th intercostal space with your index finger. At the level of the 5th intercostal space, mark an **+** at midsternal line below your mark for V1-V2 level. This **X** is your reference level **E** for V4, V5 and V6 (see Figure 7).

Trouble locating the 5th intercostal space? Here is the remedy:

In overweight persons and in women with tender breast tissue, it is often difficult to locate the 5th intercostal space. Do the following:

Mark the cross for **E** 1 ¼ in (3 cm) below your reference level **X** for V1 and V2. (In smaller adults, 1 in. (2.5 cm) is enough) (see Figure 7).

E.6 **Left Midaxillary Line**

The left elbow must be supported properly. Move the left elbow laterally without moving it anteriorly or posteriorly, while observing the anterior and posterior axillary folds. Follow a line exactly in the vertical midplane of the thorax down where the line meets the horizontal plane of Point **E**. Using your marker, make a vertical one inch long line there as an approximate location of **V6**.

Exact Location of **V6**
-Using your HEARTSQUARE (Figure 3), you will find the exact location of **V6**.
-Place the HEARTSQUARE with the wider arm (E arm) horizontally at level E. Try to keep the ruler as close to horizontal as possible.
-With the narrower arm vertically, slide it until the arrow points to the mark at the midaxillary line. Mark this as the exact location of **V6**.

Exact Location of **V4**
-Keeping the HEARTSQUARE in the horizontal position with the arrow pointing to **V6,** observe the reading at **E** (16.0 in the example in Figure 3). Take this same **E** reading on the vertical (V6) scale and follow with your marking pen the diagonal towards the chest and mark the location of **V4**. Fix the sliding arm with your thumb, remove the HEARTSQUARE and note the reading **E** and **V6** (to the nearest 0.5 units). (Note that **V6** reading is the distance from the arrow to the intersection of the horizontal arm.
-Enter the **E** and **V6** measurements as three digits (last digit 0 or 5) in the height and weight field of the MAC1200, as well as in your ECG Log (Figure 8).
(Note: If the HEARTSQUARE is too small for participant, enter 000 as the E and V6 measurements.)
Locations of **V3** and **V5**
-Mark **V3** exactly halfway between **V2** and **V4**.
-Mark **V5** exactly halfway between **V4** and **V6**.

E.7 **Recording the ECG**

For baseline or scheduled ECG:
-Enter all relevant information as shown in E.2-Participant Data Entry to the MAC1200 (above).
-Ask the participant to relax, breathe normally and remain still.
-Re-check all participant data entries.
-Record the ECG following the guidelines in the GEMS/IT MAC1200 Operations Manual.
-Inspect the record immediately for quality. Repeat the recording if you see any quality problems.

E.8 **Examples of Technical Problems with ECG Recordings (Figures 9a,b,c,d,e,f,g)**

- **Excessive Baseline Drift [Figure 9a]**: This occurs if the participant is moving around or there is tension on the lead wires. Ask participant to lie still for a few seconds. Drift in excess of 1 mm between baseline points (QRS onset) of any two successive complexes is a sign of excessive drift.
- **Excessive Muscle Noise; Electrodes Falling Off [9b]**: Participant is tense or may be cold. Use a blanket to cover the participant. Check the Acquisition Module to ensure that the wires are not pulling. Be sure to establish a good electrode connection. Lay a towel across the wires, if necessary. Adjusting the angle of the clip at the electrode often helps. You may need to tape down the chest leads; use only hypoallergenic medical tape to prevent allergic reactions. Use a U loop with the electrode wires, i.e., the wire should not cross but remain open like a U; never loop the wires.

- **Motion Artefacts [9c]**: This indicates loose electrodes. This may cause sudden jumps in some ECG leads. Check each electrode to ensure that it is secure. Periodic 60 HZ noise is sometimes visible in the record. This may be caused by poor electrode contact, faulty grounding, or AC interference from a nearby machine. Make a visual check of this before recording the ECG. *Note:* Jewelry does not cause 60 HZ noise.
- **RA/RL Lead Reversal [9d]:** This ECG shows Lead II is flat. Check each ECG before disconnecting the Participant. Check the Limb Lead connections.
- **RA/LA Lead Reversal [9e]:** {P,Q,R,S,T are portrayed upside down}
- **Suspect V1/V3 or V2/V3 Lead Reversal (9f):** The positive QRS deflection in **V3** is smaller than in **V1** or **V2**.
- **Correct Sequence from V1 – V6 [9g]:** Figure 9g shows an ECG with the correct connections to each electrode location.

F. Transmitting ECGs from ACCORD Clinics to the CERC

-The telephone number programmed into the MAC1200 should be: 3367161248

-If you need prefixes, enter them in the "Outside Line" field, e.g., Access Code 9,1 - separate fields with commas, i.e., 123456,,,9,1 (where Access Code is 123456; then 9 = outside line; 1 = long distance); or contact GEMS/IT for assistance with this step. This is done only once in the Communication Setup.

-Fax lines work well for transmission of ECGs.

-Visually check all participant information on the LCD to ensure correct entry.

-Delete all ECGs which are duplicates. Correct all ECGs with incorrect information before transmitting ECGs to the CERC.

-Delete transmitted ECGs ONLY after you have received email or verbal confirmation of receipt of ECGs from the CERC.

****

For those sites that have had their 1200s replaced with the 5.2 version, please refer to page 12 at the end of the text portion of this chapter.

If you have problems, please refer first to your MAC1200 Operations Manual for more detailed instructions for transmitting before contacting the CERC at EPICARE OR the GEMS/IT Technical Support Line for ACCORD at 1-800-558-7044, ext. 4618.

G.1 Certification Procedures from CERC

Each technician must record three (3) good quality grade ECGs with the following specifications:

Last Name: Technician's Last Name
First Name: Technician's First Name
ID: 999999999
Enter information in the remaining fields as if an actual participant.
Tracings need to be approximately 20 minutes apart.

A certificate will be issued with the name as entered in the name field on the Certification ECGs.

All ECG technicians must go through the certification process before they are allowed to record study ECGs.

G.2 Certification Requirements to be Completed by ACCORD Clinics

See Figure 10.

G.3 Recertification Procedures

Recertification will be required every two years and will follow exactly the certification requirements outlined in Section G.1.

SUMMARY OF ECG ACQUISITION AND TRANSMISSION

-Call the CERC with questions regarding ECG recording procedures. Leave a detailed message with your name, study name and telephone number.
-Keep a record of the ECGs transmitted to the CERC in your ECG Log (optional) (Fig. 8).
-Always observe the Liquid Crystal Display to check for technical quality/lead reversals.
-Observe ECG on the LCD until a good quality, clean signal appears before recording the ECG.
-Delete all ECGs which are duplicates or poor quality prior to transmission.
-Check ECG participant data on the LCD to ensure that correct information is entered. Change/correct all incorrect information.
-Identify Test and Certification ECGs with an ID of : 999999999.
-Transmit ECGs to the CERC.
-After recording ECG, clean any residual electrode paste from electrode area on participant.
-Use caution in helping the participant off the bed or table.
-Delete recorded and stored ECGs ONLY when email or verbal confirmation is received from the CERC.
-REMEMBER: The MAC1200 stores up to 35 ECGs; however, it is recommended that ECGs be transmitted prior to reaching this maximum storage capacity.
-Check supplies often and always allow sufficient time for replenishing when needed (see again ordering information on page 5).

TRANSMITTAL OF ECGS TO THE CERC AT EPICARE AT WAKE FOREST UNIVERSITY

These steps for transmitting ECG should be followed by those ACCORD sites that have had their 1200s replaced with the 5.2 version.

1. Secure the modem cable into the 9-pin connector found on the right side of the MAC1200 and the 25-pin connector found on the rear of the modem.

2. Plug one end of the phone cable into the connector marked "line" on the rear of the modem and the other into any "analog" (fax) phone line.

3. Turn the modem On.

4. Start at the 12 lead screen.

5. While holding the **Shift key** down, press the **Store/Retrieve key**.

6. Press the down arrow until desired ECG is underlined, then hold the **shift key** and the **up arrow** together to select the desired ECG to be transmitted. The screen will show black squares on the right and left side of the ECG selected for transmission. To skip an ECG press the **down arrow**. Repeat this procedure until all ECGs that are to be transmitted have been selected.

7. Once selection is made, press the **Enter key**. This will return you to the top of the screen.

8. Then use the **right arrow** to highlight *Send* and press the **Enter key**.

9. Another screen will appear that states, "TO start transmission press "Enter".

10. Once transmission is complete press the **start/stop key**, on the far bottom right of the keyboard, to return to the 12 lead screen.

11. For immediate confirmation, call the CERC at EPICARE during office hours. Please leave a detailed message with your telephone number, name and clinic name if voice mail answers and your call will be returned. Otherwise, email confirmation will be sent the morning following the day of transmission.

17. Central Drug Distribution Procedure

17.1 Responsibilities for Drug Accountability

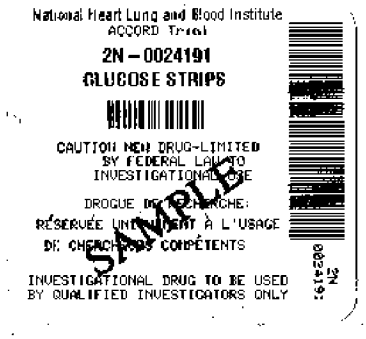
The principal investigator (PI) at each participating clinical site is responsible for a complete and accurate accounting of all ACCORD study materials received and dispensed by the facility. The Drug Distribution Center (DDC) in Albuquerque, New Mexico, will provide forms, instructions, and assistance as necessary to assure proper use and accountability of all study drugs and supplies. The DDC will monitor the performance of each participating center in this regard. In addition, each center must observe local policies, applicable state, and federal regulations concerning custody, dispensing, and disposition of drugs and supplies.

17.2 Description of ACCORD Study Drugs, Devices, and Expendable Supplies

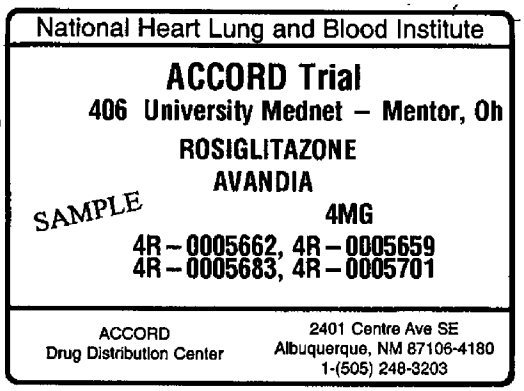
Open Label Supplies

Supplies (drugs, and ancillary supplies) used in ACCORD, with the exception of fenofibrate and placebo, are provided as open-label items. All are supplied in packaging, which can be dispensed directly to the patient without transfer to another container ("unit of issue" packaging). **Open label** medications will contain the manufacturer's label (drug, strength, quantity, expiration date, and lot number). In addition, a 2-part label affixed by the DDC contains study name, unique identification number, bar codes, and applicable federal warnings. Bottles are shipped in packages containing four (4) bottles; the box is labeled as ACCORD Study Drug with generic name, plus trade name if applicable. **Appendix A** is a list of currently supplied open label drugs and supplies for the ACCORD trial.

Sample bottle label for open label (unblinded) supplies and drug



Sample for outside package label of unblinded supplies and drug



The label for **blinded** medication (fibrate/placebo) contains the study name, the drug name is listed as "fenofibrate/placebo," the patient-specific identification bottle number with a unique bar code, and the telephone number of the Drug Distribution Center. Bottles are dispensed consecutively, according to the last two digits of the bottle number. Bottles are packaged in counts of 134.

Bottle labels for blinded drug (fenofibrate/placebo)

17.3 Custody and Storage Requirements

The ACCORD study supplies, except insulin, should be stored between 15° and 30°C (59° and 86°F) in a secure area. Insulin must be stored in a cold place between 2° and 8°C (36° and 46°F), and should not be frozen. Insulin can be kept unrefrigerated for 28 days, but should be kept refrigerated until it is dispensed to the patient. Unrefrigerated insulin must be completely used within the 28 day time period or discarded. Drugs and supplies may be stored either in the study clinic or pharmacy depending on local policy. If the study drug is not stored in a pharmacy, it must be kept in a locked room or locked cabinet. Refrigerated items should be stored in a specific area and distinguished from non-ACCORD medications. A temperature log should be kept to monitor storage conditions.

17.4 Shipment of Study Materials

17.4.1 Initial Shipment

After receiving notification from the Wake Forest Data Coordinating Center that all required regulatory documents have been received from the clinical site and the site is eligible to receive medication and supplies, the Drug Distribution Center will send the clinical site an initial shipment of study materials. This shipment is based upon any previous usage and par levels set by the site. New sites must complete all required paperwork prior to the Main Trial. A **Shipping Notice** listing items and quantities of all supplies shipped is included with each shipment. In addition, a **Receiving and Assignment Record** is enclosed for each item. This form is utilized at the time of dispensing to record unique items issued to participants and provide "hard copy" documentation for the clinical site. Use of the "Receiving and Assignment

Record" also provides a temporary alternative record if scanning is not available. When a site uses the electronic record keeping function available on the web, it must be able to readily retrieve all information described by the Receiving and Assignment Record. If a site is experiencing problems maintaining the scanned data then the Receiving and Assignment Record will need to be completed to ensure proper documentation until scanning is performed. Samples of forms are included in See **Appendix B**. For instructions on printing dispensing and destruction records see **Appendix C.**

17.4.2 Subsequent Shipments

Each time an ACCORD supply item is dispensed to a patient the bar code on the label must be scanned and through this mechanism the item is assigned to the patient. The data obtained from scanning/assignment to patients is used to adjust remaining inventory levels at each site. When supplies reach the re-order point, a replacement order will be automatically generated. Thus clinical sites need not routinely order study drugs and supplies from the DDC. Inventory levels and drug/supply needs at each site are and monitored by the DDC. Maintaining adequate inventory is the responsibility of the site. As usage increases, inventory levels may be increased at the request of the site. If an inventory question or problem arises or additional study drug/supply item is needed, contact the DDC at (505) 248-3203 or you may communicate via FAX (505) 248-3205. In addition, contact the DDC if the increased use is planned or expected, such that additional supplies will be required.

17.5 Randomization Procedure – See Chapter 5 in the Manual of Procedures

17.6 Prescriptions for Study Drug

All study drugs and supplies must be ordered on either a standard prescription blank or a physician order form. Each time study drug is dispensed, the investigator or other authorized physician should write a prescription or order with the following:

1. Patient's name and current address
2. Study name [ACCORD Trial]
3. Participant I.D.
4. Bottle Number (if fenofibrate/placebo)
5. Drug Name
6. Strength
7. Quantity to be dispensed
8. Directions for use
9. Signature of investigator or other authorized physician
10. Date prescription or order is written
11. No refills (A new prescription must be written each time a patient requires more medication.)

17.7 Dispensing

Open label (nonblinded) drugs and expendable medical supplies for ACCORD are dispensed in the manufacturer's packaging. A 2-part label is affixed to each item.

The peel-off portion of this label (bar code that runs vertically on right side of label) should be removed and placed in the appropriate section of the ACCORD **"Drug Dispensing Form."** The form is subdivided into sections for glycemic medications, lipid medications, blood pressure medications, and the glucose meter and supplies. **It is extremely important that these**

bar-code labels be scanned as quickly as possible so that the information is entered into the ACCORD study web database. Information from this form is maintained daily by the DDC for inventory tracking. Furthermore, supplies are replenished based upon scanned usage data, which is received through this scanning process. Maintaining up-to-date information in the database is critical for ensuring an adequate drug supply at your clinical site.

See **Appendix B** for an example of the Drug Dispensing Form.

17.8 Labeling

The clinical site is responsible for complying with regulations on prescription labeling for Rx legend drugs. **Do not cover labels applied by the DDC or the manufacturer's lot number and expiration date.** Prescription labels should contain the following information:

1. Rx Date
2. Prescription Number (if dispensed by pharmacy)
3. Patient's Name
4. Drug Name, Strength and Quantity
5. Directions for use
6. Prescriber's Name
7. Name of facility

The DDC provides prescription labels for those sites not utilizing a pharmacy. The individual who dispenses the drug will complete necessary information on the label using a typewriter or with pen and ink (i.e. fill in the blanks) and then affix the label to the bottle, without covering the manufacturer's expiration date and lot number.

17.9 Assignment and Dispensing of Fenofibrate/Placebo

Only participants recruited into the lipid trial will receive blinded study medication (fenofibrate or placebo). Most participants in the lipid trial are also placed on simvastatin 20mg (Zocor) at randomization and will not begin the fenofibrate/placebo until the next monthly visit. All other participants will also begin the fenofibrate/placebo at randomization. See Section 5.4.2 of the MOP for detailed instructions regarding initiation of simvastatin and fenofibrate/placebo medications.

As of November 15, 2003 tablets will be shipped two bottles per box, with each bottle containing 134 tablets. Once the bottle counts are increased, only one bottle will be dispensed per study visit.

Each bottle will have a label that contains the study name, "fenofibrate/placebo," a unique identification number and bar code specific for each patient, and the telephone number of the Drug Distribution Center. See Section 17.2 for a sample label.

Each box will contain a label indicating the identification bottle numbers and consecutive numbers of the two bottles contained therein. The last two digits in the bottle identification numbers will be assigned in an ascending sequence so that boxes may be sorted for storage and individual bottles may be easily retrieved. Once the bottle with the highest ascending number is scanned and dispensed to the patient, the DDC will replenish the site with more fenofibrate/placebo for that specific patient.

Individual bottle numbers of blinded study medication are assigned to a particular participant/visit through the ACCORD web-based data entry system. Each participant will retain the specific bottle number throughout the Main Trial. To prescribe blinded study medication, complete the following steps:

1. Log-in to the ACCORD web page and click on "Clinical" and then "Data Entry".
2. Scan the participant label or enter the participant ID and click on "Begin Data Entry". For a randomized participant, this should take you directly to the main DES page for that participant, which is divided into three sections: Participant Background Information, Visit Log, and Forms List.
3. Under Participant Background Information click on the button labeled "Dispense Fenofibrate/Placebo." This will lead to a screen labeled "Lipid Medication Management", which has two options: 1) Dispense Medication, or 2) Display all previous assignments.
4. Click on 1) Dispense Medication to proceed to the Lipid Medication Dispensing page, where you'll be asked to select the current or most recent visit, specify the number of bottles to be dispensed, and provide a reason if dispensing more than 1 bottle.
5. Click on the "Assign Bottles" button to display the Lipid Medication Dispensing Results, where the identification number of the bottle(s) assigned to that participant is (are) displayed.
6. Record the bottle number(s) on the prescription blank or physician order form, so that the correct bottle(s) can be dispensed to the participant along with their other study medications.
7. When the medication is dispensed to the participant, remove the peel-off portion of the 2-part label and place it in the appropriate section of the ACCORD Drug Dispensing Form as you would with any other study medication.

17.10 Emergency Code Breaks

The treatment code will only be broken (unblinded) if that knowledge, exactly which study drug (fenofibrate or placebo) the patient is taking, is essential to the medical management of the patient. Unblindings are discouraged, however, the patient's safety must always be paramount. In those situations where the investigator feels it is essential to break the code, he/she is instructed to contact the ACCORD Drug Distribution Center (DDC) which provides 24-hours/day, 7-days/week coverage. Be prepared to provide the following information:

1. Study Name
2. Site Name
3. Name of person calling and their telephone number
4. Patient Identification Number
5. Reason that code break is necessary
6. Name of physician requesting code break

Code breaks after normal business hours will involve use of the PCC's emergency answering service, therefore a pharmacist is paged will respond within a short period of time.

17.11 Expired Drugs and Supplies

The site should print a list of drugs that will expire within the next 135 days (<4 months) from the dispensing website each month. This report is site-specific and lists the bottle ID numbers that will expire in the next 4 months. This form can be used for removal of expired drug once the DDC replenishes the inventory. The list will be sorted by drug name and strength. Each bottle number, lot, and expiration date is included in the data. All expired drugs that are removed for destruction can be noted on the form.

Unless otherwise directed by the DCC expired drugs and supplies will be destroyed by the local clinical sites, in accordance with local policies for drug destruction. They will not be returned to the Drug Distribution Center. When destroying expired drug, clinical sites must enter the drug destruction sub-menu on the ACCORD web site and scan the bottle to a generic destruction bar code. Through this mechanism, expired drugs are assigned to a generic destruction bar code. This process updates inventory at all clinical sites. The **"ACCORD Local Destruction Documentation"** form should then be printed through the website for documentation of study drug disposition at the clinical site. Data regarding the destruction of expired drugs are necessary to adjust the remaining inventory and maintain appropriate supplies.

17.12 ACCORD Supplies From Site to Site

Once drugs and supplies are shipped from the DDC to a clinical site, products may not be returned to the DDC. Any excess ACCORD supplies may be transferred to another clinical site as needed. A site that wishes to transfer a drug must complete their portion of the Drug Transfer Form and include that form in the shipping box. Upon arrival of the drug(s), the receiving site will complete their portion of the Drug Transfer Form and fax it immediately to the DDC. The DDC will provide overnight shipping information or labels. See **Appendix B** for a copy of this form. Once the form is received by the DDC, the supplies will be transferred in the electronic database from the original site to the receiving site.

17.13 Loss of Inventory

Any loss of inventory should be documented in writing (memorandum or e-mail) and sent to the Drug Distribution Center. The document will be signed by the Principal Investigator and will include a brief description of circumstances relating to the loss, listing quantities of drug, supplies or devices, and corrective action to prevent future losses of inventory. The Drug Distribution Center address is as follows:

ATTN: ACCORD Trial Project Manager
VA Cooperative Studies Program
Clinical Research Pharmacy Coordinating Center
2401 Centre Avenue, SE
Albuquerque, NM 87106-4180

Appendix A – Drugs, Devices and Supplies

ACCORD Intervention	Drug Class	Available to	Generic	Trade Name (May Change During the Study)	Strength/ Size	Unit	Dosing
			(Note: All tablets/capsules are supplied in packages of 4 bottles)				
GLYCEMIA INTERVENTION DRUGS							
	sufonylurea	all	Glimepiride	Amaryl	2mg	100s	QD
	sufonylurea	all	Glimepiride	Amaryl	4mg	100s	QD
	biguanide	all	Metformin	Glucophage	500mg	100s	QD - TID
	biguanide	all	Metformin	Glucophage	1000mg	100s	QD or BID
	meglitinide	Canada	Repaglinide	Gluconorm	0.5 mg	100s	TID w/meals
	meglitinide	Canada	Repaglinide	Gluconorm	1 mg	100s	TID w/meals
	meglitinide	Canada	Repaglinide	Gluconorm	2 mg	100s	TID w/meals
	meglitinide	U.S.	Repaglinide	Prandin	0.5mg	100s	TID w/meals
	meglitinide	U.S.	Repaglinide	Prandin	1mg	100s	TID w/meals
	meglitinide	U.S.	Repaglinide	Prandin	2mg	100s	TID w/meals
	thiazolidinedione	All	Rosiglitazone	Avandia	2mg	60s	QD or BID
	thiazolidine dione	all	Rosiglitazone	Avandia	4mg	100s	QD or BID
	thiazolidine dione	all	Rosiglitazone	Avandia	8mg	100s	QD or BID
	insulin	Canada	Human Regular	Novolin ge Toronto	5 x 3 ml	pkg	Variable
	insulin	Canada	Human Regular	Novolin ge Toronto	10 ml	vial	Variable
	insulin	Canada	Human Isophane	Novolin ge NPH	5 x 3 ml	pkg	Variable
	insulin	Canada	Human Isophane	Novolin ge NPH	10 ml	vial	Variable
	insulin	Canada	Human 30/70	Novolin ge 30/70	5 x 3 ml	pkg	Variable
	insulin	U.S.	Human Regular	Novolin R	5 x 3 ml	pkg	Variable
	insulin	U.S.	Human Regular	Novolin R	10 ml	vial	Variable
	insulin	U.S.	Human NPH	Novolin N	5 x 3 ml	pkg	Variable
	insulin	U.S.	Human NPH	Novolin N	10 ml	vial	Variable
	insulin	U.S.	Human mixed	Novolin 70/30	5 x 3 ml	pkg	Variable

ACCORD Intervention	Drug Class	Available to	Generic	Trade Name (May Change During the Study)	Strength/ Size	Unit	Dosing
	insulin	all	Insulin Aspart	Novo Rapid	5 x 3 ml	pkg	Variable
	insulin	all	Insulin Glargine	Lantus	10 ml	vial	QD
	glucose	all	Glucose	Dex 4	4 grams	50s	Variable
LIPID INTERVENTION DRUGS							
	fibrate	Lipid patients	Fenofibrate/ Placebo	Tricor/Placebo	160mg	134	QD
	Fibrate	Lipid patients	Fenofibrate/Placebo	Tricor/Placebo	54mg	134	QD
	statin	Lipid patients	Simvastatin	Zocor	20mg	90s	QPM
	Statin	Lipid patients	Simvastatin	Zocor	40mg	90s	QPM
BLOOD PRESSURE INTERVENTION DRUGS							
	Note: Combination drugs are listed after single drugs						
	ACE-inhibitor	all	Benazepril	Lotensin	10mg	100s	QD or BID
	ACE-inhibitor	all	Benazepril	Lotensin	20mg	100s	QD or BID
	ACE-inhibitor	all	Lisinopril	Zestril	10mg	100s	QD
	ACE-inhibitor	all	Lisinopril	Zestril	20mg	100s	QD
	ACE-inhibitor	all	Lisinopril	Zestril	40mg	100s	QD
	ACE inhibitor	all	Ramipril	Altace	2.5mg	100s	QD
	ACE inhibitor	all	Ramipril	Altace	5mg	100s	QD
	ACE inhibitor	all	Ramipril	Altace	10mg	100s	QD
	thiazide diuretic	all	Chlorthalidone	Thalitone	15mg	100s	QD
	thiazide diuretic	all	Chlorthalidone	Thalitone	25mg	100s	QD
	beta blocker	all	Metoprolol	Toprol XL	50mg	100s	QD
	beta blocker	all	Metoprolol	Toprol XL	100mg	100s	QD
	beta blocker	all	Metoprolol	Toprol XL	200mg	100s	QD
	CCB non-DHP	all	Diltiazem	Tiazac	120mg	90s	QD
	CCB non-DHP	all	Diltiazem	Tiazac	180mg	90s	QD
	CCB non-DHP	all	Diltiazem	Tiazac	240mg	90s	QD

ACCORD Intervention	Drug Class	Available to	Generic	Trade Name (May Change During the Study)	Strength/ Size	Unit	Dosing
	CCB non-DHP	all	Diltiazem	Tiazac	300mg	90s	QD
	alpha blocker	all	Terazosin	Hytrin	1mg	100s	QD or BID
	alpha blocker	all	Terazosin	Hytrin	5mg	100s	QD or BID
	alpha blocker	all	Terazosin	Hytrin	10mg	100s	QD or BID
	ARB	all	Candesartan	Atacand	8mg	30s	QD or BID
	ARB	all	Candesartan	Atacand	16mg	90s	QD or BID
	ARB	all	Candesartan	Atacand	32mg	90s	QD or BID
	ARB	all	Valsartan (Diovan)	Diovan	80mg	100s	QD
	ARB	all	Valsartan (Diovan)	Diovan	160mg	100s	QD
	loop diuretic	all	Furosemide	Lasix	20mg	100s	QD or BID
	loop diuretic	all	Furosemide	Lasix	40mg	100s	QD or BID
	loop diuretic	all	Furosemide	Lasix	80mg	100s	QD or BID
	sympatholytic	all	Reserpine		0.1mg	100s	QD
	sympatholytic	all	Reserpine		0.25mg	100s	QD
	vasodilator	all	Hydralazine	Apresoline	25mg	100s	QID
	vasodilator	all	Hydralazine	Apresoline	50mg	100s	QID
	vasodilator	all	Hydralazine	Apresoline	100mg	100s	QID
	alpha-beta blocker	all	Carvedilol	Coreg	3.125mg	100s	BID
	alpha-beta blocker	all	Carvedilol	Coreg	6.25mg	100s	BID
	alpha-beta blocker	all	Carvedilol	Coreg	12.5mg	100s	BID
	alpha-beta blocker	all	Carvedilol	Coreg	25mg	100s	BID
	Ksparing/diuretic	all	Triamterene/HCTZ	Dyazide	37.5mg/25 mg	100s	QD
	beta bl/diuretic	U.S.	Metoprolol/HCTZ	Lopressor HCT	50/25mg	100s	QD or BID
	beta bl/diuretic	U.S.	Metoprolol/HCTZ	Lopressor HCT	100/25mg	100s	QD or BID
	ACE-I/diuretic	U.S.	Benazepril/HCTZ	Lotensin HCT	10/12.5mg	100s	QD
	ACE-I/diuretic	U.S.	Benazepril/HCTZ	Lotensin HCT	20/12.5mg	100s	QD
	ACE-I/diuretic	U.S.	Benazepril/HCTZ	Lotensin HCT	20/25mg	100s	QD
	ACE-I/diuretic	all	Lisinopril/HCTZ	Zestoretic	10/12.5mg	100s	QD

ACCORD Intervention	Drug Class	Available to	Generic	Trade Name (May Change During the Study)	Strength/ Size	Unit	Dosing
	ACE-I/diuretic	all	Lisinopril/HCTZ	Zestoretic	20/12.5mg	100s	QD
	ACE-I/diuretic	all	Lisinopril/HCTZ	Zestoretic	20/25mg	100s	QD
	ARB/diuretic	U.S.	Candesartan/HCTZ	Atacand HCT	16/12.5mg	90s	QD
	ARB/diuretic	U.S.	Candesartan/HCTZ	Atacand HCT	32/12.5mg	90s	QD
	ARB/diuretic	U.S.	Valsartan/HCTZ	Diovan HCT	80/12.5mg	100s	QD
	ARB/diuretic	U.S.	Valsartan/HCTZ	Diovan HCT	160/12.5mg	100s	QD
	CCB/ACE-I	U.S.	Amlodipine/Benazepril	Lotrel	5/10mg	100s	QD
	CCB/ACE-I	U.S.	Amlodipine/Benazepril	Lotrel	5/20mg	100s	QD
	Potassium	all	Potassium Chloride	K-DUR 20	20 mEq	100s	QD
SUPPLIES / DEVICES							
		all	Insulin Pen	Novo Pen 3.0 Silver	-	ea	_____
		all	Needles 30g for Pen	NovoFine 30	100s	bx	_____
		all	Insulin Syringe with Needle (29.5g/1ml)		100s	bx	_____
		all	Insulin Syringe with Needle (29.5g/0.5ml)		100s	bx	_____
		All	Insulin syringe with needle (30g/1cc)		100	bx	
		All	Insuline syringe with needle (30g/1cc)		100	bx	
		All	Glucagons emergency kit		1	ea	

Appendix B

10/07/2002 SHIPPING NOTICE
ACCORD

VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (161-I)
2101 Centro Avenue, SE, Albuquerque, NM 87106-4160
FTS 700-572-2580/(505)248-3203

VAMC New York
Pharmacy Service(119)
423 East 23rd Street
New York NY 10010

ACCORD - Action to Control Cardiovascular Risk in Diabetes

The following boxes have been shipped to site: **707**

GLUCOPHAGE 500MG (3S)	3 BOX(ES)
INSULIN SYRINGE (6E)	6 BOX(ES)
NOVO FINE 30G NEEDLES (5M)	6 BOX(ES)

STUDY DRUG RECEIPT NOTIFICATION

Person Completing this Form: _____
Print Name

Date Study Drug Received: 10/8/02 _____ 2 (am/pm)
Date Time

Was shipping container received intact? [Yes] [No]

Upon receipt of study drug(s), please complete this form and IMMEDIATELY fax to Pharmacy Coordinating Center at (505) 248-3205

If you have any questions about this shipment, please call

cc: Study Coordinator

ACCORD Local Destruction Documentation

Sites are authorized to destroy expired or returned ACCORD study drug locally. Documentation of this destruction must be provided to the Drug Distribution Center (DDC) using this form or through scanning in the ACCORD web site.

Site Name: _____ Site Number: _____

Drug Name	Strength	Lot #	Expiration Date	Unit Size (bottle/vial/pack)	Number of Units Destroyed	Reason for Destruction

I, _____, certify that these study drugs have been destroyed using a method in compliance with our Federal, State and Local Regulations.

Date: _____ _____

Participating Investigator Signature

FAX/Mail original to DDC
Retain a copy for your records.

ACCORD ORDER FORM

To be completed and faxed to the Drug Distribution Center WHEN ITEMS ARE NEEDED. After completing

forms, PLEASE FAX ALL 4 PAGES. For unneeded items, leave "Quantity Ordered" blank.

*****In order for items to be added to your weekly shipment, order form MUST be faxed in by COB Thursday.*** All orders received after Thursday afternoon will be held until the following week. **

SITE NAME _____

SITE NUMBER _____ *DATE* _____

PERSON COMPLETING FORM _____

TELEPHONE NUMBER _____

Note: All tablets/capsules are packaged in boxes of 4 bottles

Drug Code	Therapeutic Class	Available to	Item	Strength / Size	Unit	Quantity Ordered (Bx)
GLYCEMIA INTERVENTION DRUGS						
2K	sufonylurea	all	Glimepiride (Amaryl)	2mg	100s	_____
2L	sufonylurea	all	Glimepiride (Amaryl)	4mg	100s	_____
3S	biguanide	all	Metformin (Glucophage)	500mg	100s	_____
3T	biguanide	all	Metformin (Glucophage)	1000mg	100s	_____
6A	meglitinide	Canada	Repaglinide (Gluconorm)	0.5 mg	100s	_____
6B	meglitinide	Canada	Repaglinide (Gluconorm)	1 mg	100s	_____
6C	meglitinide	Canada	Repaglinide (Gluconorm)	2 mg	100s	_____
4K	meglitinide	U.S.	Repaglinide (Prandin)	0.5mg	100s	_____
4L	meglitinide	U.S.	Repaglinide (Prandin)	1mg	100s	_____
4M	meglitinide	U.S.	Repaglinide (Prandin)	2mg	100s	_____
7E	TZD	all	Rosiglitazone (Avandia)	2mg	60s	_____
4R	TZD	all	Rosiglitazone (Avandia)	4mg	100s	_____
4S	TZD	all	Rosiglitazone (Avandia)	8mg	100s	_____
6L	insulin	Canada	Human Regular (Novolin ge Toronto)	5 x 3 ml	pkg	_____
6K	insulin	Canada	Human Regular (Novolin ge Toronto)	10 ml	vial	_____
6G	insulin	Canada	Human Isophane (Novolin ge NPH)	5 x 3 ml	pkg	_____
6F	insulin	Canada	Human Isophane (Novolin ge NPH)	10 ml	vial	_____
6H	insulin	Canada	Human Zinc suspension (Novolin ge Lente)	10 ml	vial	_____
6M	insulin	Canada	Human 30/70 (Novolin ge 30/70)	5 x 3 ml	pkg	_____
7A	insulin	Canada	Insulin Aspart (NovoRapid)	10 ml	vial	_____
6T	insulin	Canada	Insulin Aspart (NovoRapid)	5x3 ml	pkg	_____

Drug Code	Therapeutic Class	Available to	Item	Strength / Size	Unit	Quantity Ordered (Bx)

Fax to:
Fax #:

3D	insulin	U.S.	Human Regular (Novolin R)	5 x 3 ml	pkg	_____
3G	insulin	U.S.	Human Regular (Novolin R)	10 ml	vial	_____
3C	insulin	U.S.	Human NPH (Novolin N)	5 x 3 ml	pkg	_____
3F	insulin	U.S.	Human NPH (Novolin N)	10 ml	vial	_____
3E	insulin	U.S.	Human zinc suspension (Novolin L)	10 ml	vial	_____
3B	insulin	U.S.	Human mixed (Novolin 70/30)	5 x 3 ml	pkg	_____
6N	Insulin	U.S.	Human Mixed (Novolin 70/30)	10 ml	vial	_____
6P	insulin	all	Insulin Aspart (NovoLog)	10 ml	vial	_____
1C	insulin	all	Insulin Aspart (NovoLog)	5 x 3 ml	pkg	_____
3R	insulin	all	Insulin Glargine (Lantus)	10 ml	vial	_____
5K	glucose	all	Glucose (Dex 4)	4 grams	50s	_____
6D	glucose	all	Glucose (Dex 4)	4 grams	10s	_____

LIPID INTERVENTION DRUGS

5B	statin	all	Simvastatin (Zocor)	20mg	90s	_____

BLOOD PRESSURE INTERVENTION DRUGS

Note: Combination drugs are listed after single drugs

1D	ACE-inhibitor	all	Benazepril (Lotensin)	10mg	100s	_____
1E	ACE-inhibitor	all	Benazepril (Lotensin)	20mg	100s	_____
3J	ACE-inhibitor	all	Lisinopril (Zestril)	10mg	100s	_____
3K	ACE-inhibitor	all	Lisinopril (Zestril)	20mg	100s	_____
3L	ACE-inhibitor	all	Lisinopril (Zestril)	40mg	100s	_____
4G	ACE inhibitor	all	Ramipril (Altace)	2.5mg	100s	_____
4H	ACE inhibitor	all	Ramipril (Altace)	5mg	100s	_____
4J	ACE inhibitor	all	Ramipril (Altace)	10mg	100s	_____
1T	diuretic	all	Chlorthalidone (Thalitone)	15mg	100s	_____
2A	diuretic	all	Chlorthalidone (Thalitone)	25mg	100s	_____
4C	beta blocker	all	Metoprolol (Toprol XL)	50mg	100s	_____
4A	beta blocker	all	Metoprolol (Toprol XL)	100mg	100s	_____
4B	beta blocker	all	Metoprolol (Toprol XL)	200mg	100s	_____
2B	CCB non-DHP	all	Diltiazem (Tiazac)	120mg	90s	_____
2C	CCB non-DHP	all	Diltiazem (Tiazac)	180mg	90s	_____
2D	CCB non-DHP	all	Diltiazem (Tiazac)	240mg	90s	_____
2E	CCB non-DHP	all	Diltiazem (Tiazac)	300mg	90s	_____

5D	alpha blocker	all	Terazosin (Hytrin)	1mg	100s	_____
5E	alpha blocker	all	Terazosin (Hytrin)	5mg	100s	_____
5C	alpha blocker	all	Terazosin (Hytrin)	10mg	100s	_____
1K	ARB	all	Candesartan (Atacand)	8mg	30s	_____
1L	ARB	all	Candesartan (Atacand)	16mg	90s	_____
1M	ARB	all	Candesartan (Atacand)	32mg	90s	_____
5F	ARB	all	Valsartan (Diovan)	80mg	100s	_____
5G	ARB	all	Valsartan (Diovan)	160mg	100s	_____
2G	loop diuretic	all	Furosemide	20mg	100s	_____
2H	loop diuretic	all	Furosemide	40mg	100s	_____
2J	loop diuretic	all	Furosemide	80mg	100s	_____
4N	sympatholytic	all	Reserpine	0.1mg	100s	_____
4P	sympatholytic	all	Reserpine	0.25mg	100s	_____
2S	vasodilator	all	Hydralazine	25mg	100s	_____
2T	vasodilator	all	Hydralazine	50mg	100s	_____
3A	vasodilator	all	Hydralazine	100mg	100s	_____
IN	alpha-beta blocker	all	Carvedilol (Coreg)	3.125mg	100s	_____
IP	alpha-beta blocker	all	Carvedilol (Coreg)	6.25mg	100s	_____
1R	alpha-beta blocker	all	Carvedilol (Coreg)	12.5mg	100s	_____
1S	alpha-beta blocker	all	Carvedilol (Coreg)	25mg	100s	_____
2R	Ksparing/diuretic	all	Triamterene/HCTZ (Dyazide)	37.5mg/25 mg	100s	_____
4E	beta bl/diuretic	U.S.	Metoprolol/HCTZ (Lopressor HCT)	50/25mg	100s	_____
4D	beta bl/diuretic	U.S.	Metoprolol/HCTZ (Lopressor HCT)	100/25mg	100s	_____
1G	ACE-I/diuretic	U.S.	Benazepril/HCTZ (Lotensin HCT)	10/12.5mg	100s	_____
1F	ACE-I/diuretic	U.S.	Benazepril/HCTZ (Lotensin HCT)	20/12.5mg	100s	_____
1H	ACE-I/diuretic	U.S.	Benazepril/HCTZ (Lotensin HCT)	20/25mg	100s	_____
3M	ACE-I/diuretic	all	Lisinopril/HCTZ (Zestoretic)	10/12.5mg	100s	_____
3N	ACE-I/diuretic	all	Lisinopril/HCTZ (Zestoretic)	20/12.5mg	100s	_____
3P	ACE-I/diuretic	all	Lisinopril/HCTZ (Zestoretic)	20/25mg	100s	_____
5P	ARB/diuretic	U.S.	Candesartan/HCTZ (Atacand HCT)	16mg/12.5mg	90s	_____
5R	ARB/diuretic	U.S.	Candesartan/HCTZ (Atacand HCT)	32mg/12.5mg	90s	_____

5J	ARB/diuretic	U.S.	Valsartan/HCTZ (Diovan HCT)	80mg/12.5mg	100s	_____
5H	ARB/diuretic	U.S.	Valsartan/HCTZ (Diovan HCT)	160mg/12.5mg	100s	_____
1A	CCB/ACE-I	U.S.	Amlodipine/Benazepril (Lotrel)	5/10mg	100s	_____
1B	CCB/ACE-I	U.S.	Amlodipine/Benazepril (Lotrel)	5/20mg	100s	_____
6J	Potassium	all	Potassium Chloride	20 mEq	100s	_____

SUPPLIES/DEVICES

5O	all	Insulin Pen (Novo Pen 3.0 Silver)	-	ea	_____
5M	all	Needles 30g for Pen (NovoFine 30)	100s	bx	_____
6E	all	Insulin Syringe with Needle (29g/1ml)	100s	bx	_____
6R	all	Lo-Dose Insulin Syringe with Needle (29g/0.5ml)	100s	bx	_____
7C	all	BL Insulin Syringe with Needle (30g/1ml) 5/16 short needle	100s	bx	_____
7D	all	Accusure Insulin Syringe with Needle (30g/0.5ml) 5/16 short needle	100s	bx	_____
7B	all	Glucagon Emergency Kit	-	ea	_____
	all	Child Resistant Closures – 33 mm	-	bx	_____
	all	Child Resistant Closures – 38 mm	-	bx	_____
	all	Rolls of Prescription Labels - English	-	roll	_____
	all	Rolls of Prescription Labels - French	-	roll	_____
	all	Rolls of Prescription Labels - Spanish	-	roll	_____

Fax to:
Fax #:

DATE: _____

DRUG TRANSFER NOTICE
ACCORD

Fax this immediately to:

Pharmaceutical Project Manager
VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center
2401 Centre Avenue SE, Albuquerque, NM 87106-4180

The following bottles have been shipped **From:** **SITE No.:** _____

To: **SITE No.:** _____

DRUG/STRENGTH _____

BOTTLE NUMBERS: _____
_____
_____
_____
_____
_____
_____
_____

DRUG/STRENGTH _____

BOTTLE NUMBERS: _____
_____
_____
_____
_____
_____
_____
_____

DRUG/STRENGTH _____

BOTTLE NUMBERS: _____
_____
_____
_____
_____
_____
_____
_____

DRUG/STRENGTH _____

BOTTLE NUMBERS: _____
_____
_____
_____
_____
_____
_____
_____

Person Completing this Form _____

Date Drug Transferred to New Site: _____

UPON RECEIPT OF THE STUDY DRUG:

Person Accepting Drug: _____

Date Drug Received: _____

*Fax copy immediately to

Appendix C

Procedure for printing dispensing and destruction records

A. ACCORD REPORTS

Currently there are two methods to access information about site drug disposition reports. One method is to use the report button on the dispense window after entering patient number. Another method is to access the destruction page from "Drug Destruction" link entering a site number and clicking on submit. At this time a report button will become available. This report page gives you information about dispensing, destruction, expiration and inventory. The report is filtered by the site before any other filters are applied.

Dispensed reports can be filtered by:
Dispense Date
Scan Date
Person (login id)
Drug Code (2 characters)
Patient
Visit
Date Range

Destructions reports can be filtered by:
Dispense Date
Scan Date
Person (login id)
Drug Code (2 char)
Date Range

Expiration reports can be filtered by:
Lot Number
Expiration Date
Expire Before Date
Date Range

Inventory report has no filter and is simple the current inventory at given site. This inventory is not a real time balance and is current as of the "As of Date" listed. On the Inventory report Drug Code description can be obtained by clicking on the listed drug code.

All information for reports is updated Monday morning and is a reflection of data entered as of the Friday before.

18. Adherence

18.1 Overview of Adherence within the ACCORD Clinical Trial

During a long and complicated trial like ACCORD, participants may have difficulties adhering to the protocol. It is therefore necessary to have in place policies and procedures to which the clinical trial staff can refer to in order to maintain and enhance adherence. The goal is to help participants maintain adherence to the protocol or better yet to prevent non-adherence to the study protocol. This is one of the most difficult activities of any clinical trial. Adherence will focus on the following essentials:

1. Create a team at each clinical site that will monitor adherence and intervene when it is threatened
2. Assure at least minimum adherence: knowing the primary outcome for every participant in the study
3. Maintain adherence in the majority of the study population by having an efficient and updated communication system
4. Focus on participants with threatened or reduced adherence
5. Focus on participants not completing the protocol
6. Maintain good communication with referring physician and centers
7. Have the clinical center PI promote adherence

Adherence plays a central role in addressing the primary question of the trial. It is therefore crucial that adherence management be started early in the study and maintained throughout. Success can be achieved in multiple ways including, empowering the participant as well as giving them a role in their own adherence.

18.2 Promoting Good Adherence

Participant adherence (to study medication and to follow-up visits) is a key component to the scientific integrity of a clinical trial Promoting good adherence begins with prevention strategies with early recognition and implementation of remedies for potential problem situations. At the end of the ACCORD Study, the primary analysis to detect a potential treatment difference between the treatment groups will be based on the original randomization scheme, meaning that even if a participant no longer attends clinic visits or stops adhering to the treatment targets for the 3 arms of the trial the data from this individual will still be analyzed (for the main study analysis). This approach, known as the *"intent to treat" analysis*, is summarized by the phrase *"once randomized, always analyzed,"* meaning that no matter how much follow-up data may be missing due to missed visits, primary analysis of this person's data will be relegated to the originally assigned treatment group. This is why promotion and prevention of adherence, and prompt resolution of non-adherence are so important to ACCORD.

Although it may seem counterintuitive to analyze a person's data according to original treatment assignment even if that person took little or none of the assigned study drug, there is a number of compelling methodological reasons for doing so. For example, dropouts in a clinical trial may not occur randomly, but may be related to the assigned treatment arm. For example, a participant may stop taking his/her study medication due

to an unknown, unexpected side effect of the study medication that has yet to be determined. It is only by retaining a person's data in the original treatment group that we can, across the entire study population, ascertain such unexpected adverse events.

18.2.1 Prevention Strategies

Promoting good adherence begins with prevention strategies such as early recognition and implementation of remedies for potential problem situations. Adherence is the primary focus of study activity following randomization and continues to be a challenge up until the last follow-up visit. There is no universal plan that promotes good adherence in every participant. Thoughtful consideration and customizing a retention plan for each participant are critical to each clinic's success in maintaining adherence in the majority of participants.

Initial Contact/Participant & Staff Relationship

- The first clinic visit (i.e., the screening visit) is critical, in terms of the participant gaining a clear understanding of the study requirements, in great part through the informed consent process. (Research suggests that many participants do not understand the concept of randomization even though it is described in the consent process. This would suggest that emphasis needs to be placed on this aspect of the trial.)
- Use the screening process to also screen for any behavior that might signal a potential non-adherer (e.g., repeated missed appointments), and consider such factors in deciding if this individual would potentially be an adherent participant
- Develop a good rapport and foster trust with the participant. Encourage questions when participants lack clarity and convey a sense of concern and caring (e.g., visit participants when hospitalized, if possible)
- Make every effort to ensure that each participant gains a clear understanding of the study requirements (Consenting Process)
- Develop rapport and trust with participant
- Maintenance of constant "caretaker" at the field center/clinic site (Study Coordinator, PI)
- Keep the participant informed about any new developments in the trial, and periodically remind him/her that he/she should refrain from using any non-study Gingko products
- Communicate with participants' health care providers as well as with participant's family and friends (including their proxies) to gain their support for the study. This would include periodically keeping personal physicians informed about their patients' progress in the study as well as providing them with key study laboratory or other data that might impact on the safety and well-being of the study subject (if the participant agrees to this).
- Ensure participant continuity of care, as participants "bond" with study staff and enjoy interacting with the same individuals throughout the course of the trial.
- Ensure that study staff has received local training not only on study conduct and operations, but also on how to communicate effectively with study participants and especial specific subgroups such as the elderly and minority participants. This would

involve providing prompt (and standardized) answers to participants' questions, being sensitive to the needs and expectations of this study cohort and its cultural diversity, offering praise and appreciation to study participants for their commitment to the trial, discussing non-adherence in a non-threatening, non-judgmental fashion, and demonstrating professionalism in conjunction with personalized care. Periodic refresher training should be conducted to ensure the continued high quality of participant/staff interactions and communications.

Convenience & Accessibility

- Address transportation issues with participant
- Address participants' longevity in the geographic area and comfort with the clinics location
- Provide parking or a travel stipend

Routine Contact

- Update participant contact information sheet regularly
- Stay in touch with the participants' life "outside the study"

Participant Tracking

- Scheduling system including follow-up for "no shows"
- Visit reminders
- Thank you holiday and birthday cards
- Newsletters
- Hold regular staff meetings to strategize ways to improve participant adherence

In an "intention to treat" outcome trial such as ACCORD, it is imperative that the trial be able to document the status of each randomized participant at the close of the trial to insure the scientific integrity and credibility of the study's results. Primary responsibility for securing and documenting participant status lies with the individual clinical sites.

It is inevitable that in a trial of this magnitude, complexity and duration, we will lose some participants through fatal events, withdrawal of consent to participate ("true refusals") and attrition, where participants leave the study on their own without notification and fail to maintain contact at any level with the study personnel. While there is little that we, as a study, can do to prevent the first type of loss, there are actions we can take to minimize participant loss from the latter two.

Prevention is the key to any successful proactive approach for minimizing participant loss. In addition to efforts taken to create a positive clinical trial experience (e.g. welcoming, responsive environment and competent, convenient care) complete and accurate collection of participant contact information will facilitate efforts to locate participants should the need ever arise. Regular review (at least annually) and updates of the contact information as needed will prove to be an invaluable tool in activities undertaken to locate a participant should they ever become lost.

The ACCORD Participant Contact Information Form has been revised to allow the sites to collect crucial participant contact information (including contact information for at two close personal contacts) that may be entered and retained in the local site database and accessed if needed to facilitate efforts to locate a participant that fails to keep up with study follow-up as requested and required by the protocol. It is critical that this information be complete and accurate as possible and updated regularly as needed as this will serve as the starting point from which all efforts, whether local or central (through the Coordinating Center), will begin if it becomes necessary to engage in larger scale activities to locate a participant or obtain participant vital status information from a family member, close personal contact and/or national databases (e.g. National Death Index). However, it does remain the primary responsibility of the clinical site to collect, update and use this contact information if the participant becomes lost. Guidance and support for fulfilling this responsibility can and will be provided as needed by the Clinical Center Network Offices and ACCORD Coordinating Center.

Incentives / Participant appreciation

- Participant parties
- Small, inexpensive incentive items for participant appreciation
- Birthday cards

18.2.2 Recognition of Adherence Challenges / Implementation of Solutions

- Review of participant charts on a regular basis for threatened or reduced adherence
- Focus on participants who are not completing the protocol
- Formulate a plan of action utilizing a staff team approach
- Implement retention activities in a timely, and organized fashion
- Track activities success/failure and re-evaluate approach as needed

18.3 Monitoring Adherence for Medication

The precision with which medication adherence monitoring can be done in a large clinical trial on free-living participants is less than optimal. Caron and Roth and Roth and Caron in their classical studies demonstrated that the precision of adherence assessment with which participants or medical staff, regardless of specific position, level of training, or degree of familiarity with the participant, assesses the level of participant adherence is very substantially in error, between 30% and 50% off in the majority of cases. This has been aversive enough to many clinical trial investigators so that pill counts have been largely abandoned, and the semi-quantitative assessment of greater than or less than 80% seems to be of little use. Although the data can be collected, it ultimately must be acknowledged to be imprecise and may ultimately be misleading.

We propose to monitor adherence in a semi-quantitative fashion with the following designations for all medication to be taken in all three arms of the trial. Participants will be asked to assess for each medication whether or not they are taking each medication regularly (in every intended instance or almost every intended instance), irregularly, or not at all. While this leaves only two categories of responses for those who

are actually taking the medication, previous instances of self-report combined with pill counts suggest that most participants will be either taking the medication well, with lesser numbers or not at all. The term "irregularly" is sufficiently precise or imprecise so that it will be descriptive of the remainder. This approach is somewhat different than that done previously where participants have been asked to report whether or not they are taking greater than or less than 80%. The rationale is that most people will wish to report adherence greater than 80% and that those reporting will tend to report slightly higher numbers for those over 80%. The more general description is less judgmental and therefore should be associated with more accurate reporting. There will be inherent difficulties in assessing the data collected quantitatively, but this is a little different than previous trials. We hope to be able to used the information collected in the clinic practically for the encouragement of participant's performance overall in the trial. This can be done without precise numbers and with more general information as collected.

Participants may take fewer study pills than the protocol calls for due to a number of reasons:

- Forgetfulness
- Side effects (perceived or real)
- Misunderstood directions on how to take the study medication
- Disrupted schedule
- Illness or hospitalization
- Loss of study medication
- Lack of belief in the study intervention
- Difficulty swallowing pills
- Lack of support of trial involvement by family, friends or health care provider
- Disruption in personal life (family crisis, financial or health problems, etc.)

Thus, reasons for under-adherence are numerous, and often complex. Study staff must do their best to ascertain what barriers to good adherence exist for the participant, then try to work with the participant in a non-threatening, positive manner, to determine ways to improve pill adherence, in the face of some of these obstacles. There may be times when it is best that study staff postpone discussions about adherence with the participant and/or his/her family, as when a personal crisis has occurred or if the participant is hospitalized.

If forgetfulness is a problem, study staff may suggest that participants use cues or reminders to facilitate study medication adherence. With regard to side effects these must be documented and followed till they are stabilized or resolved. Whether or not to temporarily discontinue the study medication secondary to a reported adverse event should be a decision made between the study clinicians and the participant (perhaps involving, at times, the participant's health care giver.) Discontinuing the study medication over an agreed-upon period of time to observe if the AE resolves is one approach. Another would be to down-titrate the study medication to see if the AE clears up. The main concern, of course, is participant safely. Study staff should feel free to call the Network Coordinators to discuss these issues at any time.

If non-adherence relates to a lack of family support of the study, invite the participant's family members to the clinic so that issues of concern can be voiced and addressed. (Consider offering refreshments for this purpose.) If family members refuse to come to the clinic, and you feel it is appropriate, consider asking if a study staff member could visit the family for the same purpose, or even speak to them by phone. The same approach could be used to communicate with health care providers who have doubts about their patients' involvement in the study.

If family problems exist, or if there are other personal problems that the participant is experiencing, it is best to listen sympathetically, realizing that taking time to listen is in itself an investment towards better adherence.

The best approaches to dealing with non-adherence involve understanding, praise (for being in the study), positive reinforcement of those behaviors that support adherence, continued communication with the participant, and, if appropriate, efforts to gain support for the study from family members and personal health care givers. Never admonish or criticize a participant because of poor adherence.

Glucose monitoring data - Participant SMBG monitoring will be necessary several times a day during the study. It will be used as the single measure of adherence assessment in the pre-randomization run-in period. The rationale for the selection of this variable is as follows. The most important activity in the ACCORD trial will be adherence to the respective glycemic control regimens. In order to obtain and maintain the targeted differential in the HbA1c identified by the protocol it will be necessary for the Intensive Glycemia group to conduct SMBG several times a day. If screenees are unwilling or unable to perform SMBG on a consistent basis prior to randomization, it will be unlikely that they will become successful at this activity when enrolled in the trial. SMBG will be required $\leq$ 3 times/day in the standard intervention and may be required up to 8 times per day in the intensive intervention arm. The minimum of 2 determinations recorded daily from each participant seems a reasonable compromise for the run-in period.

18. 4 Situation Regarding The Temporary Closure of Canadian Clinical Site Due To Severe Acute Respiratory Syndrome (SARS)

18.4.1 Summary

Since March 2003, there have been two outbreaks of SARS in Canada with the majority of cases clustered in the greater Toronto area. During the first outbreak (now referred to as 'SARS I') the Ontario provincial government declared a health emergency and instituted a number of strict measures to control the outbreak across the entire province. Theses measures consisted of limiting hospital admissions and outpatient activity to only urgent cases (restrictions on outpatient activity were placed specifically on offices and clinics located within a hospital setting). For the most part, none of the Ontario ACCORD clinical Centers (London, Hamilton, Toronto, Ottawa) were able to bring in research participants during April 2003. Between April 28th and May 12th,

outpatient activity (including research-related visits) returned to 100% of pre-SARS levels. However, on May 23rd, a second outbreak of SARS was declared within Toronto, involving previously unrecognized cases that had contracted SARS at the end of the first outbreak. While Toronto-area hospitals have resumed full SARS precautions, no restrictions have been placed on outpatient activity during this second outbreak. However, in Toronto we are still experiencing reduced volumes in out diabetes and other outpatient clinics from patients canceling their appointments because of the fear of SARS.

19. Quality Control Procedures

19.1 Overview

Quality control and assurance are the responsibility of every member of the ACCORD team. This section of the MOP will described the quality control and assurance philosophy and procedures to be used in ACCORD.

19.2 Division of Responsibilities

In order to maximize the quality of all of the data obtained in the ACCORD Trial, all members of the ACCORD Team must strive for excellence. Everyone is responsible for mastering the material covered in the protocol and the MOP. All clinic personnel are responsible for achieving and maintaining a high level of understanding and performance of all clinic procedures. The Quality Assurance Matrix (Table 19.2.1.) provides a detailed description of the study units that are responsible for various aspects of quality assurance. A brief description follows here.

19.2.1 Coordinating Center

The Coordinating Center is responsible for the following:

1. maintaining the integrity of the protocol, MOP, training binder and regulatory document binder through any revisions (as well as other important study materials) and placing this material on the ACCORD Web site,
2. organizing and, with the collaboration of the Steering Committee, conducting central training sessions,
3. developing a data entry system that incorporates real-time data quality assurance features, such as range and logic checks and limited double data entry,
4. generating data query reports for dissemination to clinics and clinical center network monitoring centers,
5. monitoring site initiation requirements,
6. monitoring the randomization process to ensure appropriate allocation of participants eligible for both studies,
7. generating web-based reports describing clinic, network and study performance with respect to:

a) recruitment
b) visit adherence
c) glycemic control
d) blood pressure control
e) blinded fibrate/placebo adherence
f) data entry, including double data entry reports
g) outcomes documentation submission
h) quality control of point of care HbA1c measurement devices

8. producing case reports for 10 participants per clinic per year for review during annual site visits,

9. receiving, maintaining and distributing to the MP&QC Subcommittee copies of clinic site visit reports,
10. monitoring 100% of all consent forms,
11. monitoring documentation of 100% of primary outcomes,
12. performing double data entry for all adjudication forms,
13. participating in MP&QC Subcommittee endeavors,
14. monitoring the performance of the Clinical Center Network Sites,
15. participating in clinic and other study component site visits as needed,
16. maintaining documentation of network and core component monitoring activities,
17. providing rapid feedback to the CCN, Core Laboratories, and MP&QC Subcommittee on the quality of data submitted and proposed corrections,
18. developing procedures, in collaboration with the MP&QC Subcommittees, for having blind duplicate blood and ECG readings performed at the Core Laboratories,
19. providing leadership to each Core Laboratory for their development and distribution of specific measurement procedures and timely data gathering.

19.2.2 Clinical Center Networks

The Clinical Center Networks are responsible for the following:

1. maintaining current copies of the protocol, MOP, training binder and regulatory document binder through any revisions (as well as other important study materials),
2. contributing to central training sessions,
3. assuring that the clinic sites have adequately trained personnel,
4. collaborate with and assist the CC in implementation and standardization of the protocol within their network
5. monitoring the performance of the clinic sites in all aspects of the study, including:
   a) clinic burden and responses to data edit queries
   b) performance as indicated on monthly reports described above (CC responsibility #7)
   c) communicating on at least a monthly basis regarding site performance from monthly reports
   d) communicating areas of concern to the clinic sites,
   e) collaborating in the development of plans to solve problems faced by the clinic sites,
6. conducting sites visits on at least an annual basis with each clinic site,
7. reviewing the participant charts for 10 participants per clinic per year during annual site visits,
8. producing and submitting to the CC a site visit report for each site visit,
9. following up on issues of concern identified during site visits,
10. maintaining documentation of clinic monitoring activities,
11. participating in MP&QC Subcommittee endeavors,
12. participating in other study component site visits as needed.

19.2.3 Clinical Sites

The Clinic sites are responsible for

1. maintaining current copies of the protocol, MOP, training binder and regulatory document binder through any revisions (as well as other important study materials),

2. attending central training sessions,
3. assuring that the clinic site has adequately trained personnel, throughout all changes in personnel,
4. maintaining adequate source documentation to support participant data forms, including eligibility, follow-up and events ascertainment,
5. performing double data entry for the standard set of participant-visit-form by each new data entry person,
6. reviewing, and developing plans to respond to data edit queries and performance reports described above (CC responsibility #7)
7. developing plans to address areas of concern,
8. facilitating sites visits on at least an annual basis,
9. providing the participant charts for 10 participants per clinic per year during annual site visits,
10. reviewing and responding to the CCN site visit report for each site visit.

19.2.4 Measurement Procedures and Quality Control Subcommittee

The committee structure within the ACCORD Trial has been designed to assure quality in all aspects of protocol implementation. The responsibilities of each committee are shown in figure 19.2.1. The Measurement Procedures and Quality Control Subcommittee has special responsibility for assuring quality of data collection as described in additional detail below:

1. monitoring the performance of the clinic sites and networks in all aspects of the study, including:
   a) clinic burden and responses to data edit queries
   b) performance as indicated on monthly reports
   c) data entry, including double data entry reports
   d) outcomes documentation submission (in collaboration with the Outcomes Subcommittee),
   e) data quality for forms submitted by the clinical sites,
   f) performance of quality control procedures related to the point of care HbA1c measurement device,
2. communicating areas of concern to the clinic network monitoring centers,
3. collaborating in the development of plans to solve problems faced by the networks and clinics,
4. reviewing 10% of site visit reports on regular basis to evaluate the CCN reports and effectiveness for clinical sites,
5. monitoring data quality and performance of the central laboratory and ECG reading center,
6. monitoring agreement between the point of care HbA1c measurement device and the central laboratory, and
7. providing reports regarding the quality of study implementation and conduct to the Steering Committee.

19.3 QC Procedures to Communicate Timely Information about the Progress of the Study

Of utmost importance are reports that monitor glycemic treatment and control, blood pressure treatment and control, and adherence to blinded fibrate/placebo therapy. These web-based reports are generated on a daily basis for the study overall and for each network and site. These reports are generated by the CC. Reports will permit tracking "trends" in control across follow-up visits and calendar months.

Numerous other reports are generated to communicate information about Study progress. On the ACCORD Web Site, information will be available randomizations, visit adherence and data entry timeliness.

19.4 Procedures to Maximize the Uniformity of Procedures and Measurements and the Quality of Data Entered on Case Report Forms

The development of the MOP and study forms provide the foundation for the development of additional procedures to maximize the uniformity of procedures and measurements and the quality of data entered on case report forms. Central training sessions will be held to train clinic investigators and staff in study procedures. At least one individual from each network-monitoring center will receive intensive training in order to function as a trainer as needed for refresher training and in cases of staff turnover. The existing clinic staff will be the front-line trainers of new clinic staff with assistance from the appropriate network-monitoring center. The need for refresher training will be judged during the annual clinic site visits. The training materials developed for each training sessions will be made available to the network monitoring centers and disseminated as needed to new staff and existing staff responsible for their training.

Training materials will include materials designed to familiar investigators and staff with

1. the overall goals and specific hypotheses of the study;
2. the pathophysiology of diabetes, dyslipidemia and hypertension;
3. the medical, nutritional and lifestyle approaches to the therapy of diabetes, dyslipidemia and hypertension;
4. important cardiovascular disease clinical prevention strategies;
5. study medication accountability procedures;
6. participant screening, recruitment and randomization procedures and strategies;
7. label generation procedures and use of the bar code readers;
8. data collection procedures, including assessments related to medical history, physical examination, automated blood pressure measurement, phlebotomy and other body fluids, use and quality control procedures related to the point of care HbA1c measurement device, electrocardiography and study outcomes;
9. case report form completion procedures and appropriate source documentation; and
10. web-based data entry procedures; and
11. a review of regulatory requirements and procedures.

Special quality control aspects of the data collection process have been described in detail in Chapter 10. Approaches to assuring the quality of data entry will include

1. double data entry of a standard set of participant clinic visit forms sets for each data entry person;
2. double data entry of all average BP values for BP Trial participants;
3. double data entry of all adjudication forms (forms documenting final event status);
4. range and logic checks; and
5. the generation of data edit queries and data quality reports.

Additional aspects of the study plan that will contribute to maximizing the quality of data include the use of

1. standard of equipment for measurement of point of care HgbA1c and clinic BP values;
2. a central lab for HbA1c, lipids and other biochemical assays; and
3. a central ECG reading center.

19.5 Data Entry and Management

An overview of data entry procedures is contained in Chapter 10. The data entry system is an important component of the overall QC plan for ACCORD. The system uses scannable labels that are placed on the top of each form. These labels contain a coding for the participant's Id and acrostic. This will help to ensure that Id's are always entered correctly in the database. Some real-time data entry checks are performed:

1. Checks to make certain that acrostics contained on the label match the hand-entered acrostic at the top of each form. This will ensure that the correct label has been placed on each form.
2. Eligibility checks prior to randomization assignment.
3. Checks to make certain that forms cannot be entered for a subsequent visit until the status of a previous visit has been entered.
4. Range checks on individual items.
5. An audit process that identifies values that have been changed after having been previously saved to the database.

The system also permits printing of recently entered forms for comparison to data collection forms.

19.6 Clinic Monitoring

Quality Control Monitoring at the site visits should involve the following-(to be done once a year)

1. assessment of recruitment strategy (if appropriate according to trial schedule);
2. confirm presence of regulatory documents (IRB approval and annual renewal);
3. evaluate protocol adherence including verification of consents, inclusion criteria, and source documentation for 10 participant charts per year;
4. assure that the participants are being seen according to protocol guidelines;
5. assure that the participants are having interventions implemented according to the protocol guidelines;
6. confirm presence of lab reports, ECG's, etc;

7. review drug accountability log, confirm adequate drug supplies and aid in drug recall procedure;
8. review point of care HbA1c measurement device quality control log;
9. confirm adequate study supplies (including Manual of Operations, protocol, forms);
10. collection of specified case report forms or source documentation for events;
11. trouble-shoot problems (e.g. retraining of new personnel, searching for lost to follow-up participants, or editing on-site corrections) ;
12. aid in correcting questions or edits for site to correct;
13. follow-up report to the site;
14. follow-up report to the coordinating center and project office, if necessary; and
15. confirmation from the site that requested follow-up procedures were completed.

Table 19.2.1. Quality Assurance Responsibility of Study Components

Function	Project Office	Coordinating Center	Committee	Special Center	CCN	Clinic
Recruitment	Participate in committee functions	Generate reports, support committee	R & R: Review report and advise CCN & other study committees as appropriate. Other Committees to respond as appropriate.	NA	Review report, consider advice and interact with clinic	Review report, consider and act on advice
Randomizations	Participate in committee functions	Generate reports, support committee	R & R: Review report and advise CCN & other study committees as appropriate. Other Committees to respond as appropriate.	NA	Review report, consider advice and interact with clinic	Review report, consider and act on advice
Visit Adherence	Participate in committee functions	Generate reports, support committee	R & R: Review report and advise CCN & other study committees as appropriate. Other Committees to respond as appropriate.	NA	Review report, consider advice and interact with clinic	Review report, consider and act on advice
Data Entry	Participate in committee functions	Generate reports, support committee	MPQC: Review report and advise CCN & other study committees as appropriate. Other Committees to respond as appropriate.	NA	Review report, consider advice and interact with clinic	Review report, consider and act on advice

Function	Project Office	Coordinating Center	Committee	Special Center	CCN	Clinic
Clinic Medical Data Quality	Participate in committee functions	Generate reports, support committee	MPQC: Review report and advise CCN; BP: Review BP data quality and advise CCN Both: Advise other study committees as appropriate. Other Committees to respond as appropriate.	NA	Review report, consider advice and interact with clinic	Review report, consider and act on advice
Clinic HUI/HRQL/Cost Data Quality	Participate in committee functions	Generate reports, support committee	HRQL/Cost: Review report and advise CCN & other study committees as appropriate. Other Committees to respond as appropriate.	NA	Review report, consider advice and interact with clinic	Review report, consider and act on advice
Clinic Diet/PA/ Background Therapy Data Quality	Participate in committee functions	Generate reports, support committee	Lifestyle/Background: Review report and advise CCN & other study committees as appropriate. Other Committees to respond as appropriate.	NA	Review report, consider advice and interact with clinic	Review report, consider and act on advice
ECG Data Quality	Participate in committee functions	Collaborate with ECG Reading Center in generating reports, support committee	MPQC: Review report and advise CCN & other study committees as appropriate. Other Committees to respond as appropriate.	ECG Reading Center: Collaborate with CC in generating report, participate on MPQC	Review report, consider advice and interact with clinic	Review report, consider and act on advice

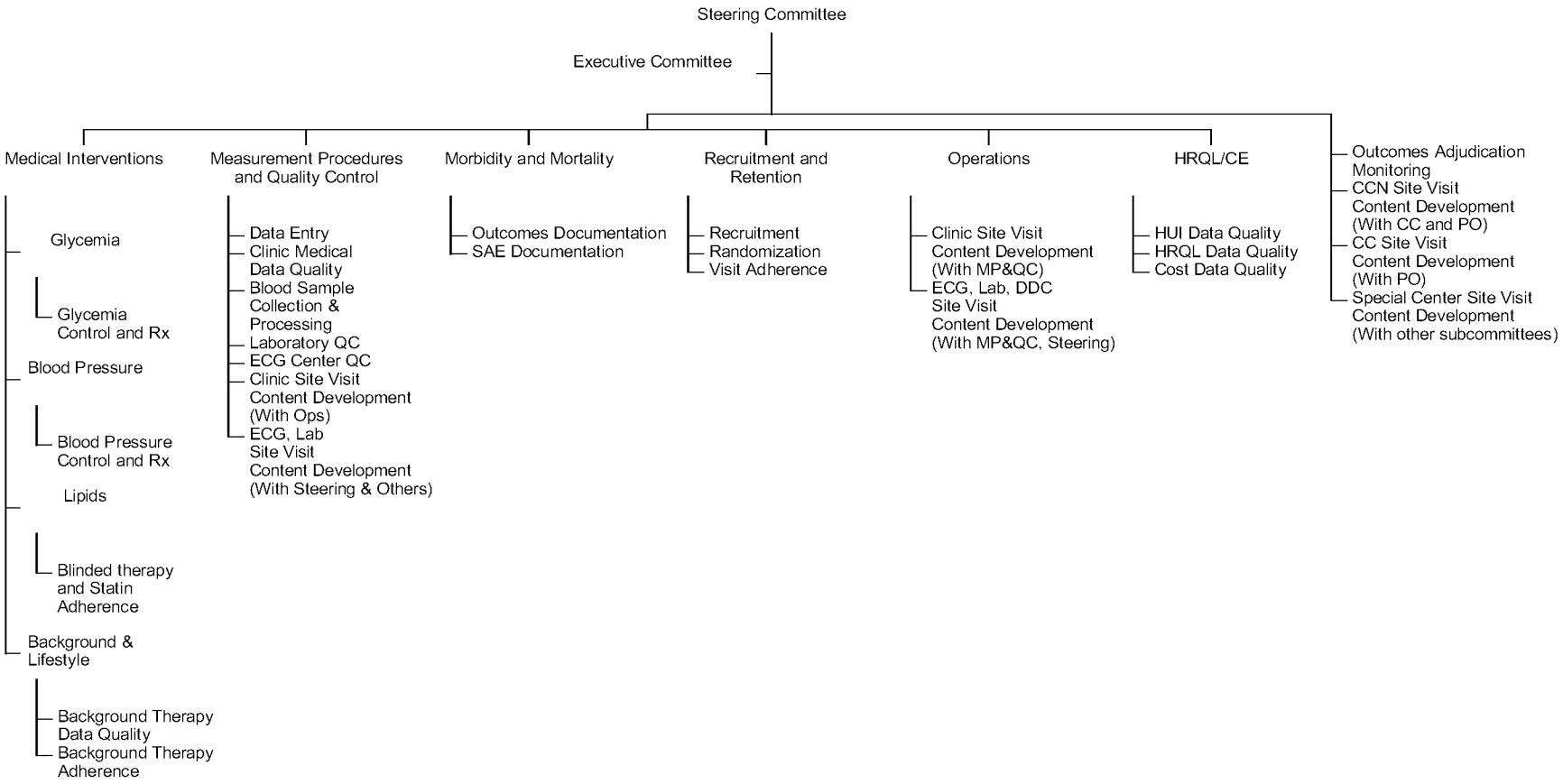
Function	Project Office	Coordinating Center	Committee	Special Center	CCN	Clinic
Lab Sample Collection and Shipping Quality	Participate in committee functions	Collaborate with Lab in generating reports, support committee	MPQC: Review report and advise CCN & other study committees as appropriate. Other Committees to respond as appropriate.	Lab: Collaborate with CC in generating report, participate on MPQC	Review report, consider advice and interact with clinic	Review report, consider and act on advice
Lab Data Quality	Participate in committee functions	Generate reports, support committees	MPQC: Review laboratory data, advise Lab & other study committees as appropriate. Other Committees to respond as appropriate.	Lab: Collaborate with CC in generating report, participate on MPQC	NA	NA
Point of Care HbA1c Measurement Device Quality	Participate in committee functions	Generate reports, support committees	MPQC: Review reports, advise Lab & other study committees as appropriate. Other Committees to respond as appropriate.	Lab: Participate on MPQC	Review reports, consider advice and interact with clinic	Follow QC procedures for device; maintain QC log for device; review reports, consider and act on advice
Glycemic Control	Participate in committee functions	Generate reports, support committee	Glycemia: Review reports and advise CCN & other study committees as appropriate. Other Committees to respond as appropriate.	NA	Review report, consider advice and interact with clinic	Review report, consider and act on advice

Function	Project Office	Coordinating Center	Committee	Special Center	CCN	Clinic
BP Control	Participate in committee functions	Generate reports, support committee	BP: Review reports and advise CCN & other study committees as appropriate. Other Committees to respond as appropriate.	NA	Review report, consider advice and interact with clinic	Review report, consider and act on advice
Lipid Rx Adherence	Participate in committee functions	Generate reports, support committee	Lipids: Review reports and advise CCN & other study committees as appropriate. Other Committees to respond as appropriate.	NA	Review report, consider advice and interact with clinic	Review report, consider and act on advice
Outcomes & SAE Documentation	Participate in committee functions	Generate reports, support committee	M&M: Review reports and advise CCN & other study committees as appropriate. Other Committees to respond as appropriate.	NA	Review report, consider advice and interact with clinic	Review report, consider and act on advice
Outcomes Adjudication	Participate in committee functions	Generate reports, support committee	Steering Committee: Review reports and advise M&M & other study committees as appropriate. Other Committees to respond as appropriate.	NA	NA	NA

Function	Project Office	Coordinating Center	Committee	Special Center	CCN	Clinic
Monitoring Clinics	Participate in committee functions	Generate reports, support CCN, Maintain copies of site visit reports; Advise other study committees as appropriate. Other Committees to respond as appropriate.	Operations & MPQC: Develop site visit content and procedures	ALL: Contribute to development of site visit content and procedures	Conduct site visits, generate reports to clinic and CC	Facilitate site visits, review reports and act on recommendations
Monitoring CCNs	Participate in committee functions & site visit teams	Generate reports, Conduct site visits, generate site visit reports to CCN and PO & other study committees as appropriate. Other Committees to respond as appropriate.	Steering Committee: Contribute to development of site visit content and procedures	ALL: Contribute to development of site visit content and procedures	Facilitate site visits, review reports and act on recommendations	NA: ? 1 clinic available for visit
Monitoring CC	Participate in committee functions & site visit teams; Create site visit report. Advise other study committees as appropriate. Other Committees to respond as appropriate.	Facilitate site visit, review reports and act on recommendations	Steering Committee: Contribute to development of site visit content and procedures	ALL: Contribute to development of site visit content and procedures	Contribute to development of site visit content and procedures; Participate in site visits as needed.	Participate in site visits as needed

Function	Project Office	Coordinating Center	Committee	Special Center	CCN	Clinic
Monitoring Special Centers (ECG, Lab)	Participate in committee functions & site visit teams	Generate reports, Conduct site visits, generate site visit reports to Special Center and PO & other study committees as appropriate. Other Committees to respond as appropriate.	Steering Committee and all relevant subcommittees (i.e., MPQC, Medical Interventions, Operations): Contribute to development of site visit content and procedures; Participate in site visits	ALL: Facilitate site visits, review reports and act on recommendations	Contribute to development of site visit content and procedures; Participate in site visits as needed.	Participate in site visits as needed

Figure 19.2.1. ACCORD QC System: Committee Responsibilities



20. DATA ANALYSIS

20.1 Overview

The Coordinating Center will be responsible for conducting data analyses in accordance with the analysis plans described in the ACCORD Protocol. The Design and Analysis Subcommittee will oversee analyses of study data and will be responsible for determining what reports should be presented to the Steering Committee. The Publications and Presentations Subcommittee will serve as an additional check on the quality of analyses to ensure that study data are presented in a consistent manner. The Data Safety and Monitoring Board will monitor the study data and oversee patient safety. The DSMB will have access to unblinded study data throughout the course of the study. Unless requested by the DSMB, there will be no unblinded results of safety and endpoint data (aggregated across all Clinical Networks) presented to study investigators or the public. Only after all participants have completed the study and all events have been adjudicated will unblinded analyses be presented to study investigators or the public.

Participants in the ACCORD trial were recruited as two separate cohorts: 1184 Vanguard participants were recruited in January 2001 through May 2002, whereas recruitment of the remaining 8916 participants was initiated in January 2003. The final analysis of ACCORD will use events from all ACCORD participants. Details on primary and secondary analyses planned for ACCORD are contained in section 7.2 of the ACCORD Protocol. Details on other types of analyses, including data monitoring reports are contained in this Chapter.

20.2 Analyses of Drug Safety

The Data and Safety Monitoring Board will have primary responsibility for monitoring the accumulating study data for signs of adverse trends in morbidity/mortality and drug toxicity. Possible adverse effects of the study drugs will be assessed at each follow-up visit by patient history. These effects will include hypoglycemia episodes and, in the lipid component, muscle pain, among other effects. Reports of frequencies of adverse effects will be generated by intervention arm and by combinations of study drugs. During the Vanguard, reports on severe hypoglycemia rates by treatment group were available to CS and CCN personnel. These reports will not be available to these personnel during the post-Vanguard phase. They will be reviewed on a regular basis by a restricted group of study personnel chosen by the ACCORD Steering Committee.

20.3 Interim Analyses: Routine Reporting

A large number of reports will be available to the Clinical Sites and CCNs through the ACCORD web site and through periodic email distribution. These reports will monitor randomization, drug distribution, data quality, and glycemia, lipid and blood pressure control, among other items. Some components of these reports is described below.

Participant recruitment— Randomization reports are generated on a instantaneous basis on the ACCORD web site and will be periodically distributed via email. These reports indicate

the number of participants randomized by CCN, Site, and ethnicity. Reports on eligibility and yield are also available.

Drug Distribution – The Drug Distribution Center (DDC) will provide individual clinics with reports to aid in inventory management. Though most of the DDC's communication with clinical sites will be via direct phone or email contact, some summary reports and notices may be posted on the study web site on an as needed basis.

Data Quality -- These reports track patient adherence to scheduled visits, timeliness of visits, and data entry items that need reconciliation, among other items. The following reports will be available on the study web site:

a) Performance Profile - a four-part report that summarizes clinic performance with respect to clinic visit adherence and phone contact monitoring; data entry timeliness and completeness; and glycemia and blood pressure control, and lipid therapy adherence. This report will contains links to more detailed listings of participants who have not met study treatment goals, or for whom forms or visits are missing or not reconciled. Both study-wide and CCN-wide versions of this report will be available on the study web site as well; however, links to individual participants will not be provided for these higher-level versions.
b) Missed Visit Reconciliation - a report that can be generated by the clinical sites in real time that lists participants with visits that are expected but have not been documented as having occurred or as missed in the web data base.
c) Unresolved Data entry - a report that can be generated by the clinical sites in real time that lists specific forms that are expected but have not been documented as collected or omitted in the web data base.

Glycemic Control – From a glycemic perspective, the post-Vanguard trial will have 2 goals:

a) the median achieved HbA1c in the intensive group will be less than 6.0%, and
b) the difference (delta) in HbA1c between the standard and intensive groups will be 1.5%.

The median HbA1c achieved in the intensive group and the difference between this value and the median HbA1c achieved in the standard group will be assessed for participants at each visit where a central lab HbA1c is obtained. Regular reports will be used to assess success in meeting these criteria for glycemic control. Other reports will track the number of oral agents that participants are taking and the number of participants on insulin, among other items. In accordance with motions passed by the ACCORD Steering Committee, all clinical sites within a CCN will be able to view summary reports (delta and success meeting the treatment goals) for other clinical sites within their own CCN, each CCN and ACCORD overall, but not summaries of site data from other Clinical Sites.

Lipid Control – Routine assessment of the fibrate intervention will be based on adherence. The target adherence rate to fibrate and any necessary statin is at least 80% as measured by simple self-report. The Lipid component of the ACCORD trial is blinded.

Unblinded adherence reports will be generated only for the Data Safety and Monitoring Committee and blinded reports will be generated for the ACCORD Steering Committee.

Blood Pressure Control -- The study target is 20 mm Hg difference between the two BP arms. Evidence suggests that a 10-12 mm Hg difference will produce a 20% effect on CVD events. The mean systolic blood pressure (SBP) achieved in the intensive therapy group and the difference between this value and the mean SBP achieved in the standard group will be assessed at each visit where the protocol requires a blood pressure measurement. Regular reports describing achieved blood pressure, mean number and types of medications prescribed, and compliance with the ACCORD protocol by recruitment cohort, treatment group and visit will be used to assess the success of the blood pressure intervention.

20.4 Interim Analsyes: Unblinded Analyses for the DSMB

The role and composition of the Data and Safety Monitoring Board are described in Section 13.8 of the ACCORD protocol. Reports to be provided to the DSMB to aid in their monitoring of ACCORD during the post-Vanguard phase are described in section 7.4.b of the ACCORD Protocol. These interim reports will be reviewed periodically by the Data and Safety Monitoring Board. Material for DSMB meetings will be distributed two weeks in advance of the meetings. The analyses will include data on recruitment, outcome measures, any side- or safety effects, adherence, and quality control, and will be designed in cooperation with the DSMB. Interim analyses of the intervention effectiveness will be performed at times coinciding with the meetings of the DSMB, and will be controlled to protect the overall Type I error of the trial. These results will be for the use of the DSMB and will not be revealed to the investigators. The purpose of these analyses will be for the DSMB to assess the trial progress with respect to intervention efficacy and safety, for possible recommendations regarding early termination of the entire trial or any individual intervention.

Interim analyses will be performed periodically for the Data and Safety Monitoring Board (DSMB). Records of hospitalizations and deaths will be available before final adjudication and classification by the Morbidity and Mortality Subcommittee, and these will be used for interim analyses of the primary outcome. A clear plan for how to terminate those arms found inferior will be developed with the input of the DSMB. Group sequential procedures, though they contribute critical information, will be considered as only one of several factors in the decision to stop or continue components of ACCORD.

20.5 Interim Analyses: Data Storage and Processing at the Coordinating Center

Every week the SQL database will be converted to SAS datasets. Backups of these databases will be saved off-line on magnetic tape. Analytical databases, used specifically for DSMB and Steering Committee reports will also be saved off-line on magnetic tape. All patient data sent to the Coordinating Center is encrypted and all databases are protected by passwords that must be supplied before the data can be accessed.

20.6 Final Reports

Upon study completion, after all clinic and laboratory data have been collected and filtered through the quality control routines, the SQL database will be converted to SAS datasets and certified. The database will be taken off-line and archived on magnetic tape and/or CD-ROM. The final SAS datasets will be certified and issued version numbers to synchronize analytic efforts and distributed in accordance with ACCORD Steering Committee and NHLBI policy. The choice of media on which to copy and distribute copies of the database to the investigators will depend upon the systems and media available at that point in time. Final data tapes and documentation will be sent to NHLBI. Final reports will be based on these final certified databases.

21. Procedures for Inactive Participants and Missed Visits

21.1 Procedures for Inactive Participants

All ACCORD participants are assigned to take part in two distinct clinical trials (i.e., each participant takes part in either the Glycemia and Blood Pressure trials, or the Glycemia and Lipid trials). For purposes of the study, we define the following terms related to trial participation status:

- **Active** status – an ACCORD participant is considered to be active in a given trial if his or her medication therapy for that trial is managed by the ACCORD study. In all cases, if the participant receives his/her medication for a given trial from the ACCORD study clinic, then the participant is active in that trial. There may be instances where an ACCORD physician is managing the participant's medications in accordance with the study protocol, but the participant is obtaining medications from a (non-ACCORD) pharmacy of his/her choosing; in such situations, the participant is considered to be active as well.
- **Inactive** status – an ACCORD participant is considered to be inactive in a particular trial if his or her medication therapy for that trial is no longer being managed by the study *and* he/she has not withdrawn consent for regular measurement (follow-up) visits or event monitoring is still being performed.

During the course of the study, some participants may become "inactive" in one or both of their ACCORD trials. For example, a participant in the Glycemia/Blood Pressure Trials may decide that he/she no longer wishes to participate in the Blood Pressure trial, but is willing to continue to have his/her glycemia management performed by the ACCORD study. In such a situation, that participant would be "active" in the Glycemia Trial but "inactive" in the Blood Pressure Trial. Participants also may withdraw from active participation in both of their assigned trials, but agree to be followed for events (and may even attend clinic visits every 2, 4 or 12 months). Such participants would be considered "inactive" for both of their trials.

A participant's active/inactive status will affect form completion. Obviously, when a participant is active in a particular trial, all of the forms related to the management of that trial should be completed according to the study protocol. Generally, once a participant becomes inactive in a given trial, the management information related to that trial is no longer collected; however, *participants who are inactive in the Glycemia Trial must continue to be monitored for hypoglycemic events*. Below is a brief summary of forms to complete when a participant is inactive in one or both trials.

- Glycemia Trial forms – complete parts I and II of the appropriate management form (i.e., **Intensive** or **Standard Glycemia Management**) at both the clinic and phone visits designated by the protocol. Intensive arm Glycemia Trial participants should also have parts I and II of the form administered at planned phone calls unless they refuse phone monitoring. An area is provided on both the **Intensive** and **Standard Glycemia Management** forms to document the participant's trial activity status. Do not complete the **Glycemia Medications Log**.

- Blood Pressure Trial forms – do not complete the **Intensive** or **Standard Blood Pressure Management** forms or **Blood Pressure Medications Log** for inactive BP Trial participants.
- Lipid Trial form – do not complete the **Lipid Medications Management Form** for inactive Lipid Trial participants. Note: in order for a participant to be inactive in the Lipid Trial, he/she must have discontinued use of *both* study simvastatin and blinded medications. If the participant has either of these medications provided by the ACCORD study, then he/she is still considered active in the Lipid Trial.
- Other forms – the **Interval History/Follow-up Form** and **Annual History and Physical Exam Form** should be completed (as extensively as possible) for all participants, regardless of trial activity status. Both forms have areas to document activity status for each trial and whether the form was administered by phone. Additionally, the **Encounter and Disposition Form** should be completed to document all protocol mandated clinic visits that were missed as a result of trial inactivity and/or non-compliance. Also use this form to document any forms and/or procedures expected but not performed for each planned clinic visit.

If an inactive participant is part of one or more sub-studies, then any forms related to those sub-studies should be administered according to protocol if possible. At the discretion of the clinic PI and study coordinator, inactive participants should be asked and encouraged at each encounter to resume active participation in the trial(s).

21.2 Procedures for Missed Visits

In ACCORD, post-randomization visit schedules are based on target months of contact as specified in the study Protocol (see Chapter2, Tables 2.2A-2.2F for a complete specification of the follow-up contact schedule by treatment arm and trial). By design, follow-up contact for all participants falls into one of the following three categories: (1) at least monthly for participants randomized to the *intensive* glycemia arm; (2) at least bi-monthly for participants randomized to the *standard* glycemia arm and *intensive* blood pressure arm; and (3) at least three times per year for participants randomized to the *standard* glycemia arm and either the *standard* blood pressure arm or the Lipid Trial. For purposes of visit classification, the follow-up periods under each of the three schemes are divided into continuous data windows. In order to encourage timely visit adherence, the study MOP specifies "target dates" and "target windows" which define recommended intervals in which follow-up contact should be accomplished. (See Tables 21.2-21.4 below for precise specification of target days, target windows, and data windows for each of the three aforementioned schemes).

In ACCORD, a **missed visit** (or **missed phone contact**) occurs when a given data window lapses without the planned contact having occurred. When a clinic visit has been missed, it should be documented as such by completing an ***Encounter and Disposition Form***. The visit is specified as missed by responding "No" to question 2 in the "Scheduled Clinic Visit" area ("Was this visit completed as planned?"), "No" to the inner question ("Was partial information collected?"), and then specifying the reason that the visit was missed. For *intensive* arm glycemia participants, a missed phone visit should be documented by completing Part I (Contact Type) of the ***Intensive***

Glycemia Management Form, responding "No" to the third sub-question ("Was the contact completed as planned?"), and then specifying the reason that the call was missed.

Generally, once a visit has been missed (i.e., the data window has lapsed without data collection) it cannot be retroactively made up. However, some items and procedures should be collected late for certain "key" follow-up visits. **Key** follow-up visits are those visits where events ascertainment is performed or central laboratory measurements are collected. Table 21.1 below summarizes the visit types and actions to be taken if missed.

In order to complete documentation of data collected late for a visit that was missed on the ***Encounter and Disposition Form***, one should indicate "Yes" for question 1 ("Was information collected during this visit for a previously missed visit?") in the "Scheduled Clinic Visit" area, and specify the code of the missed visit in the area provided. This procedure applies to phone visits that are performed in clinic because the participant missed an earlier clinic visit.

Table 21.1 Action for Missed Visits, by Follow-up Schedule

Trial and Treatment Category	Visit Code(s)	'Key' Visit	Missed Visit Action
Intensive Glycemia	F04.0, F08.0, F12.0,... [every 4 months]	Yes	Document visit as "missed" on ***Encounter/Disposition Form***. Bring participant to clinic as soon as possible *up to 2 weeks prior* to target window for next scheduled clinic visit (i.e., perform a clinic visit for what would ordinarily be a phone contact); otherwise, collect "key" information at next scheduled clinic visit. To collect "key" information, administer ***Interval History and Follow-up Form*** (or ***Annual History and Physical Exam Form*** if annual visit was missed). Collect appropriate outcome information if an outcome event has occurred. Collect blood specimens and perform ECG if specified for missed visit (see Protocol Tables 2.2A-2.2F). Administer ***Intensive Glycemia Management Form*** (and accompanying med log) as usual. If participant is in one or more substudies, administer associated forms if appropriate for the missed visit. If the participant is in the BP Trial and missed visit data are collected late by substituting a clinic visit for regular phone contact, inquire about possible medication changes and complete a PRN ***BP Medications Log*** if necessary. If participant is in Lipid Trial, administer PRN ***Lipid Medications Management Form***.

(Table continued on following page.)

Table 21.1 Action for Missed Visits, by Follow-up Schedule (continued)

Trial and Treatment Category	Visit Code(s)	'Key' Visit	Missed Visit Action
Intensive Glycemia	F00.5, F01.5, F02.5, F03.5, F05.0, F07.0,… [all phone contacts]	No	Document visit as "missed" on Part I of the ***Intensive Glycemia Management Form***. Contact participant by phone before next scheduled clinic visit if possible. Administer PRN ***Intensive Glycemia Management Form*** (and accompanying med log) if necessary to document med change or hypoglycemic event.
Standard Glycemia and *Intensive* BP	F04.0, F08.0, F12.0,… [every 4 months]	Yes	Document visit as "missed" on ***Encounter/Disposition Form***. Bring participant to clinic as soon as possible *up to 2 weeks prior* to target window for next scheduled visit; otherwise, collect "key" information at next scheduled clinic visit. To collect "key" information, administer ***Interval History and Follow-up Form*** (or ***Annual History and Physical Exam Form*** if annual visit was missed). Collect appropriate outcome information if an outcome event has occurred. Collect blood specimens and perform ECG if specified for missed visit (see Protocol Tables 2.2A-2.2F). If participant is in substudy, administer associated forms if appropriate for that visit. Administer PRN ***Standard Glycemia Management Form*** and ***Intensive BP Management Form***, and document any glycemia or BP medications changes on medications logs if necessary. If indicated, complete ***Milepost Blood Pressure Exception Form***.
Standard Glycemia and *Intensive* BP	F01.0, F02.0, F03.0, F06.0, F08.0, F10.0, F14.0, F16.0,…	No	Document visit as "missed" on ***Encounter/Disposition Form***. Bring participant to clinic as soon as possible *up to 2 weeks prior* to target window for next scheduled visit; otherwise, bring in during target window for next scheduled visit. Administer PRN ***Intensive BP Management Form*** (and accompanying med log) if necessary to document a needed med change.

(Table continued on following page.)

Table 21.1 Action for Missed Visits, by Follow-up Schedule (continued)

Trial and Treatment Category	Visit Code(s)	'Key' Visit	Missed Visit Action
Standard Glycemia and *Standard* BP or Lipid Trial	F04.0, F08.0, F12.0,… [every 4 months]	Yes	Document visit as "missed" on ***Encounter/Disposition Form***. Bring participant to clinic as soon as possible *up to 2 weeks prior* to target window for next scheduled visit; otherwise, bring in during target window for next scheduled visit. If participant is brought in before next visit target window, collect "key' information by administering ***Interval History and Follow-up Form*** (or ***Annual History and Physical Exam Form*** if annual visit was missed). Collect appropriate outcome information if an outcome event has occurred. Collect blood specimens and perform ECG if specified for missed visit (see Protocol Tables 2.2A-2.2F). If participant is in substudy, administer associated forms if appropriate for that visit. **Note**: all "key" information collected should be entered on the web under the visit code of the visit that was missed. The participant should still be brought back to the clinic during the target window for his next regularly scheduled visit. Complete PRN ***Standard Glycemia Management Form*** (and accompanying med log). If participant is in BP Trial, complete PRN ***Standard BP Medications*** (and accompanying med log). If participant is in Lipid Trial, complete PRN ***Lipid Medications Management Form***.

21.3 Follow-up Window Definitions

Distinct visit patterns are defined by the following three treatment/trial assignments: (1) intensive arm Glycemia Trial assignment (regardless of Blood Pressure or Lipid trial assignment); (2) standard arm Glycemia Trial assignment and intensive arm Blood Pressure Trial assignment; or (3) standard arm Glycemia Trial assignment and either standard Blood Pressure Trial assignment or assignment to the Lipid Trial (both treatment arms). Tables 21.2-21.4 below specify the visit codes, target month and day of follow-up, lower and upper target windows, and lower and upper data windows for each of the three assignment scenarios. Target windows define the *recommended* time interval in which a visit should occur. Data windows define the interval in which a visit *must* occur in order to avoid being missed. These tables are used to generate the participant-specific visit schedules that can be viewed in the ACCORD web data entry area.

Table 21.2 Intensive Glycemia Follow-up Windows

Visit Code	Target Month	Target Days	Target Lower	Target Upper	Lower Data Window	Upper Data Window	Visit Type
F00.5	0.5	15	8	22	7	22	PHONE
F01.0	1	30	23	37	23	38	CLINIC
F01.5	1.5	46	39	53	39	53	PHONE
F02.0	2	61	54	68	54	68	CLINIC
F02.5	2.5	76	69	83	69	83	PHONE
F03.0	3	91	84	98	84	99	CLINIC
F03.5	3.5	107	100	114	100	114	PHONE
F04.0	4	122	115	129	115	137	CLINIC
F05.0	5	152	145	159	138	167	PHONE
F06.0	6	183	169	197	168	198	CLINIC
F07.0	7	213	206	220	199	228	PHONE
F08.0	8	244	230	258	229	259	CLINIC
F09.0	9	274	267	281	260	289	PHONE
F10.0	10	304	290	318	290	319	CLINIC
F11.0	11	335	328	342	320	350	PHONE
F12.0	12	365	351	380	351	380	CLINIC
F13.0	13	396	389	403	381	411	PHONE
F14.0	14	426	412	440	412	441	CLINIC
F15.0	15	457	450	464	442	472	PHONE
F16.0	16	487	473	501	473	502	CLINIC
F17.0	17	517	510	524	503	532	PHONE
F18.0	18	548	534	562	533	563	CLINIC
F19.0	19	578	571	585	564	593	PHONE
F20.0	20	609	595	623	594	624	CLINIC
F21.0	21	639	632	646	625	654	PHONE
F22.0	22	670	656	684	655	685	CLINIC
F23.0	23	700	693	707	686	715	PHONE
F24.0	24	731	716	746	716	746	CLINIC
F25.0	25	761	754	768	747	776	PHONE
F26.0	26	791	777	805	777	806	CLINIC
F27.0	27	822	815	829	807	837	PHONE
F28.0	28	852	838	866	838	867	CLINIC
F29.0	29	883	876	890	868	898	PHONE
F30.0	30	913	899	927	899	928	CLINIC
F31.0	31	944	937	951	929	959	PHONE
F32.0	32	974	960	988	960	989	CLINIC
F33.0	33	1004	997	1011	990	1019	PHONE
F34.0	34	1035	1021	1049	1020	1050	CLINIC
F35.0	35	1065	1058	1072	1051	1080	PHONE
F36.0	36	1096	1081	1111	1081	1111	CLINIC
F37.0	37	1126	1119	1133	1112	1141	PHONE
F38.0	38	1157	1143	1171	1142	1172	CLINIC
F39.0	39	1187	1180	1194	1173	1202	PHONE
F40.0	40	1218	1204	1232	1203	1233	CLINIC
F41.0	41	1248	1241	1255	1234	1263	PHONE
F42.0	42	1278	1264	1292	1264	1293	CLINIC

Table 21.2 Intensive Glycemia Follow-up Windows (continued)

Visit Code	Target Month	Target Days	Target Lower	Target Upper	Lower Data Window	Upper Data Window	Visit Type
F43.0	43	1309	1302	1316	1294	1324	PHONE
F44.0	44	1339	1325	1353	1325	1354	CLINIC
F45.0	45	1370	1363	1377	1355	1385	PHONE
F46.0	46	1400	1386	1414	1386	1415	CLINIC
F47.0	47	1431	1424	1438	1416	1446	PHONE
F48.0	48	1461	1447	1476	1447	1476	CLINIC
F49.0	49	1491	1484	1498	1477	1506	PHONE
F50.0	50	1522	1508	1536	1507	1537	CLINIC
F51.0	51	1552	1545	1559	1538	1567	PHONE
F52.0	52	1583	1569	1597	1568	1598	CLINIC
F53.0	53	1613	1606	1620	1599	1628	PHONE
F54.0	54	1644	1630	1658	1629	1659	CLINIC
F55.0	55	1674	1667	1681	1660	1689	PHONE
F56.0	56	1705	1691	1719	1690	1720	CLINIC
F57.0	57	1735	1728	1742	1721	1750	PHONE
F58.0	58	1765	1751	1779	1751	1780	CLINIC
F59.0	59	1796	1789	1803	1781	1811	PHONE
F60.0	60	1826	1812	1841	1812	1841	CLINIC
F61.0	61	1857	1850	1864	1842	1872	PHONE
F62.0	62	1887	1873	1901	1873	1902	CLINIC
F63.0	63	1918	1911	1925	1903	1933	PHONE
F64.0	64	1948	1934	1962	1934	1963	CLINIC
F65.0	65	1978	1971	1985	1964	1993	PHONE
F66.0	66	2009	1995	2023	1994	2024	CLINIC
F67.0	67	2039	2032	2046	2025	2054	PHONE
F68.0	68	2070	2056	2084	2055	2085	CLINIC
F69.0	69	2100	2093	2107	2086	2115	PHONE
F70.0	70	2131	2117	2145	2116	2146	CLINIC
F71.0	71	2161	2154	2168	2147	2176	PHONE
F72.0	72	2192	2177	2207	2177	2207	CLINIC
F73.0	73	2222	2215	2229	2208	2237	PHONE
F74.0	74	2252	2238	2266	2238	2267	CLINIC
F75.0	75	2283	2276	2290	2268	2298	PHONE
F76.0	76	2313	2299	2327	2299	2328	CLINIC
F77.0	77	2344	2337	2351	2329	2359	PHONE
F78.0	78	2374	2360	2388	2360	2389	CLINIC
F79.0	79	2405	2398	2412	2390	2420	PHONE
F80.0	80	2435	2421	2449	2421	2450	CLINIC
F81.0	81	2465	2458	2472	2451	2480	PHONE
F82.0	82	2496	2482	2510	2481	2511	CLINIC
F83.0	83	2526	2519	2533	2512	2541	PHONE
F84.0	84	2557	2542	2572	2542	2572	CLINIC
F85.0	85	2587	2580	2594	2573	2602	PHONE
F86.0	86	2618	2604	2632	2603	2633	CLINIC
F87.0	87	2648	2641	2655	2634	2663	PHONE
F88.0	88	2679	2665	2693	2664	2694	CLINIC

Table 21.2 Intensive Glycemia Follow-up Windows (continued)

Visit Code	Target Month	Target Days	Target Lower	Target Upper	Lower Data Window	Upper Data Window	Visit Type
F89.0	89	2709	2702	2716	2695	2724	PHONE
F90.0	90	2739	2725	2753	2725	2754	CLINIC
F91.0	91	2770	2763	2777	2755	2785	PHONE
F92.0	92	2800	2786	2814	2786	2815	CLINIC
F93.0	93	2831	2824	2838	2816	2846	PHONE
F94.0	94	2861	2847	2875	2847	2876	CLINIC
F95.0	95	2892	2885	2899	2877	2907	PHONE
F96.0	96	2922	2908	2929	2908	2937	CLINIC
F97.0/EXIT*	97	2952	2945	2959	2938	2967	PHONE
F98.0/EXIT*	98	2983	2969	2997	2968	2998	CLINIC
F99.0/EXIT*	99	3013	3006	3020	2999	3028	PHONE
F100/EXIT*	100	3044	3030	3058	3029	3059	CLINIC
F101/EXIT*	101	3074	3067	3081	3060	3089	PHONE
F102/EXIT*	102	3105	3090	3135	3090	3135	CLINIC

Visit Code: the follow-up visit code descriptor.

Target Month: the target month of follow-up as specified in the study Protocol (see Chapter 2, Tables 2.2A-2.2F).

Target Days: the target number of days post-randomization used to determine the target date of follow-up for the current visit. This number is used by the web-based visit scheduler to compute and display target follow-up dates. In general,

Target Days = round(**Target Month***30.4375)

Target Lower and **Target Upper**: the target lower and upper windows for the current visit. These define the earliest and latest "recommended" dates that the participant should be brought to the clinic (or called) to administer the current visit. In the *intensive* glycemia arm, Target Lower and Target Upper are computed as:

Target Days +/- 7 for phone contacts;

Target Days +/- 14 for clinic visits other than the annual visit;

Same as **Lower Data Window** and **Upper Data Window** for annual clinic visits (typically TargetDays-15).

Lower Data Window and **Upper Data Window**: the lower and upper data windows for the current visit. These define the interval in which data can be collected and still be classified as part of the specified visit. Lower and upper windows are calculated by equal bisection of the interval between two **Target Days**, and are always continuous.

Visit Type: the type of visit (clinic or phone contact), as specified by the study Protocol.

***Note**: more than one visit has been designated as "EXIT" since study close out will occur over a six month time frame. The individualized participant schedules will designate the proper "EXIT" visit.

Table 21.3 Standard Glycemia/Intensive Blood Pressure Follow-up Windows

Visit Code	Target Month	Target Days	Target Lower	Target Upper	Lower Data Window	Upper Data Window	Visit Type
F01.0	1	30	16	44	15	45	CLINIC
F02.0	2	61	47	75	46	76	CLINIC
F03.0	3	91	77	105	77	106	CLINIC
F04.0	4	122	108	136	107	152	CLINIC
F06.0	6	183	169	197	153	213	CLINIC
F08.0	8	244	230	258	214	274	CLINIC
F10.0	10	304	290	318	275	334	CLINIC
F12.0	12	365	335	395	335	395	CLINIC
F14.0	14	426	412	440	396	456	CLINIC
F16.0	16	487	473	501	457	517	CLINIC
F18.0	18	548	534	562	518	578	CLINIC
F20.0	20	609	595	623	579	639	CLINIC
F22.0	22	670	656	684	640	700	CLINIC
F24.0	24	731	701	761	701	761	CLINIC
F26.0	26	791	777	805	762	821	CLINIC
F28.0	28	852	838	866	822	882	CLINIC
F30.0	30	913	899	927	883	943	CLINIC
F32.0	32	974	960	988	944	1004	CLINIC
F34.0	34	1035	1021	1049	1005	1065	CLINIC
F36.0	36	1096	1066	1126	1066	1126	CLINIC
F38.0	38	1157	1143	1171	1127	1187	CLINIC
F40.0	40	1218	1204	1232	1188	1248	CLINIC
F42.0	42	1278	1264	1292	1249	1308	CLINIC
F44.0	44	1339	1325	1353	1309	1369	CLINIC
F46.0	46	1400	1386	1414	1370	1430	CLINIC
F48.0	48	1461	1431	1491	1431	1491	CLINIC
F50.0	50	1522	1508	1536	1492	1552	CLINIC
F52.0	52	1583	1569	1597	1553	1613	CLINIC
F54.0	54	1644	1630	1658	1614	1674	CLINIC
F56.0	56	1705	1691	1719	1675	1735	CLINIC
F58.0	58	1765	1751	1779	1736	1795	CLINIC
F60.0	60	1826	1796	1856	1796	1856	CLINIC
F62.0	62	1887	1873	1901	1857	1917	CLINIC
F64.0	64	1948	1934	1962	1918	1978	CLINIC
F66.0	66	2009	1995	2023	1979	2039	CLINIC
F68.0	68	2070	2056	2084	2040	2100	CLINIC
F70.0	70	2131	2117	2145	2101	2161	CLINIC
F72.0	72	2192	2162	2222	2162	2222	CLINIC
F74.0	74	2252	2238	2266	2223	2282	CLINIC
F76.0	76	2313	2299	2327	2283	2343	CLINIC
F78.0	78	2374	2360	2388	2344	2404	CLINIC
F80.0	80	2435	2421	2449	2405	2465	CLINIC
F82.0	82	2496	2482	2510	2466	2526	CLINIC
F84.0	84	2557	2527	2587	2527	2587	CLINIC
F86.0	86	2618	2604	2632	2588	2648	CLINIC
F88.0	88	2679	2665	2693	2649	2709	CLINIC

Table 21.3 Standard Glycemia/Intensive Blood Pressure Follow-up Windows (continued)

Visit Code	Target Month	Target Days	Target Lower	Target Upper	Lower Data Window	Upper Data Window	Visit Type
F90.0	90	2739	2725	2753	2710	2769	CLINIC
F92.0	92	2800	2786	2814	2770	2830	CLINIC
F94.0	94	2861	2847	2875	2831	2891	CLINIC
F96.0	96	2922	2892	2952	2892	2952	CLINIC
F98.0/EXIT*	98	2983	2969	2997	2953	3013	CLINIC
F100/EXIT*	100	3044	3030	3058	3014	3074	CLINIC
F102/EXIT*	102	3105	3075	3135	3075	3135	CLINIC

Visit Code: the follow-up visit code descriptor.

Target Month: the target month of follow-up as specified in the study Protocol (see Chapter 2, Tables 2.2A-2.2F).

Target Days: the target number of days post-randomization used to determine the target date of follow-up for the current visit. This number is used by the web-based visit scheduler to compute and display target follow-up dates. In general,

Target Days = round(**Target Month***30.4375)

Target Lower and **Target Upper**: the target lower and upper windows for the current visit. These define the earliest and latest "recommended" dates that the participant should be brought to the clinic (or called) to administer the current visit. In the standard glycemia/intensive blood pressure arm, Target Lower and Target Upper are computed as:

Target Days +/- 14 for clinic visits other than the annual visit;

Target Days +/- 30 for annual clinic visits.

Lower Data Window and **Upper Data Window**: the lower and upper data windows for the current visit. These define the interval in which data can be collected and still be classified as part of the specified visit. Lower and upper windows are calculated by equal bisection of the interval between two **Target Days**, and are always continuous.

Visit Type: the type of visit (clinic or phone contact), as specified by the study Protocol.

***Note**: more than one visit has been designated as "EXIT" since study close out will occur over a six month time frame. The individualized participant schedules will designate the proper "EXIT" visit.

Table 21.4 Standard Glycemia/Standard Blood Pressure or Lipid Trial Follow-up Windows

Visit Code	Target Month	Target Days	Target Lower	Target Upper	Lower Data Window	Upper Data Window	Visit Type
F01.0	1	30	16	44	15	76	CLINIC
F04.0	4	122	108	136	77	183	CLINIC
F08.0	8	244	230	258	184	304	CLINIC
F12.0	12	365	335	395	305	426	CLINIC
F16.0	16	487	473	501	427	548	CLINIC
F20.0	20	609	595	623	549	670	CLINIC
F24.0	24	731	701	761	671	791	CLINIC
F28.0	28	852	838	866	792	913	CLINIC
F32.0	32	974	960	988	914	1035	CLINIC
F36.0	36	1096	1066	1126	1036	1157	CLINIC
F40.0	40	1218	1204	1232	1158	1278	CLINIC
F44.0	44	1339	1325	1353	1279	1400	CLINIC
F48.0	48	1461	1431	1491	1401	1522	CLINIC
F52.0	52	1583	1569	1597	1523	1644	CLINIC
F56.0	56	1705	1691	1719	1645	1765	CLINIC
F60.0	60	1826	1796	1856	1766	1887	CLINIC
F64.0	64	1948	1934	1962	1888	2009	CLINIC
F68.0	68	2070	2056	2084	2010	2131	CLINIC
F72.0	72	2192	2162	2222	2132	2252	CLINIC
F76.0	76	2313	2299	2327	2253	2374	CLINIC
F80.0	80	2435	2421	2449	2375	2496	CLINIC
F84.0	84	2557	2527	2587	2497	2618	CLINIC
F88.0	88	2679	2665	2693	2619	2739	CLINIC
F92.0	92	2800	2786	2814	2740	2861	CLINIC
F96.0	96	2922	2892	2952	2862	2983	CLINIC
F100/EXIT*	100	3044	3030	3058	2984	3105	CLINIC
F104/EXIT*	104	3166	3136	3196	3106	3196	CLINIC

Visit Code: the follow-up visit code descriptor.

Target Month: the target month of follow-up as specified in the study Protocol (see Chapter 2, Tables 2.2A-2.2F).

Target Days: the target number of days post-randomization used to determine the target date of follow-up for the current visit. This number is used by the web-based visit scheduler to compute and display target follow-up dates. In general,

Target Days = round(**Target Month***30.4375)

Target Lower and **Target Upper**: the target lower and upper windows for the current visit. These define the earliest and latest "recommended" dates that the participant should be brought to the clinic (or called) to administer the current visit. In the standard glycemia/intensive blood pressure arm, Target Lower and Target Upper are computed as:

Target Days +/- 14 for clinic visits other than the annual visit;

Target Days +/- 30 for annual clinic visits.

Lower Window and **Upper Window**: the lower and upper data windows for the current visit. These define the interval in which data can be collected and still be classified as part of the specified visit. Lower and upper windows are calculated by equal bisection of the interval between two **Target Days**, and are always continuous.

Visit Type: the type of visit (clinic or phone contact), as specified by the study Protocol.

***Note**: more than one visit has been designated as "EXIT" since study close out will occur over a six month time frame. The individualized participant schedules will designate the proper "EXIT" visit.

APPENDIX A.1
Instructions for Accessing the ACCORD Web Site

All Clinical Center Networks (CCN) and Clinical Sites have access to trial-related information via the World Wide Web (WWW). A web site specifically dedicated to the ACCORD trial is located on the WWW at http://www.accordtrial.org. Once this site is accessed, the trial logo appears. After the user clicks on the logo several links appear. The viewer may either log in to the web site if he/she has a valid ACCORD username and password, or click on each of the links to view the following information:

- What is ACCORD? – contains a patient information guide explaining the ACCORD Study
- Study Purpose link – contains the ACCORD Protocol Abstract
- Study Funding Link – contains the ACCORD sponsor, collaborators, and acknowledges the contributions of companies
- Key Personnel Link – list the ACCORD key study personnel
- Conflict of Interest link – contains the ACCORD Conflict of Interest Policy
- Submit A Substudy link – contains information on how to submit an ancillary study
- Eye Substudy Info – contains information on the ACCORD Eye Substudy
- MIND Substudy Info – contains information on the ACCORD MIND Substudy
- Password Reminder – contains an area where a person can provide an email address to receive an email notification if a password is forgotten (for valid ACCORD account users)
- ACCORD Key Slides – contains key slides describing the ACCORD Study
- Suggestion Box – a place where people can write in suggestions or comments
- Find out if you Qualify – contains a brief screening form to see if a person qualifies
- A Map of the USA and Canada – allows the user to find an ACCORD clinical site closest to him/her

The Coordinating Center provides all participating CCN and Clinical Site personnel with user names and passwords to login to the web site. In order to login to the site, the user must type in their user name and password, and click on the "Login" button. Once the user name and password are accepted, the user is navigated to the "Home Page" screen which contains information on the ACCORD Central Units Holidays for 2005 and links to the Data Confidentiality Statement and Screening and Randomization reports.

Other links that are available are the:

- Sitemap Link
- Directory Link
- Committees Link
- Documents Link
- Reports Link
- Clinical Link
- FAQ Link
- Logout Link

The "Directory" link at the top of the page contains the following links:

- Alphabetical listing – contains an alphabetical listing of staff participating in the trial. There are two ways for the user to obtain contact information for a particular individual. The user can click on the desired name or click on the site number. Either method will provide the user with contact information for a specific individual. The user can also click on the e-mail address provided in this link to send an electronic message to the specified individual.
- Study Administration, Sponsoring agencies and Central Units– contains links to the ACCORD Coordinating Center, NHLBI, NIDDK, NEI, Chemlab, ECG, DDC, Abbott, Abbott Canada, NetGroup, Omron, Consultants, EYE, Fundus Photograph Reading Center, MIND, and MRI Learning Center. Once a study administration group is selected, the user can view the list of individuals associated with that group. The user can click on an individual name to view contact information for the selected person. The user can also click on the e-mail address provided in this link to send an electronic message to the specified individual.
- Clinical Center Networks by number – provides links to all CCNs. Once a particular CCN is selected, the user can view a list of CCN staff. The user can click on a particular name to view contact information for the selected individual. The user can also click on the e-mail address provided in this link to send an electronic message to the specified individual.
- Clinical Sites – provides links to all Clinical Center Sites. Once a clinical site is chosen, a list of site staff appears. An individual name may be selected to view contact information for the particular individual. The user can also click on the e-mail address provided in this link to send an electronic message to the specified individual.
- Site Contact Information – contains a table with a list of contact information for all the CCNs and sites
- Email Groups – contains information on directions on how to email groups of people

Other links on the sitemap are:

- Committees – contains links to Scheduled Conference Calls, a Subcommittee /Working Group list, and links to all Subcommittee and Working Group's members, minutes and documents. Selection of a particular committee member name displays the contact information for the specified person. The user can also click on the e-mail address provided in this link to send an electronic message to the specified individual.
- Documents – contains links to all Reference Documents (i.e., Post Vanguard Protocol, MOP), slide shows, training, Survival Kit, Drug Distribution Center information, Informed Consent, Conflict of Interest information, Ancillary Study proposal information, Ancillary Documents for ACCORD MIND, Ancillary Documents for ACCORD Eye, Order Forms, Computer Information and Miscellaneous items.
- Reports – contains links to relevant reports on downloadable formats.
- Clinical – contains links to the Visit Tickler, web based data entry and data edits.

- FAQs – contains links to Weekly Updates, questions related to the 3 interventions, Glycemia management tips, and Contact information for equipment in the US and Canada

Once the user is finished viewing the web site, the user may click on the "Log out" link. The user may then close out of the site.

The web site will be continually updated to include capabilities for remote data entry, training materials for measurement and data entry personnel, as well as site-specific reports relating to patient demographics and recruitment goals. All reports will be available on downloadable formats.

APPENDIX A.2
Action to Control Cardiovascular Risk in Diabetes Trial
Publications and Presentations Policy

Table of Contents

I. Introduction and Definitions

Description of the Action to Control Cardiovascular Risk in Diabetes Trial

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is a landmark clinical trial whose objective is to study the effect of the treatment of blood glucose, blood pressure, and lipid alterations on cardiovascular morbidity and mortality in patients with type 2 diabetes mellitus (DM). This study is sponsored by the National Institutes of Health (NHLBI, NIDDK, NEI) and aims at recruiting 10,000 patients with type 2 DM who will be randomized to receive different levels of therapeutic intervention for treatment of their blood sugar, blood pressure, and lipid alterations over a minimum of 4 years

Roles of the Publications and Presentations Subcommittee

The Publications and Presentations (P&P) Subcommittee of the ACCORD trial is one of the subcommittees of the ACCORD organization whose missions are:

- To adopt the policies and procedures by which ACCORD investigators will conduct analyses, write manuscripts, and make presentations.
- To stimulate scientific presentations and papers from ACCORD investigators and to assure that abstracts, presentations, and publications of ACCORD materials are accurate and objective, and do not compromise the scientific integrity of this collaborative study.
- To approve manuscripts and presentations, to assign writing group members, and to monitor the progress of all proposed manuscripts to ensure their prompt completion and publication.
- To establish procedures that allow the ACCORD Steering Committee and the NHLBI to exercise review responsibility in a timely fashion for ACCORD publications and presentations.
- To assure and expedite orderly and timely presentations to the scientific community of all pertinent data resulting from ACCORD.
- To maintain a complete up-to-date list of ACCORD presentations and publications, and to distribute such lists to all ACCORD investigators at the Semi-annual ACCORD Steering Committee Meetings.
- To assure that membership in writing committees for ACCORD papers will serve as an opportunity to participate in formulating plans for analysis and the writing of manuscripts by active participation in the preparation of the respective paper.
- To assure that all investigators, particularly those of junior rank, have the opportunity to participate and be recognized in the study-wide ACCORD papers. For publications, presentations, and ancillary studies, it is essential that equal opportunity exist for all investigators of ACCORD to participate. Involvement shall be open equally to all investigators of all Clinical Center Networks, including the clinical sites, the Coordinating Center, and the Program Office. All of these units shall have equal status with regard to developing protocols, participating in such studies as approved by the P&P and the SC, and collaborating in the development and publication of research papers and abstracts based upon the ACCORD data.

- To review ancillary studies and make a recommendation to the Steering Committee regarding the proposals.

Overview of Characteristics of ACCORD Manuscripts/Presentations

It is anticipated that a wide variety of manuscripts/presentations will be developed from ACCORD. Manuscripts/presentations from the ACCORD study will be concerned with the design of the ACCORD study, the description of the ACCORD population at baseline, descriptions of treatment effects on the major endpoints, and reports of findings related to secondary endpoints, sub-studies, and ancillary studies. Authors will be encouraged to use data collected at all Clinical Sites when the hypothesis of interest can be addressed using such data. When the hypothesis of interest can be addressed only through use of a subset of data collected specifically at a limited number of Clinical Sites, it may be acceptable to perform analyses using data from a subset of Clinical Sites. ACCORD manuscripts will fall into three possible categories relative to policy for authorship. These categories are:

I. Category I manuscripts will include the main design paper, the primary outcome paper and important secondary outcome papers. The author will be the "ACCORD Study Group". Writing team members will be listed on the title page, only if the journal preferred for publication absolutely requires it. The entire Roster of ACCORD investigators will be listed in an appendix in the back of the manuscript.

II. Category II manuscripts will include databank papers which include all subjects and all sites or substudy papers which include some sites and subjects. The authors will be A, B, C, D, etc. for the ACCORD Study Group.

III. Category III manuscripts will include ancillary study papers. In addition to listing the individual investigators both inside and outside the ACCORD Study Group as authors, the P & P committee will reserve the option of requiring that the "ACCORD Study Group" itself be named as an author. This policy shall be made known to prospective ancillary study investigators prior to approval of an ancillary study.

Definition of an Ancillary Study

An ancillary study is an investigation that is not part of the ACCORD protocol but uses ACCORD participants, samples, or data collected by ACCORD. In most cases, an ancillary study will involve acquisition of additional data that are not compiled as part of the standard ACCORD data set.

Data Storage and Analysis

The Coordinating Center will be responsible for the collection, storage, and analysis of all collaborative ACCORD study data. In addition, analyses of the databank and sub-studies will be performed by the Coordinating Center. In two circumstances,

distributed data analysis may be determined to be necessary by the P&P and Steering Committee. These situations are when

- proposed analyses require special expertise that does not exist at the Coordinating Center, or
- priorities for analyses of other manuscripts make it unlikely that a particular analysis will be completed by the Coordinating Center within a reasonable time period.

In both of these situations, verification of final distributed analyses will be performed at the Coordinating Center. In the case of ancillary studies, the Coordinating Center will review the data analyses of manuscripts using the ACCORD database.

II. Publication of ACCORD Data

The publication process of an ACCORD manuscript starts with the submission of a manuscript proposal.

Formulation of the ACCORD Manuscript Proposal

The manuscript proposal should consist of the following:

- Manuscript title
- Initiating investigator name and center, including contact information
- Important key words
- Introduction/background
- Hypothesis
- Analysis Plan (including specific variables required) and Methods Section
- Summary/Conclusion Section
- References
- Proposed timeline

The completed manuscript proposal shall be submitted to the Presentation and Publications (P&P) Subcommittee for review.

The manuscript will be reviewed by the P&P Subcommittee:

- to ascertain that the formal manuscript proposal format has been followed.
- to determine that a clear and accurate analysis plan is included in the proposal.
- to determine if there is overlap between the proposed manuscript and any other papers that have been proposed or are in progress. In such cases the investigator will be encouraged to collaborate on the existing proposal/manuscript.

Upon approval by the P&P Subcommittee the manuscript proposal shall be given a manuscript number and entered in the Manuscript Schedule Matrix. The manuscript description shall also be entered into the Description of ACCORD Manuscripts Document (report).

The Manuscript Proposal shall be submitted to the ACCORD Steering Committee for review and Writing Group nominations. This review process should take no more

than 4 weeks. After the approval of a manuscript proposal, the Manuscript Proposal will be appropriately modified and will be made available to all PI's as a record of ongoing projects and maintained as part of the ACCORD Web Site.

Selection of Writing Group Members

Nomination of additional Writing Group members to the list of submitted names present on a proposal is the responsibility of the ACCORD Steering Committee. The P&P Subcommittee will review the nominees to ascertain:

- whether any investigator able to significantly enhance the Writing Group was omitted.
- if each potential member to ACCORD writing projects is committed to full participation in the Writing Group.

Each CCN that collects or processes the data used in a paper, and each unit represented on the Steering Committee may nominate a representative on the Writing Group. The PI shall decide whether his/her CCN will participate. A second author from the same CCN may be added on manuscripts where necessary to take advantage of unique expertise and the amount of work performed on behalf of ACCORD. The PI from that CCN must write to the P&P requesting the addition of second author and justifying the addition.

Based on the nominations received from the CCN PIs, the Publications Committee will select a Writing Group and Chairperson for each manuscript. Generally the Writing group will consist of at least five members.

After approval, the list of the Writing Group will be entered in the Manuscript Proposal (report). The Chairperson will also be informed via a memo listing all the Writing Group members with a copy to the PI of the center as well.

When a start date has been determined the Chairperson of each Writing Group will be notified of the start date and his/her responsibilities by the Chair of the P&P Subcommittee. The Writing Group Chairperson should contact each member of the Writing Group to develop an initial planning outline of the paper, the data request, and assignment for writing different segments of the paper.

Responsibilities of Writing Group Members

The Writing Group Chairperson is responsible for all phases of manuscript preparation, from conception through publication. Responsibilities include:

- preparation of outlines, the *identification* of data analyses needed from the Coordinating Center, interim status reports and their submission to the P&P Subcommittee.
- assignment of tasks to Writing Group members, *specification of* clear deadlines for completion of these tasks, *and ascertainment* that the tasks are completed on schedule.

- confirmation that the manuscript has approval of the Writing Group before submission of its Penultimate Draft to the P&P Subcommittee.
- determination of the order of authorship on the manuscript. A major criterion for this determination shall be the effort and contribution made by the members of the Writing Group in preparation of the manuscript. Disagreement about the order of authors, which cannot be resolved by the Chair of the Writing Group, will be resolved by the Publications and Presentations Subcommittee, with the Steering Committee as the final arbitrator.
- recommendation of a journal to which the manuscript should be submitted.
- correspondence with co-authors, communication with the Coordinating Center and the P&P Subcommittee, responses to the NHLBI review, and to journal editors.

Members of the Writing Group are responsible for performance of tasks assigned by the Chairperson within the allotted time period. Each member is expected to actively participate in the preparation of the manuscript. If a Writing Group member does not accomplish the tasks assigned to him/her and has not contributed to the manuscript, he/she can be removed from the Writing Group. The Chairman of the Writing Group must send a letter to the Chairman of the P&P Subcommittee requesting the removal *of* a particular Writing Group member.

Selection of the journal for initial submission of the manuscript is delegated to the Writing Group, with input from the P&P Subcommittee and the Steering Committee.

Authority to Modify Writing Groups

The P&P Subcommittee may change the composition of the Writing Groups that have failed to produce the required manuscript according to the schedule originally agreed upon by the Group and the P&P Subcommittee. When a delay develops, the Chairperson of the Writing Group will be notified by the Chairperson of the P&P Subcommittee. A decision to remove or reassign the responsibility of Writing Group members will be made by the P&P Subcommittee. A decision to disband a Writing Group will be made by the P&P Subcommittee. These decisions will be reported to the Steering Committee for their approval.

Starting an Approved Manuscript Proposal

The procedure to begin work on an approved ACCORD manuscript proposal varies. The P&P Subcommittee can officially start a proposal and notify the writing group chair, or the writing group chair can request to start a manuscript. The following is the procedure when the P&P Subcommittee officially starts manuscripts.

- Twice a year the P&P Subcommittee will review all manuscript proposals that have not been started, but have been approved, and have a writing group assigned. These proposals will be assigned a priority number. The priority number is based on scientific merit, public interest, data availability, writing group chair availability, and coordinating center staff availability. As Coordinating Center analysts become available manuscripts will be *started* according to the priority list.

- The Writing Group Chair submits a memo to the P&P Subcommittee requesting to start the manuscript.
- The P&P Subcommittee will compile a listing of manuscripts which can be started.
- The P&P Subcommittee assistant will contact the writing group chairs of these selected proposals and ascertain if they are prepared to begin work on a selected manuscript.
- If the Writing Group chair can begin work on the manuscript, he/she will be sent an official start up packet. If the Writing Group Chair cannot start the manuscript, it will be noted in the manuscript proposal file and the proposal will be reviewed again in six months.

Example of a Manuscript Proposal

MANUSCRIPT TITLE: Are Normal Glycosylated Hemoglobin Values Achievable in Type 2 Diabetes. Results of the ACCORD Feasibility Study

INITIATING INVESTIGATOR:

(Developed in collaboration with

KEY WORDS: Type 2 diabetes mellitus, therapy, randomized controlled clinical trial, glycemic control, metformin, sulfonylurea, thiazolidinedione, insulin, hypoglycemia

INTRODUCTION: Multicenter prospective clinical trials reported to date have demonstrated proportional improvements in clinical outcomes associated with interventions to improve glycemic control (1-4). To date these studies have not achieved mean hemoglobin A1c (HbA1c) levels values below ~7% in type 1 and type 2 diabetes. Epidemiological analyses of these studies suggest that benefits continue to accrue into the normal range (<6%). The ACCORD study seeks to explore the hypothesis that intensive glycemic management with an aim to achieve normal HbA1c will be associated with improvements in cardiovascular outcomes when compared to standard therapy with targets similar to those explored in prior clinical trials. The Vanguard Phase of the ACCORD study will randomize approximately 3000 patients in the first year of study.

HYPOTHESES/QUESTIONS: In middle-aged and older people with type 2 diabetes at risk for cardiovasclar disease, can an aggressive approach to glycemic control that starts with 2 oral agents, uses explicit guidelines for titrating therapy, features intensive ambulatory follow-up and targets a HbA1c <6% safely achieve better glycemic control than a standard approach that starts with monotherapy, uses less intense follow-up and targets a HbA1c of 7.5%? Does such an intensive approach result in a HbA1c that is >=1% lower than the standard approach? Are there protocol issues that predict response to the interventions.

ANALYSIS PLAN/METHODS: In this paper we will explore 12 month (and perhaps 18 month) glycemic control data in the first 1000 people randomized in the ACCORD study with the primary aim to determine whether the glycemic targets established for the study can be achieved in the intensive treatment arm. The glycemic control in the standard therapy arm will be examined in parallel, for comparison purposes and to address whether the study will achieve a 1% separation between groups in HbA1c.

The primary analysis will be the average hemoglobin A1c achieved by visit during the first year in the two-glycemic arms of the study. Supplementary analysis will explore:

- the reduction in HbA1c from baseline by visit
- proportion achieving respective target levels by visit

- proportion of subjects achieving targets on one, two, three and four classes of drugs
- among subjects requiring insulin, total daily insulin dose and number of injections
- among subjects achieving targets
    - the number of titration steps required to achieve targets
    - the number of therapeutic classes required in each group and average doses
    - the number of dose titration steps required
    - the effectiveness of each additional agent added and each titration step will be analyzed individually in subjects achieving targets
    - adverse events (hypoglycemia, weight gain)
    - among subjects not achieving targets
    - the number of titration steps attempted
    - the number of therapeutic classes prescribed
    - the number of dose titration steps performed
    - the effectiveness of each additional agent added and each titration step will be analyzed individually in subjects not achieving targets
    - adverse events (hypoglycemia, weight gain)

In subjects that do not achieve glycemic targets, analysis of intervention at each visit will be explored to see if inadequate responses are related to protocol violations (in not intensifying therapy when targets are not achieved), hypoglycemia, other adverse events, or subject preference. This analysis is primarily aimed at determining whether there are protocol issues, which could be addressed to improve goal attainment and to estimate whether further reduction in HbA1c as a result of continued intensification of therapy is likely.

Additionally, we will explore the response of various predefined subsets to the ACCORD glycemic intervention protocol to establish whether the study inclusion and exclusion criteria were adequate to enroll a population that could meet treatment targets. The baseline characteristics and inclusion and exclusion criteria to be examined include:

- Age
- Sex
- Race
- BMI
- Duration of diabetes
- Baseline therapy (no, one, two classes of agents)
- Baseline insulin dose expressed in units/kg/d
- Baseline glycosylated hemoglobin
- Baseline C-peptide
- Primary prevention (by risk factor subgroup) or secondary intervention

SUMMARY/CONCLUSIONS: These analyses will be required as part of the analysis of the Vanguard phase in any case. As such a clinical trial has never been attempted, the data would be of considerable interest to the medical community.

REFERENCES:
1. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment if diabetes on the development and progression of the long-term complications of insulin-dependent diabetes mellitus. N Engl J Med 329:977-986, 1993.
2. Ohkubo Y, Kishikawa H, Araki E, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diab Res Clin Practice 28:103-117, 1995.
3. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352(9131): 837-853, 1998.
4. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352(9131): 854-65, 1998.

TIMELINE: Data analysis theoretically could begin approximately October 2001. Depending on the number of subjects enrolled, it may be desirable to delay full analysis.

Schedule for Manuscript Preparation

The expected schedule for the development of a manuscript is described below and shown in the enclosed ACCORD Publication Schedule. Any deviation from this schedule must be approved by the P&P Subcommittee. Failure to adhere to this schedule is a basis for replacing the Chair and/or replacing members of the Group who may cause the delay, or for disbanding the Writing Group.

After final approval of a Writing Group by the P&P Subcommittee, and after the official determination by the P&P Subcommittee of the start date of the Writing Group task, each group will have 60 days to submit to the P&P Subcommittee:

- a detailed outline of the proposed manuscript, and
- a data analysis request developed in cooperation with the Coordinating Center.

Note: The representative of the Coordinating Center on each Writing Group will provide liaison between the group and the Coordinating Center in development of the data analysis request. While it is recognized that data analysis is an interactive process and some analyses may continue until the final draft of the paper is prepared, it is anticipated that the majority of the analytical work will take place during the second step of manuscript preparation. Careful preparation of the initial data analysis request is of great importance since this will facilitate efficient data analyses by the Coordinating Center.

The letter codes which appear in the ACCORD publication schedule to denote the time table for each stage in the preparation of the manuscripts are described below:

S After final approval of the Writing Group composition by the Steering Committee and after the official determination by the P&P Subcommittee of the start date of the Writing Group task, the Writing Group will have 60 days to prepare a data analysis request developed in cooperation with the Coordinating Center and submitted to the Coordinating Center.

I The initial analysis performed by the Coordinating Center will be sent to the Chair of the Writing Group within 30 days of receipt of the data analysis request.

A1 Within the next 30 days the Chair of the Writing Group should work with the Coordinating Center to complete sufficient data analysis to start writing a first draft.

D1 Thirty (30) days after receipt of the bulk of the data analysis request (90 days after submission of the data analysis request) a first draft of the paper is due. This draft should be sent to the members of the Writing Group with a copy to the Chair of the P&P Subcommittee at the Coordinating Center.

A2 This is the second phase of data analysis after the Writing Group has reviewed the first draft and suggested modifications/additions. There are 30 days allocated to this phase.

D2 This is the second draft which should be completed 30 days after completion of the second analysis. This draft should be circulated to all Writing Group members with a copy to the Chair of the P&P Subcommittee at the Coordinating Center.

A3 This is the third phase of analysis which is given 30 days for completion.

P The Penultimate draft becomes due within the next 30 days after the completion of the third data analysis phase. A Penultimate draft should be sufficiently developed for subsequent submission to NHLBI and the Steering Committee for review. After review by Writing Group members, and all Writing Group members have signed off, the Penultimate draft should be sent to the Coordinating Center and will be forwarded to the Chair of the P&P Subcommittee. The draft should include a cover letter stating that this copy is ready for review by the P&P Subcommittee as a Penultimate Draft.

R The P&P Subcommittee has 30 days to review the manuscript and determine if it is ready as a Penultimate draft for review by the Steering Committee and NHLBI. If it is approved by the P&P Subcommittee, it will be forwarded to the Steering Committee and NHLBI for review. If it is not approved by the P&P Subcommittee, the draft will be returned to the Writing Group Chair with comments regarding the necessary revisions. After approval of the Penultimate Draft by the P&P Subcommittee the Coordinating Center will initiate verification of the results. Completion of verification is expected within 30 days and the P&P Subcommittee and the Writing Group will be notified by letter.

N Within 30 days of receiving Steering Committee, NHLBI and P&P Subcommittee comments, final revisions are to be made on the manuscript and circulated to Writing Group members for the final sign-off by co-authors.

J After verification is complete a final copy of the manuscript with the cover letter to the journal should be sent to the Coordinating Center *and* in addition to all co-authors. This draft will be forwarded to the Chair of the P&P Subcommittee. The Chair of the P&P Subcommittee at the Coordinating Center should also be sent copies of all subsequent communications with the journal. The Coordinating Center will pay for the first 150 reprints from the Journal. The Journal reprint form must be sent to the Coordinating Center to the attention of the P&P Subcommittee assistant. The P&P

Subcommittee assistant will maintain a library of manuscript reprints. These reprints will be filed numerically by the ACCORD manuscript numbers as they appear on the schedule matrix. The P&P Subcommittee assistant will respond to reprint request cards by mailing reprints from the Coordinating Center. The Writing Group Chair will receive 25 reprints and a reprint will be mailed to each Writing Group Member, each member of the P&P Subcommittee and each member of the Steering Committee.

Example ACCORD Publication Schedule Table

Paper #	Title	Jan	Feb	March	April	May	…
1	Design of the ACCORD Trial	S	I	A1	A1		
2	Lipid Interventions in ACCORD		S	S	I		
…							

Steering Committee and NHLBI Review of Penultimate Drafts

After the Penultimate Draft has been reviewed and approved by the P&P Subcommittee it will be sent to the ACCORD Steering Committee and NHLBI for review. The Steering Committee has 14 to 30 days to review the draft. NHLBI may take as long as 30 days for the review. Category I papers will receive statistical review at both NHLBI and the Data Coordinating Center. All other papers will receive at least one statistical review. All comments received by the Steering Committee are sent to the Coordinating Center. The P&P Subcommittee Assistant will send the comments to the Writing Group Chair. The names will be removed from all comments. The Writing Group chair will be encouraged, but not required, to incorporate the review suggestions into his/her draft.

If review sheets are returned to the Coordinating Center with a check in the "approval with modifications" or "I do not approve" box the following policy applies:

- The Writing Group Chair should revise the draft and also send a memo to the P&P Subcommittee.
- If the Writing Group Chair chooses not to revise the draft he/she must reply with rebuttal comments.
- The P&P Subcommittee will review the revised draft and compare it with the suggested comments, and if approved by the P&P Subcommittee, the manuscript will be cleared for journal submission.

Priority Assignment for Publication Related Analysis

The ACCORD Steering Committee will determine priorities for scheduling a start date for a Manuscript. A priority rating of 1 indicates highest priority and a 5 indicates the lowest priority. Manuscripts in the first priority are scheduled to start if:

- the writing group chair is available, and has no other obligations, and
- Coordinating Center staff are available.

Dealing with Coordinating Center Staff: Guidelines for Writing Group Chairs

- Communicate with the identified Coordinating Center representative of the specific Writing Group for all requests and questions on analyses.
- Be sure that data requests are made within the scheduled time frame; interactive analyses will be allowed within the window of the analysis schedule.

- Use the first set of substantial data analyses that are received for the first draft of the paper.
- Plan systematically for the analysis of your data.
- If the data lead to a split in the original paper into more than one, an official request from the chairperson of the Writing Group must be made to the P&P Subcommittee. The request should describe the revised contents of the original manuscript and the proposed paper.
- If the Coordinating Center falls behind on an analysis deadline, the Chairperson of the Writing Group should inform the P&P Subcommittee Chair; if there is a problem, deadlines can be changed.

Authorship Policy

The main authors of a manuscript or abstract will be those in the Writing Group. Each Writing Group will determine the order of authorship. In general, the Chairperson of the Writing Group will take major responsibility for writing and thus will be the first and corresponding author. For manuscripts and abstracts in which the work reported reflects the collaborative effort of most sites and Principal Investigators (Category II Papers), the author line should be followed with the phrase "for the Action to Control Cardiovascular Risk in Diabetes Study Group". It is the intent of the ACCORD that all individuals who have worked in the design and conduct of the study to claim authorship credit for such papers. When conflicts arise regarding the order of authors or whether authorship for the entire study should be included, a final decision can be made by the Publications and Presentation Committee.

Reprints and Page Charges

At the present time, the allocation of cost of page charges and reprints of all ACCORD manuscripts has not been discussed yet with the Steering Committee and the NIH.

III. Presentation of ACCORD Data

ACCORD WEB Sites

ACCORD Clinical Networks may wish to have WEB sites, in addition to the official site maintained by the Data Coordinating Center, to promote communication within their own Network. Material placed on all ACCORD WEB sites that can be accessed by the general public (i.e. areas that are not password protected) must be approved by the ACCORD P&P Subcommittee. The P&P Subcommittee will not need to approve information that is password protected on any ACCORD Web site.

ACCORD Presentations

The P&P Subcommittee of ACCORD will be responsible for ensuring that all presentations, and abstracts developed based on the ACCORD design, or data generated from the ACCORD study, are of the highest quality. The categories of

abstracts/presentations and/or recruitment materials that should adhere to ACCORD P&P Subcommittee policies include:

- Presentations and/or materials provided to physicians or members of the community for purposes of recruitment,
- Presentations given at meetings sponsored by industry, and
- Presentations given at local, national or international meetings.

The Project Manager of the Data Coordinating Center should be notified of all presentations so that the P&P Subcommittee can keep appropriate records.

Presentations for Recruitment Purposes

For purposes of recruitment, all approved materials will be maintained at the Data Coordinating Center. A standard set of PowerPoint slides, developed in collaborations with the ACCORD Recruitment and Retention Subcommittee, will be downloadable from the ACCORD Web Site. Recruitment materials will also be available by contacting the Project Manager at the Data Coordinating Center. Recruitment presentations based solely on previously approved ACCORD recruitment material do not need prior approval by the ACCORD P&P Subcommittee. Any material to be distributed to the public for recruitment, in addition to approved ACCORD recruitment material, must be approved by the P&P Subcommittee and Project Office. The process for submission of additional ACCORD recruitment material, that has not been previously approved, is as follows:

- Submit to the Project Manager at the Data Coordinating Center,
- Review of material by ACCORD P&P Subcommittee,
- Notification of approval/disapproval for such material within one week.

Invited Presentations Given at Local, National or International Scientific Meetings of Events Sponsored by Industry

Invitations received by ACCORD investigators to give presentations are subject to the following policies:

1. General invitations directed to the Chair of the Steering Committee, the Chair of the P&P Subcommittee, or NIH will be forwarded to the P&P Subcommittee to decide who is to represent ACCORD. In the case of invitations to national or international meeting, the selection of the P&P Subcommittee shall be reviewed by the Steering Committee.
2. Any ACCORD investigator who receives a personal invitation to make a presentation should immediately notify the P&P Subcommittee of the Sponsor, date and topic of the presentation.
3. All presentations in response to such invitations should be based on published ACCORD reports. If information is to be presented that is not based on previously approved reports, prior approval must be granted by the P&P Subcommittee and the NHLBI Project Office. The approval process for these presentations will follow the same guidelines as specified for ACCORD abstracts.
4. Requests to present or discuss at local meetings (e.g. Grand Rounds) any previously published or presented by abstract ACCORD data do not need prior clearance by the

P&P Subcommittee; however, as for all presentations, the ACCORD P&P Subcommittee should be notified of these presentations.

Preparation and Submission of Abstracts for Meetings

The ACCORD Publications and Presentations Committee is to maintain a current list of all relevant meetings and their deadlines for submission of abstracts. This report should be updated in January of each year and distributed to all PI's no later than January 31st.

No abstract shall be submitted to any national or international organization for consideration prior to approval by the ACCORD P&P Subcommittee, the ACCORD Steering Committee, and clearance by NHLBI. Abstracts of papers for presentations are expected to be based on active manuscripts. If an abstract is based upon an existing Penultimate draft, which has been reviewed by the P&P Subcommittee, it can be submitted up to two weeks prior to the deadline. If it is based upon a study for which there has been no prior review, it must be submitted four weeks prior to the deadline. The Writing Group Chair is also responsible for getting the approval of co-authors prior to submission for approval. Late submissions will be accepted only in special circumstances.

Abstract Review Procedure

1. All new abstracts should be sent to the attention of the P&P Subcommittee Program Assistant. The abstract is logged in at the Coordinating Center.
2. If possible, abstracts will be reviewed at a regular P&P Subcommittee Conference call. If not the abstract will be faxed to all P&P Subcommittee members for a response within 48 hours.
3. If the P&P Subcommittee review is favorable, the abstract will be sent simultaneously to the Steering Committee and NHLBI Project Office for review. The Steering Committee and NHLBI will have 48 hours to review and respond to the abstract.
4. Review comments if any will be sent to the Writing Group Chair as soon as they are received at the Coordinating Center.
5. If an abstract is approved, the Writing Group Chair will be notified by the P&P Subcommittee Chair. The Writing Group Chair will be given clearance to submit the abstract.
6. Final copies of the approved abstract should be submitted to the meeting directly by the Writing Group Chairman and a copy sent to the P&P Subcommittee. P&P Subcommittee members and Steering Committee members will receive a copy of all abstracts submitted.

Additional Policies for Abstracts:

- It is permissible to submit previously cleared abstracts to other meetings; copies should be sent to the Data Coordinating Center for inclusion in the listings of publications and presentations.

- In order for the Data Coordinating Center to meet the need for data requests for abstracts and allow sufficient time for writing the abstract, the writing committees should plan well in advance and be selective in their data requests. That is, only tables that relate to the major topics of the abstract should be requested.
- All abstracts [as well as one set of the actual slides (or PowerPoint file) plus one set of paper copies for each abstract] should be submitted to the Data Coordinating Center for archival purposes. Slides should conform to standards set by the ACCORD P&P Subcommittee.
- A standard set of PowerPoint slides representing design and rationale of trial will be developed from the design paper contents by the ACCORD P&P Subcommittee and placed on the ACCORD Web Site for downloading. Presenters are encouraged to use these slides as part of any presentation.

IV. Ancillary Studies

Definition

An ancillary study is an investigation that is not part of the ACCORD protocol but uses ACCORD participants, samples, or data collected by ACCORD. In most cases, an ancillary study will involve acquisition of additional data that are not compiled as part of the standard ACCORD data set.

Investigators are encouraged to propose and conduct ancillary studies. Such studies enhance the value of ACCORD and ensure the continued interest of the diverse group of investigators who are critical to the successes of the study as a whole. They provide an exceptional opportunity for investigators, either within or outside of ACCORD, to conduct additional projects at minimal cost. In general, ancillary studies will require outside (non ACCORD) funding.

Review Process

To protect the integrity of ACCORD, all ancillary studies must be reviewed and approved before access to ACCORD data or participants is permitted. Investigators will not be allowed access to the ACCORD subjects or data set without approval. The review process by which approval will be granted is as follows:

1. New ancillary study proposals should be sent to the Publication and Presentation Committee at the Coordinating Center. The P&P Subcommittee assistant will review the proposal to ascertain that the form (see appendix A) is completed satisfactorily and establish a file. If the form is incomplete the P&P Subcommittee Assistant will contact the Investigator on the proposal and request that they fill in the form completely. Ancillary study forms can be obtained by calling the ACCORD Coordinating Center and requesting to speak to the P&P Subcommittee Assistant.
2. P&P Subcommittee Assistant will review the ancillary study to determine if issues pertaining to participant or Clinical Center burden and/or Coordinating Center use need to be addressed.

3. When the application is complete, the study proposal will be sent to the Committee for review. The P&P Subcommittee will have 2 to 4 weeks to review the proposal and make a recommendation to the Steering Committee.
4. The P&P Subcommittee may request the proposer of an ancillary study to respond to questions, suggestions or critique of the proposal before making a recommendation to the Steering Committee.
5. The P&P Subcommittee review comments will be attached to the ancillary study proposal before the proposal is submitted to the Steering Committee.
6. Approval/disapproval will be made by the Steering Committee.
7. The approved ancillary study proposal will be sent to the Monitoring Board for final review and approval.

Separate informed consent must be obtained from all ancillary study participants. This should clearly identify the ancillary study as one being performed in addition to the main study and inform subjects that their participation in the ancillary study is not necessary for them to continue in ACCORD. Confidentiality of individually identifiable data about ACCORD subjects must be assured.

An ACCORD principal investigator or co-investigator must be included as the principal investigator and/or co-investigator in every ancillary study proposal. If Coordinating Center resources are to be used, arrangements must be made with the Coordinating Center director. In general, costs associated with ancillary study data management at the Coordinating Center must be budgeted into each ancillary study. In order to avoid misunderstandings, all communication with the ACCORD Coordinating Center must take place between the senior ACCORD investigator involved in the ancillary study and the Coordinating Center liaison. Following final approval of an ancillary study, there can be no substantial changes in the type or amount of data requested from the Coordinating Center.

All proposed ancillary studies must be submitted to the P&P Subcommittee in time for review, circulation to appropriate committees, and to obtain clearance prior to submission to a funding agency. As beneficiaries of a collaborative study, each investigator must realize that other investigators must be given an opportunity to participate in proposed studies and to offer a critique of the proposal. Such collaboration will often strengthen the ancillary study. Studies submitted for approval less than 60 days prior to a funding application deadline may not receive approval.

In order to expedite review of ancillary studies, ACCORD has developed an information form (see appendix A) that provides a synopsis of the proposed study and describes its impact on the participants or resources of ACCORD. In addition, investigators should provide a two- to three-page summary of the proposed study to the review group.

The summary should contain:
Identifiers:

1. Initiating investigators, collaborators, sites involved
2. Planned starting date, conclusion date
3. Estimated cost, funding plans, and current status

Design and Methods:

1. Brief background and rationale
2. Study questions or hypothesis (1-3)
3. Sample size justification
4. Methods, data to be collected
5. Burden on participants
6. Impact on the main study

Data Handling:

1. Data needed from the main study for analysis of ancillary study
2. Impact on Coordinating Center or local sites

Reviewers will use this information to assess the priority of the study in relation to ACCORD objectives, and most importantly, determine its potential impact on the main study (ACCORD). Highest priority will be given to studies which:

- do not interfere with the main ACCORD objectives,
- have the highest scientific merit,
- produce the least burden on ACCORD participants and staff,
- have objectives closest to those of ACCORD,
- require the unique characteristics of the ACCORD cohort, and
- provide opportunities for more junior investigators to serve as the PI of a project.

The review groups will also work with the investigators proposing the study to ensure that each of the ACCORD centers that is interested in participating is given the opportunity. The review groups will present their evaluations of the proposal to the Steering Committee.

The Steering Committee will review the proposal primarily to determine that it will not compromise, unduly complicate, or jeopardize the conduct of the ACCORD. Review of proposed ancillary studies for scientific merit is not the primary responsibility of this review process, but is a necessary consideration with allocated access to scarce ACCORD resources. All ancillary study proposals approved by the Steering committee will also be sent to the ACCORD Monitoring Board for review and comment.

The Publications and Presentations Committee will record the progress of approved ancillary studies since the composite impact of the total number of active studies may be unforeseen without central monitoring. Investigators with approved ancillary studies will report to the Chairman of the Publications and Presentations Subcommittee every twelve months regarding the status of study funding, initiation and terminations dates, success of data collection, and any presentations and publications

derived from the ancillary study. A written progress report on ancillary studies will be made twice a year at the request of the P&P Subcommittee. This written report will be submitted to the Steering Committee during their annual meetings.

Publications and Presentations Resulting from Ancillary Studies

Publications resulting from ancillary studies follow the same procedures as other papers. Potential papers from ancillary studies must follow the following guidelines:

1. Submit a formal manuscript proposal, which consists of a title, proposed Writing Group, introduction, analysis plan, conclusion, and references.
2. The P&P Subcommittee will submit the proposal to the Steering Committee requesting nominations with special expertise.
3. When the Writing Group has been finalized, and a memo from the P&P Subcommittee has confirmed the final Writing Group, the manuscript can be started.
4. Ancillary study papers are not tracked and do not need to adhere to a timeline.
5. The P&P Subcommittee does request that the writing process involves the whole Writing Group, i.e.; drafts circulated regularly to the Writing Group.
6. The P&P Subcommittee does need to review the Penultimate Draft arising from an ancillary study. In addition, review by the Coordinating Center biostatisticians is required for all manuscripts reporting data obtained from the Coordinating Center database.
7. If the Penultimate Draft is approved by the P&P Subcommittee, the draft will be submitted to the ACCORD Steering Committee and NHLBI for final review.
8. The Chairperson of the Writing Group for the paper is responsible for reporting to the P&P Subcommittee on the paper's progress.
9. The final published article must be sent to the Coordinating Center.

Abstracts generated from ancillary studies must follow the same guidelines for all ACCORD abstracts. The initial receipt of the proposed abstract must reach the Chairman of the P&P Subcommittee a) preferably two weeks prior to the deadline for the abstract's submission if data from an ACCORD paper in progress is used and b) four weeks in advance if new data analysis is needed and not already reviewed by the P&P Subcommittee. Before the proposal reaches the P&P Chairman it should have been approved by all co-authors.

Data Request for an Existing Ancillary Study

As a study progresses, an ACCORD investigator may request additional data. This data may be released to the ACCORD investigator if any of the following apply:

a. The data was originally listed in the principal ancillary study.
b. The data are currently available for distribution to all ACCORD investigators.
c. The new data request was generated as a result of findings from the originally planned analyses.
d. A detailed justification for additional data is submitted with the writing group proposal.

*** Pertaining to item d: If an investigator anticipates the need for additional data, he/she may submit a revision, or a modification to the original ancillary study. This revision and/or modification must be reviewed by the P&P Subcommittee, Steering Committee and NHLBI. The revision and/or modification must support the need for additional data. If no revision or modification is on file, an additional data request sent directly to the coordinating center will be denied.

V. Other Issues

Invited Presentations and Review Articles

Invited presentations and review articles pose particular ambiguities with regard to equitable distribution of authorship, because the material often draws upon the work of several Writing Groups. When results from all components of the ACCORD trial are published or presented in summary fashion, it becomes virtually impossible to acknowledge the contributions of everyone involved. Nevertheless, the following guidelines are suggested as a means of distributing credit as fairly as possible.

The senior author or speaker will identify a reasonably small number of Writing Groups whose data are involved and whose members have contributed to the development of the manuscript or material used for presentation.

He or she will also identify a limited number of authors. The senior author or presenter will then solicit from each Writing Group chairperson the names of appropriate individuals to receive credit in that article or presentation. It will be the responsibility of each chairperson to contact everyone in the Writing Group concerning this.

Press Releases

Any press release on any material of the ACCORD study must be cleared in advance by the Publication and Presentation Subcommittee, as well as the Steering Committee and the NIH.

Grievances

In case of disagreement between an investigator and the Publication and Presentation Subcommittee with regard to the review of a manuscript, a presentation material, or an ancillary study proposal, the author may activate a formal appeal. The format of appeal will be the following: Appeal to the Publication and Presentation Subcommittee, then to the Steering Committee, and finally to the NIH.

Revisions/Amendments to This Document

This document can be revised or amended only with approval of the ACCORD Steering Committee.

VI. Presentations and Publications Subcommittee Members

Chairperson P&P Subcommittee

Professor of Medicine
Division of Clinical & Molecular Endocrinology
Case Western Reserve University
10900 Euclid Avenue.
Cleveland, OH 44106-4951
Tel
Fax
E-mail:

Vice-Chairperson P&P Subcommittee

Associate Professor of Medicine
Director, Diabetes Care Center
University of North Carolina
5316 Highgate Drive,
Durham, NC 27713
Tel
Fax
E-mail:

Professor Section of Epidemiology
Department of Public Health Sciences
Wake Forest University School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157-1063
Tel
Fax
E-mail:

Deputy Project Officer
Leader, Clinical Trials Scientific Research Group
Division of Epidemiology & Clinical Applications
National Heart, Lung, and Blood Institute
6701 Rockledge Drive.
Bethesda, MD 20892-7936
Tel
Fax
E-mail:

Clinical Professor of Medicine and Public Health
Columbia University
College of Physicians and Surgeons & School of Public Health
Division of Epidemiology
600 West 168th St.
New York, NY 10032
Tel
Fax
E-mail:

London HSC- University Campus Site
P.O. Box 5339
London, ON N6A 5A5
Assistant:
Email:
Tel
Fax
E-mail:

Cleveland VA Medical Center
10900 Euclid Avenue,
Cleveland, OH 44106-4951
Tel
Fax
E-mail:

Professor of Medicine
Chief, Medical Service
Department of Veterans Affairs Medical Center
1500 E. Woodrow Wilson Drive
Jackson, MI 39216
Tel
Fax:
E-mail:

Division of Metabolism, Endocrinology and Nutrition
Harborview Medical Center
Seattle, WA 98105
Tel
Fax
E-mail:

Naval Medical Center Cardiology Division
34730 Bob Wilson Drive,
San Diego, CA 92134
Tel
Fax
E-mail:

Professor of Public Health Sciences/Biostatistics
Section on Biostatistics
Department of Public Health Sciences
Wake Forest University School of Medicine
Winston-Salem, NC 27157-1063
Tel
Fax
E-mail:

VA Medical Center
50 Irving Street, NW
Washington, DC 20422
Tel
Fax
E-mail:

Division of Endocrinology and Metabolism
University of Alberta Heritage Medical Research Centre
University Campus NW
Edmonton, AB T6G 2S2
Tel
Fax
E-mail:

Professor of Medicine and Molecular Pharmacology
Albert Einstein College of Medicine of Yeshiva University
Department of Medicine
1300 Morris Park Avenue
Bronx, NY 10461
Tel
Fax
E-mail:

Associate Professor of Medicine
Division of Diabetes and Endocrinology

420 Delaware St. SE
Minneapolis, Minnesota 55455
Phone:
Fax:
Email:

Deputy Director, Clinical Applications and Prevention Program
Division of Epidemiology & Clinical Applications
National Heart, Lung, and Blood Institute
6701 Rockledge Drive, MSC 7936,
Bethesda, MD 20892-7936
Tel
Fax
E-mail:

WFU School of Medicine
Department of Public Health Sciences
Medical Center Boulevard
Winston Salem, NC 27157
Tel
Fax
E-mail:

Ancillary Study Application Form

ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES (ACCORD) STUDY
INFORMATION FOR PROPOSED ANCILLARY STUDY

PART 1 - Basic Study Information and Projected Impact on ACCORD

Please answer questions as concisely as possible but provide enough information for reviewers to evaluate the potential impact of the proposed study on ACCORD participants and staff.

1. Title of Proposed Study:

2. Initiating investigator(s):

3. Collaborators*:

*Note requirement for ACCORD coinvestigator

4. Center Name(s):

5. Centers' tasks: (please check all that apply):

	Yes/No	# requested
Enrollment request?		
Examinations/Patient		
Biological samples/Patient		
Questionnaires/Patient		
Collection of data from ACCORD database?		

6. Proposed starting date:

7. Proposed ending date:

8. Proposed involvement of ACCORD participants and staff:

A. Participant involvement

Special characteristics (ex. patients free of clinical disease, with recent CVD events, etc.)

Describe sample by age and gender.

Estimated number of visits per participant to complete study:

Estimated time per participant visit (minutes):

B. Proposed use of stored ACCORD materials (blood samples, tapes, etc.):

C. ACCORD Field Center Staff involvement (describe required effort and quantitate effort required by ACCORD at each participating center):

D. Will any Coordinating Center involvement be required? yes/no

D1. If yes, has the CC been asked for an estimate of the required effort? yes/no

D2. Who provided this estimate?

D3. ACCORD Coordinating Center involvement (describe anticipated requests for data and assistance from CC and involvement in analytic phase of the proposed project, if any):

9. Estimated cost by year, number of years:

cost/yr

years

10. Source of funding:

Request to be submitted:

to whom:

date:

projected date available:

Funding already available:

from whom:

date available:

11. Reason(s) for proposed use of ACCORD cohort or samples (why not use other population):

12. Please describe the advantages to conducting this study in the ACCORD cohort.

13. Indicate other ACCORD data to be used in proposed analyses:

14. Areas of Research Expertise Needed for Review of Proposal.

15. Institution of Affiliation

PART 2 - Description of the Proposed Study

This section should be brief (1-3 pages) and should provide basic information on the specific proposed study. It should include a description of:

- Brief background and rationale
- Study questions or hypotheses (1 to 3)
- Sample size, justification
- Methods, data to be collected
- Proposed analyses

Submission will be limited to 1500 words or less.

Note: Additional documentation may be requested by the review committee if necessary to evaluate the impact of the proposed ancillary study.

See ACCORD www site to review ACCORD Ancillary Study Policy.

APPENDIX A.3
Methods for Collecting ACCORD HRQL Data

In this study, the HRQL questionnaire will be completed by the participants (i.e., self-administered). However, there may be particular circumstances when interviewer administration in the clinic is required. Although it is not anticipated that these special situations will arise often, there may be instances in which factors such as poor eyesight, poor hand-eye coordination, ill health, weather, or conflicting time commitments will necessitate a change in how the questionnaire is administered. Therefore, we include suggestions in this manual to assist the clinic staff in handling these situations, and also provide instructions for interviewer-administration of the instruments.

Specific Guidelines

The way in which a questionnaire is administered to a study participant can affect the validity of the responses to the questionnaire items. For this reason, it is important to adhere to the following guidelines in administering study questionnaires.

Step 1: Review the Study Protocol

Prior to each administration of the questionnaire, it is important that the clinic staff person review the study protocol and questionnaire to refresh his/her memory as to the correct procedures to follow. This is particularly important in clinics where a small number of participants are to be recruited and/or where more than one clinic staff member will be administering the questionnaires to the study participants.

Step 2: The Data Collector

The individual administering the questionnaire plays a critical role in the process of data collection. There is the potential for the quality of the participant's responses to be affected by the general attitudes and actions of the interviewer. A relaxed and friendly manner puts the participant at ease and conveys the message that the interviewer considers the questionnaire an important part of the study. Additionally, the interviewer should dress in a neat, clean and professional manner. Dress and demeanor should convey that the interviewer is an appropriate representative of the research team.

Step 3: The Setting

The interviewer should be available to greet the participants as they arrive. If your survey area is in an office that is difficult to locate, or if you know that a participant has physical limitations, arrange to meet the participant ahead of time and escort him/her to the place where the survey will be administered. Optimally, the participant should have a comfortable and private place, which is free from interruptions or distractions to complete the questionnaire.

In order to answer questions that may arise, the data collector should be readily accessible to the respondent while the questionnaire is being completed. The questionnaire should be completed in one sitting.

Family members or friends of the participant should not be present when the patient is completing the questionnaire. Oftentimes, family members will offer to help participants complete the questionnaire, but we do not want the participants' responses to be influenced by their families or friends. If family members/friends offer to help respondents complete the questionnaire, politely decline their offer of help and indicate that you would prefer to have the patient complete the questionnaire alone. The interviewer should explain the necessity of providing privacy and confidentiality to research participants and should be prepared to suggest a place where the family member(s) or friend(s) can wait comfortably while the participant completes the questionnaire. The interviewer should be polite, but firm.

Step 4: Assessing the Physical Status of the Participant

It is possible that the clinic staff will encounter a participant with vision problems or physical conditions, which will make it difficult for him/her to complete the questionnaire on his/her own. Other participants may have problems with literacy/reading. The interviewer should determine if the participant is able to complete the questionnaire without assistance. In many cases, the participant's 'fitness' will be readily apparent. For example, some patients may not be able to hold a pencil or may tell you that they are unable to read the questionnaire due to vision problems.

It may be harder to recognize participants with low literacy skills, unless the participant verbalizes that he/she is unable to read at a level sufficient to complete the questionnaire. Cues to low reading skills may include the participant asking many questions, completing the measures very slowly, glancing up and around, appearing confused, or checking off responses without clearly reading the items. In these instances, data will be poor. Therefore, while avoiding any embarrassment to the participant, it is in the best interest of the study and the participant to determine if she is able to complete the questionnaire on her own. If you suspect he/she is unable to read, you may say to him/her: "Many individuals prefer to have the questionnaire read to them. Would you like me to read these questions to you?" If the answer is yes, read the questions to the participant, following the guidelines in the section for interviewer administration of the questionnaire. Otherwise, if the participant can complete the questionnaire on his/her own, proceed using the guidelines for self-administration of the survey.

Guidelines for Use as a Self-administered Questionnaire

Step 5: Answering Questions

The individuals collecting the data should be thoroughly familiar with the questionnaire before it is given to the participants. Interviewers will be unable to give assistance to participants if they do not have a working knowledge of the structure and content of the questionnaire. Reading the instructions for use of the HRQL questionnaire will prepare the interviewer to give assistance on an individual question, if asked.

Some of the participants will have questions about items on the questionnaire. In answering questions, survey administrators must be careful not to bias the participants' responses. The data collector may read a question to a respondent, define terms, indicate where the answer is to be marked, etc., but they should not paraphrase questions unless it is absolutely necessary. It is easy to alter the meaning of a question in this way.

Therefore, the data collector should not suggest an answer for the participant. In general, most of the participant's questions can be handled by reminding him/her to follow the directions on the questionnaire, or simply by rereading the statement to the respondent. The interviewer should read the statement exactly as it is written. The administrator should remind the participant that he/she should answer the question with the response that she believes is more true for him/her at the present time.

If a respondent tells the data collector which answer he/she has selected, the interviewer should refrain from reacting to that answer or conveying either approval or disapproval of the participant's choice. The interviewer may indicate to the participant that there are no right or wrong answers to these questions, and that the choice is his/hers as to how to respond to the statement. Under no circumstances should the survey administrator help the participant decide how to mark a questionnaire item.

Step 6 Editing the Questionnaires

An important role of the questionnaire administrator is to examine the completed surveys immediately after the participants have completed them. If the participant has skipped questions and/or filled the questionnaire out incorrectly, the staff person needs to discuss this with the participant before he/she leaves the office. Persons who have filled out the forms incorrectly should be asked to complete the questionnaires in the appropriate manner. If an item is missing or incomplete, the interviewer should ask the participant if he/she noticed the item and meant to leave it blank or simply overlooked it. If the participant declines to provide the information when it is brought to his/her attention, the interviewer should accept the participant's refusal without comment.

Step 7: Thank the Participants

Always remember to thank the participant for his/her time and interest in completing the questionnaire. Escort the participant back to their family or the waiting room, if necessary.

Step 8 Storing the Questionnaires

Once a questionnaire has been completed by a participant and edited by the survey administrator, the questionnaire should be stored in a secure place within the clinic. The questionnaire should not be left unattended where non-research staff can review the participants' responses. Information collected for research purposes can only be shared with other members of the research team, and the participants' privacy must be protected at all times. The data collector should never discuss any of the responses with anyone who is not directly involved in the study.

Guidelines for Use as an Interviewer Administered Questionnaire

The HRQL Questionnaire is designed to be self administered, but can also be used in an interview format. For a participant with physical, visual, or literacy problems, the questionnaire can be administered by reading the questions aloud to the respondent. If the interviewer has determined that the participant is unable to complete the questionnaire through self-administration, he/she should use the following guidelines in administering the questionnaire to the participant.

The Interviewer

The interviewer plays a critical role in the process of data collection. It is important that the interviewer does not influence the participant's response to any question. Since more than one interviewer may be administering the questionnaires, the following guidelines should be used to standardize the administration so that each interviewer administers the questionnaires in the same way. Variability in administration of the instruments introduces bias in data collection and reduces the quality of the data.

In the ideal situation, the interviewer's presence should not influence the participant's perception or response to a question, and different interviewers should be able to obtain the same responses from the same participant. Recognizing the limitations inherent in this ideal, there are methods that can enhance the neutrality of the interviewer. Interviewers should not provide either verbal or non-verbal responses that could influence the participant's responses. For example, an interviewer should not convey surprise, pleasure, or disapproval to any answer. The interviewer role is to obtain honest, uninfluenced responses to the questions.

The interviewer should be thoroughly familiar with the questionnaire before interviewing the first participant. This will ensure that the interviewer can easily address the participants' questions or concerns. Inexperienced interviewers should also practice completing an interview by practicing with someone who is pretending to be a participant. This will help to reduce the mechanical style that sometimes results from reading unfamiliar material.

It is important that the interviewer conveys a sense of impartiality. He or she should be gracious and adaptable to all participants regardless of whether their dress, appearance, style of speech, or personal preferences are consistent with the interviewer's values and preferences.

There are no right or wrong answers on the HRQL questionnaire. It is often helpful to tell this to the respondent if uncertainty or hesitation is observed. It is important to put the respondent at ease.

Specific Guidelines

Steps 1-4:

Follow Steps 1-4 of the self-administration of the questionnaire beginning on page 10.

Step 5: Introducing the Study Questionnaire

Introduce the questionnaire to the study participant by telling him/her that the questionnaire contains questions about their general well being. The interviewer should indicate that as a participant in the study, we are asking them to complete this questionnaire because we are interested in knowing how diabetes may affect their daily life.

When introducing the HRQL questionnaire, explain to the respondent that their responses to the measures will be kept completely confidential. That is, the respondent's identity will be protected. No one but the research staff will have access to patient names, and

data will be entered into the computer by identification number rather than a name. Results will be calculated using large groups of patients and not individuals. If results are published, no patient names or other identifying characteristics will ever be used.

Step 6: Administering the Questionnaire

Read through the directions with the participant and ask him/her if they clearly understand how the questions are to be answered. If the participant has no questions, proceed to read the statements to the respondents.

Read each statement to the respondents verbatim. The wording has been carefully selected and tested in order to insure the validity of the participant's responses. Do not paraphrase or simplify the statements. Even minor changes in wording can affect the validity of the results.

Read the questions to the respondent in the order in which they were written. Do not skip over statements and then come back to them later.

Record the participants' responses on the questionnaires as they are given. Never depend on memory to mark the participants' choices.

Step 7: Answering Questions:

The interviewer should be thoroughly familiar with the questionnaire before interviewing the first participant. This will ensure that the interviewer can easily address the participants' questions or concerns. The interviewer may repeat questions if the participant does not understand them. The interviewer should also assume responsibility for faulty communication by saying that perhaps they didn't read the questions clearly enough, etc.

Keep explanations to a minimum. Don't interpret questions. The interviewer may, for example, define a word but may not say "I think they mean...." It is easy to alter the meaning of a question in this way. In some instances, it may be necessary to paraphrase or simplify a statement for a respondent, but paraphrasing a question should only be done if absolutely necessary.

All questionnaire items have fixed response categories. All items must be answered using one of the existing response choices or the respondents' answers cannot be entered into the computer. In an interview format, if a respondent replies that none of the choices is correct, suggest that the choice that comes closest be selected. If the respondent still refuses, note this on the questionnaire.

If the participants answer, "I don't know," to a particular question, give them a little more time to think. Sometimes this response is given to cover momentary confusion and a meaningful answer will be forthcoming if a few moments are allowed for thought. The interviewer may say something like "Take a moment to think about your answer."

In the event a respondent gives an inappropriate response, repeat the question and the response categories. For example, if the question asks the respondents to indicate how

much they agree with a statement, and a participant says, "that's true," the interviewer could say, "Would you say you strongly agree, agree, etc.?"

If the respondent refuses to respond to a question for any reason, accept the refusal without reaction. Indicate the refusal on the questionnaire using the response categories listed on page N.

General Reminders:

Interviewers should be patient and polite, they should convey a sense that the respondent's answers are important. They should also allow plenty of time for the respondent to understand the questions.

Interviewers should never suggest an answer or disagree with a response. The interviewer's role is to obtain and record the respondents' answers.

Interviewers should always ask the questions and give the response categories verbatim, in the order they appear in the questionnaire.

The interviewer may, at any point in the interview, reassure the respondent that her answers will be kept confidential, that there are no right or wrong answers, and that the interview is going well.

Step 8: Editing the Questionnaires
After completing the interview with the participant, the interviewer should glance back through the questionnaire to make sure that no questions were skipped unintentionally. This will help limit problems with missing data.

Step 9: Thank the Participants
Interviewers should always remember to thank the participants for their time and interest in completing the questionnaire. They should also escort the participant back to his/her family or the waiting room, if necessary.

Step 10: Storing the Questionnaires:
Once a questionnaire has been completed by a participant and edited by the survey administrator, the questionnaire should be stored in a secure place within the clinic. The questionnaire should not be left unattended where non-research staff can review the participants' responses. Information collected for research purposes can only be shared with other members of the research team and the participants' privacy must be protected at all times. The data collector should never discuss any of the responses with anyone who is not directly involved in the study.

Appendix A.4
Model Informed Consent Document

(Consent Version Date: May 11, 2005)

ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES (ACCORD)

Principal Investigator(s)_____

You are invited to join in a research study called Action to Control Cardiovascular Risk in Diabetes (ACCORD), which is sponsored by the National Heart, Lung and Blood Institute (part of the U.S. federal government). The investigators listed above are in charge of the study. Other professional persons may help them or act for them.

What are some general things you should know about research studies? Research studies are designed to gain scientific knowledge that may help other people in the future. You may or may not receive any direct benefit from participating. There may also be risks associated with participating in research studies.

Your participation is voluntary. You may refuse to participate, or may withdraw your consent to participate in any study at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your doctor. You do not have to participate in research in order to receive treatment.

Details about this study are discussed below. It is important that you understand this information so that you can decide in a free and informed manner whether you want to participate. You will be given a copy of this consent form. You are urged to ask the investigators named above, or staff members who may assist them, any questions you have about this study at any time.

STUDY PURPOSE

What is the purpose of the study and how long will it last? Type 2 diabetes is very common in North America. People with Type 2 diabetes have a higher chance of getting heart disease or stroke than people without diabetes. The purpose of the ACCORD study is to determine the best approaches to lower the risk of heart disease and stroke in people with Type 2 diabetes.

ACCORD will answer three research questions. In diabetes, the level of sugar in the blood is too high. So the first question is to determine the effects of lowering blood sugar to a level below that normally targeted in current clinical practice, compared with a level that is usually targeted. Many diabetic patients have high blood pressure. So the second question is to determine the effects of lowering blood pressure to a level below that normally targeted in current clinical practice, compared with a level usually targeted. Many diabetic patients also have problems with their blood lipids (like cholesterol, fat-like materials in the blood). So the third question is to determine the effects of treating several components of blood lipids compared with treating only one component. Each of these questions is described in more detail below.

You are being invited to participate in ACCORD because you have Type 2 diabetes

along with other factors that increase your chance of having future heart disease and stroke, or you may already have had heart disease or stroke. Your participation in the study will last until 2009. However, study results will be reviewed regularly to see if the trial should be stopped earlier than this. Most participants will be in the ACCORD study between 5 ½ and 8 ½ years.

The total number of participants will be about 10,000 from approximately 77 clinics throughout the United States and Canada. The study will involve approximately ___ patients at the _____ clinical site. ACCORD recruited about 1,200 participants during the Vanguard (pilot) portion of the trial in 2001 and these participants are still being treated and followed.

STUDY SUMMARY

What will happen if you take part in this study? Initial visits will be conducted to determine whether you qualify for the study. These are called "screening" visits. Your medical history, blood pressure, and past blood sugar and cholesterol measurements will be reviewed to determine whether you qualify for the study. You will have a short physical exam, and one tube (about 2 teaspoonfuls) of blood may be collected and tested for creatinine (a measure of kidney function), lipids and liver function. Some urine will also be collected and tested for protein.

If you qualify for the study and volunteer to participate, your study doctor will treat your blood sugar and either your blood pressure or your blood lipids according to the ACCORD study protocol. You and your personal physician are still responsible for other parts of diabetes care, including general preventive measures, foot care, and eye care. If you are not in the blood pressure part of ACCORD, your personal physician will still be responsible for treating your blood pressure. If you are not in the blood lipids part of ACCORD, your personal physician will still be responsible for treating your blood lipids (such as blood cholesterol). In addition, you will still need to see your personal physician(s) for all other medical care.

Blood sugar treatment groups. If you qualify and consent, you will be randomly assigned (like the flip of a coin) to one of the two blood sugar goals. The "intensive" goal is a blood sugar level lower than the current recommended value. The "standard" goal is a blood sugar level similar to the current recommended value. Your current treatment for diabetes (if any) will be changed to study treatment based on the goal to which you are assigned. Your study treatment will use available and approved diabetes treatments (oral medications and/or insulin as may be required).

If you are randomized to the intensive blood sugar goal, it is very likely that you may need one or more of the following: a) at least 2 oral medications; b) 3 or more insulin injections per day; c) frequent self-adjustment of insulin; and d) frequent home glucose monitoring. This means you will probably have to take several pills, give yourself insulin injections with a small needle, and do finger sticks to test your blood sugar up to eight times a day.

The degree of control of blood sugar is best measured by a test called hemoglobin A1c.

This test gives an average of your sugar values during the past 2 to 3 months. If you are in the intensive blood sugar treatment group, the goal will be to keep your hemoglobin A1c at less than 6.0% (which is about an average blood sugar of 115 mg/dl (6.4 mmol/L)). This level is much lower than usually achieved in clinical practice. If you are in the standard blood sugar treatment group, the goal will be to keep your hemoglobin A1c value between 7.0% and 7.9% with the average around 7.5% (average blood sugar of 160 mg/dl (8.9 mmol/L)). This level is also lower than that usually achieved in clinical practice. Lowering hemoglobin A1c to this level from higher levels has been shown to reduce complications of diabetes like eye and kidney diseases. Your diabetes medications may be adjusted upwards or downwards, as your study doctors try to reach these blood goals safely.

Compared to the intensive target of a hemoglobin A1c of less than 6.0%, the standard hemoglobin A1c target of 7.5% has a somewhat higher risk for some diabetes complications. These include eye disease (retinopathy), kidney disease (nephropathy), and abnormal nerve function (neuropathy). On the other hand, a hemoglobin A1c of less than 6.0% will increase somewhat the risk for developing serious low blood sugar reactions (hypoglycemia) and weight gain. Whether the lower hemoglobin A1c target gives more or less protection against cardiovascular disease (such as heart attack or stroke) is not known. This is what ACCORD is trying to find out.

In the standard group, ACCORD will take action and recommend treatment to lower your blood sugar if your hemoglobin A1c value becomes greater than 7.9%. If your hemoglobin A1c drops below 7.0% and you are taking insulin or a secretagogue (like glimepiride or repaglinide) , we may reduce your diabetes treatment to try to bring your value above 7.0%. In the intensive group, if your hemoglobin A1c value becomes even slightly greater than 6.0%, we will increase your treatment.

Depending on your initial blood pressure and blood cholesterol results, you will also be asked to participate in either the blood pressure or cholesterol parts of the study. You must participate in one or the other (based on your qualifications) to participate fully in ACCORD.

Blood pressure treatment groups. Blood pressure lowering can prevent heart disease, stroke, and kidney disease. There is some evidence that lowering blood pressure further than current practice might help prevent heart disease and stroke in people with diabetes. This possibility needs careful testing in a study such as this one.

If you qualify for the blood pressure portion of the study, you will be randomly assigned (like the flip of a coin) to one of two blood pressure goals. The "intensive" goal is a blood pressure level lower than that already proven to reduce heart disease and stroke. The "standard" goal is a blood pressure level similar to that already proven to reduce disease. Your study doctor will choose the medications he/she feels will be best for treating your blood pressure. Therefore, your current blood pressure medication (if any) could be changed or continued. If you do not reach your blood pressure goal, your study doctor will change your treatment until you do.

Blood lipid treatment groups. Lowering blood cholesterol can prevent heart disease

and stroke. There is also some evidence that changing other blood lipids by lowering triglycerides (a type of fat in the blood) and raising HDL-cholesterol (the good cholesterol) may prevent heart disease in people with diabetes. This possibility needs careful testing in a study such as this one.

If you are eligible to participate in the blood lipid study, your current cholesterol medication treatment (if any) will be stopped and changed to the study medication. You will be treated with cholesterol-lowering medication commonly known as a "statin". The statin used in ACCORD is called simvastatin.

The dose of simvastatin you are started on will depend on your medical history. If you have had a heart attack , stroke, heart surgery, surgery on your arteries (blood vessels) or angina (chest pain) with changes in an electrocardiogram (ECG or EKG), you will be started on 40 mg of simvastatin. If you have not had any of those, you will receive 20 mg a day of simvastatin.

Regardless of your assigned dose of simvastatin, you will be randomly assigned (like the flip of a coin) to a medication known as a fibrate to lower your triglycerides and raise your HDL-cholesterol, or to a placebo (a pill that does not contain any medicine). The fibrate used in ACCORD is called fenofibrate. Neither you nor your doctor will know which study treatment (placebo or fibrate) you are receiving. If it becomes necessary to know for medical reasons, the information will be made available.

If you begin ACCORD at the 20 mg dose of simvastatin and your cholesterol levels remain higher than the currently recommended level, or if you have a heart attack, stroke, heart surgery, surgery on your arteries (blood vessels) or angina (chest pain) with changes in an electrocardiogram (ECG or EKG) during the study, your dose of simvastatin will be increased to 40 mg per day. If your cholesterol level remains too high despite treatment with the increased dose of simvastatin, you will be taken off the lipid study medications and sent to your personal doctor to get appropriate treatment to reduce your cholesterol level.

Genetic component. Genetic research will be done as part of this study. You may, if you wish, volunteer for the genetic portion of the study. If you volunteer to participate in the genetic portion of ACCORD, your blood will be stored for genetic (DNA) analysis. The genetic portion of ACCORD is described in more detail below. You do not need to agree to participate in the genetic studies to participate in the main ACCORD study.

Visit schedule and measurements. If you qualify for ACCORD and are assigned to the standard blood glucose group and either the lipid trial or the standard blood pressure group, you will be asked to visit the clinic at one month, four months, and every four months thereafter for the duration of the trial. If you are assigned to any of the other groups, you will be asked to come every month for the first four months of the study and then at least every two months thereafter until the end of the study.

At each clinic visit, your health will be reviewed, and any symptoms you may have will be discussed with the study doctor or nurse or other study staff. Your weight, blood pressure, and heart rate will be measured, and your study medications will be reviewed

to make sure you are taking them correctly. You will receive nutrition and physical activity recommendations and will be taught how to follow them. In addition, a member of your ACCORD study care team may contact you by phone between your clinic visits to determine how you are feeling and whether or not further action is required to control your blood sugar or blood pressure levels.

You will have blood specimens (up to five tablespoons) drawn every four months for the first year and once a year thereafter. These tests will measure blood sugar, potassium, kidney function, and liver function. You will also be asked to allow blood and urine specimens to be taken and stored for future non-genetic studies. Also, additional blood samples may be taken occasionally to monitor your treatments for safety, which may require you to come in for additional visits.

Some urine will be collected at the baseline visit and every two years thereafter so that it can be examined for urine protein and creatinine (a measure of kidney function). You will also have an electrocardiogram (a recording of the electrical activity of the heart, also called an ECG or an EKG) at baseline and every two years thereafter. A limited eye exam will be done every other year.

If you are in the cholesterol study, your blood cholesterol will be measured every four months during the first year and every year thereafter until the end of the study. You will also have blood drawn every four months throughout the study to check your kidney function. If you are not in the cholesterol study, you will have your cholesterol measured every year.

As part of diabetes management, you will be expected to check your own blood sugar, as discussed later. If you are assigned to the "intensive" blood sugar goal you will have more frequent blood sugar testing by the clinic. This testing will range from once per month during the first 4 months of treatment to every two months thereafter.

You also have about a 1-in-5 chance of being chosen to complete questionnaires about your quality and activities of life, and your diet and physical activity levels. These questionnaires will be given at the beginning of the study, your 1 year visit, 3 year visit, and 4 year visit. The questionnaires will take about one hour of your time. In addition, you may be chosen to participate in a group where health care costs will be monitored (and you would be asked to give permission to obtain records from any hospitalizations).

Certain medical procedures are recommended for people with diabetes that are not part of the research study. These include annual eye exams by an ophthalmologist, annual foot exams, annual flu and pneumococcal vaccinations, and electrocardiograms (ECGs or EKGs). The study eye examination does not replace the recommended annual eye exams by an experienced eye care professional, such as an ophthalmologist (a doctor who specializes in the diagnosis and treatment of eye diseases).

During the course of the trial, our central Coordinating Center at Wake Forest University School of Medicine, or its representatives may contact you, about your participation in the trial. For example, you may be asked if you are having any trouble taking any of

your medications. You may also be asked how you are feeling and whether you have been in the hospital for any reason, why and where you were hospitalized.

POTENTIAL RISKS OF PARTICIPATING IN THE ACCORD STUDY

What are the possible risks and discomforts? Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are considered to be abstinence (not having sex), oral contraceptives (the pill), intrauterine device (IUD), DepoProvera, Norplant, tubal ligation (tubes tied), or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable method, involves the careful use of condoms and/or a spermicidal foam or gel along with a diaphragm, cervical cap, or sponge. We encourage you to discuss this issue further with your doctor if you have any questions.

If you are a pregnant woman, you cannot participate in this study. Because some methods of birth control are not 100% reliable, a negative pregnancy test is required at least 10 days after your last normal menstrual period if you are a sexually active woman of childbearing potential.

This study requires that blood be drawn from a vein in your arm several times during the study. Drawing blood may result in pain at the point of puncture, a feeling of faintness, irritation of the vein, and bruising or bleeding at the site of the needle stick. There is also a very slight possibility of an infection at the needle puncture site. The study visits, procedures, and lab work might be more often than your medical conditions usually require, but they are very important for the study.

This study requires daily finger-stick measurements of your blood sugar level. You probably have experience testing your blood sugar by finger-stick before coming into the study. You need to test your blood sugar daily because it is very important for the study that you keep your blood sugar values at the assigned goal. If you are assigned to the intensive blood sugar goal, there is a good chance that at some point you will be asked to do up to eight finger sticks a day to properly correct your blood sugar. Your blood sugar checks will be reviewed by clinic personnel and will be used to figure out your treatment plan. Clinic personnel, or others working for ACCORD, may contact you to discuss your blood sugar results.

Treating blood sugar in persons with diabetes can sometimes cause blood sugar to be too low. This condition, called "hypoglycemia", can result from changing diet, exercise, or medication. Symptoms are usually mild but sometimes can be more serious.

Mild symptoms of hypoglycemia include hunger, anxiety, dizziness, or light-headedness. Sometimes there is sweating, fatigue or mild confusion, tremors (shaking) or palpitations (feeling your heart beating in your chest). Hypoglycemia may cause loss of consciousness. If this occurs while operating machinery such as driving a car, it can result in injury or even be life threatening.

In rare cases, hypoglycemia can be very severe and require emergency treatment or hospitalization. Severe hypoglycemia may cause brain damage, coma, or death. Severe hypoglycemia can occur in any patient taking medication to lower blood sugar. It is more likely to occur in those treated with insulin to achieve lower glucose targets, as in the intensive treatment group of this study.

A sugar-containing drink such as fruit juice usually quickly relieves the milder symptoms. You may be given sugar pills to raise your blood sugar if you have symptoms. Medications are sometimes needed to treat severe hypoglycemia. These may include intravenous (I.V.) fluids or injections of glucagon, a medication that rapidly increases blood sugar.

Regardless of which blood sugar treatment group you are assigned to, safety will always be of first importance when changes in the management of your blood sugar are made. Based on data from previous studies it is estimated that, in the intensive group, about six out of 100 participants will have a serious complication (such as hospitalization or emergency room visit for hypoglycemia) every year. In the standard group about 2 participants may have such a complication every year. In either group, ACCORD doctors and nurses will take action to lessen the risk of hypoglycemia should it occur too often or in a severe form. On the other hand participants in the standard group may have a somewhat higher risk of complications related to diabetes (like eye, kidney disease or abnormal nerve function). It is estimated that, in the intensive group, about one out of 100 participants will have such a complication every year. In the standard group about 1.5 participants may present such a complication every year.

If you are assigned to the intensive blood pressure group, you may experience blood pressure that is too low. Symptoms of low blood pressure may be mild, such as feeling a little lightheaded, or less often may be more severe, such as dizziness, fatigue, or fainting. Sitting or lying down often relieves these symptoms. You should notify your clinic doctor or nurse if you have these symptoms. Clinic staff will follow you closely to lower your chances of having too-low blood pressure.

What are the side effects of the medicines used in the study? All drugs have a potential risk of an allergic reaction, which if not treated quickly, could become life threatening.

You may have side effects from the specific medications chosen as treatments. Medications that may be used at this time in ACCORD are listed below. Additional medications may be chosen in the future. The ACCORD staff will tell you about any new medicines that they may give you.

Possible side effects for the classes of medications include the following. Your doctors have ways to manage these effects.

Blood sugar treatments

Sulfonylureas [glimepiride]: The most common side effects associated with this family of medicines include hypoglycemia (low blood sugar), weight gain, and allergies. Very rarely, blood cell abnormalities may occur. Your doctor has ways of managing the

blood cell abnormalities.

Biguanides [metformin]: Common side effects associated with this drug class include nausea, vomiting, diarrhea, bloating, loss of appetite, or metallic taste in the mouth. These usually get better after the first few weeks of treatment. If these treatments are stopped, the side effects will go away over a day or two. Very rarely, people can have a severe reaction known as lactic acidosis (a condition that occurs when your body fluids and tissues have too much acid in them). Lactic acidosis almost always occurs in people with advanced kidney disease, liver disease or heart failure, and in people who drink alcohol heavily. Every effort will be made to avoid using this drug in people with those conditions.

Thiazolidinediones (TZDs) [rosiglitazone, pioglitazone]: The most common side effects related to this group of medicines include fluid retention (a condition that occurs when your body holds in too much water) and weight gain. Although the 4 mg/day dose of rosiglitazone (the TZD to be used in ACCORD) is the only dose of rosiglitazone that has been approved by the U.S. FDA for use with insulin, higher doses of rosiglitazone, which you may be placed on, have been combined with insulin in medical practice. The use of drugs like rosiglitazone together with insulin may cause fluid retention, which could lead to or worsen heart failure. Heart failure is a decreased ability to pump enough blood throughout the body. Symptoms of heart failure include shortness of breath, cough, fatigue, tiredness, ankle swelling, or weight gain. If your doctor prescribes insulin together with rosiglitazone, you will be monitored closely for these symptoms, so that the medications can be adjusted or, if necessary, stopped.

Although there has been no report of liver difficulties with rosiglitazone, a related medication was removed from the market due to rare, severe liver reactions. Thus, if you require this medication, you will need to have blood tests looking for liver problems every two months for the first year after you begin the medication and once a year thereafter.

Insulin [various short-, intermediate-, or long-acting forms, including aspart and glargine]: Potential side effects related to insulin use include: low blood sugar, low potassium in the blood, allergies or skin changes.

Meglitinides [repaglinide]: Common side effects include headache, upper respiratory infections, nausea, vomiting, constipation, and diarrhea. The most serious side effect is hypoglycemia.

Alpha-Glucosidase Inhibitors [acarbose]: Side effects include flatulence (gas), diarrhea and abdominal discomfort These are generally mild to moderate in severity and usually diminish in frequency and intensity with time. Very rarely, this medication may cause skin reactions, hepatitis, and/or jaundice (yellowing of the skin or whites of the eyes, indicating possible liver problems).Blood pressure treatments

Angiotensin Converting Enzyme Inhibitors (ACE-I) [benazepril, lisinopril, ramipril]: Potential side effects associated with this type of medicine include: dizziness, headache, fatigue, nausea, diarrhea, cough, rash, high potassium in the blood, low

blood pressure upon standing, harm to kidney function and rarely angioedema (swelling of the face, lips and tongue that can result in difficulty breathing or in rare cases, death).

Diuretics [chlorthalidone, hydrochlorothiazide]: Potential side effects associated with this class of medication also known as "water pills" include: muscle cramps, nausea, vomiting, diarrhea, dizziness, rash, weakness, low blood pressure, low potassium, high blood sugar, partial or total lack of ability to perform sexual function, and gout (a painful joint condition that occurs when too much acid and salt build up in the blood stream and joints).

Beta Blockers [metoprolol]: The most common side effects associated with this group of medicines include: dizziness, fatigue, stomach upset, depression, cold hands and feet, low blood pressure, changes in heart rhythm and heart rate, and decrease in sexual function. Beta-blockers may also hide some of the symptoms but not the hazards of low blood sugar. If you begin taking these medications, you should not stop taking them without talking to your study doctor first.

Calcium Channel Blockers [isradipine, diltiazem, amlodipine, nifedipine]: The most frequent side effects associated with these medications are: ankle or foot swelling, dizziness, flushing, palpitations (awareness of your heartbeat), headache, fatigue, nausea and abdominal discomfort. Occasionally, severe hypotension (abnormally low blood pressure) may occur when starting these medications or adjusting their dose. Rarely, increased angina (chest pain) and myocardial infarctions (heart attacks) may occur in people with severe coronary artery disease. When combined with a Beta Blocker, the medication nifedipine may cause congestive heart failure (a decreased ability to pump enough blood through the body), which can be serious but is very rare.

Alpha Blockers [terazosin]: Potential side effects associated with this category include: fainting, dizziness, fatigue, swelling, low blood pressure, partial or total lack of ability to perform sexual function, changes in heart rhythm and certain blood cell abnormalities.

A-II Receptor Blockers [candesartan, valsartan]: The most common side effects are dizziness, headache, fatigue, diarrhea, muscular-skeletal pain. More serious side effects are angioedema (swelling of the face, lips and tongue that can result in difficulty breathing or in rare cases, death) and severe hypotension. This family of drugs may also affect your kidney function. Your doctor may do blood tests to see if your kidneys are performing properly.

Loop Diuretic [furosemide]: rare side effects include thrombocytopenia (low platelet count), rash, pancreatitis (inflammation of the pancreas), and jaundice (yellowing of the skin or whites of the eyes, indicating possible liver problems). Serious side effects include abnormalities in blood cells.

Sympatholytics [reserpine]: The most common side effects include dizziness, dry mouth, nausea, vomiting, nasal congestion, peripheral edema (too much fluid in the body's tissues), stomach cramps, headache, impotence, depression, nervousness,

shortness of breath, nightmares, difficulty with urination, shaky hands, and anorexia (poor appetite). More serious side effects include dysrhythmias (heart rhythm abnormalities), black tarry stools, hematemesis (vomiting blood), bradycardia (slow heart rate), chest pain, and thrombocytopenia (low platelet count).

Vasodilators [hydralazine]: Side effects include headache, tachycardia (fast heart rate), angina (chest pain), and palpitations. Rare but more serious side effects include abnormalities in blood cells and lupus-like syndrome.

Potassium Sparing Diuretics [triamterene]: The most common side effects include diarrhea, nausea, vomiting, gastrointestinal distress, dizziness, dry mouth, pruritis (itching), rash, sensitivity to light, weakness, hypotension, muscle cramps, blood chemical imbalances (such as too much potassium), impaired kidney function, elevated uric acid, blood cell abnormalities and reduced folic acid stores. More serious possible side effects include increased acid in the blood and shock due to an allergic reaction to the medication.

Alpha-beta blockers [carvedilol]: The most common side effects are dizziness and fatigue. The more serious side effects include AV block (a heart rhythm disturbance), bradycardia (slow heart rate), thrombocytopenia (low platelet count), and bronchospasm (tightening of breathing airways). Alpha-beta-blockers may also hide some of the symptoms but not the hazards of low blood sugar.

Lipid treatments

HMG-CoA Reductase Inhibitors (statins) [simvastatin]: Common side effects associated with this class of cholesterol-lowering medications include: headache, dizziness, stomach upset. Rare, but more serious side-effects are muscle aches, rash and elevated liver enzymes (indicating possible liver problems) in the blood. (Also, see 'Drug Interactions' discussed below.)

Fibrates [fenofibrate]: Potential side effects associated with these medications include: abdominal pain, stones in the gall bladder, jaundice (yellowing of the skin and/or whites of the eyes, indicating possible liver problems), headache, change in taste, elevated liver and kidney function tests, and certain abnormalities in blood cells. Your study doctor has ways to manage these blood cell abnormalities.

Fenofibrate could possibly harm the kidney. Blood tests will be done regularly to look at your kidney functioning. If your results are not normal your dose of fenofibrate or placebo (whichever you are on) will be reduced. If your values do not improve, the medication will be stopped entirely. After your dose is reduced or stopped, your study doctor will continue to monitor your kidney function. (Also, see 'Drug Interactions' discussed below.)

Drug Interactions

What are some of the ways the study drugs can interact? The Food and Drug Administration (FDA) has approved all drugs that will be used in ACCORD. Most have been used for many years. Therefore, we know much about the way these drugs work and how they interact with other drugs - especially other treatments that will be used in

this study.

Researchers know that using a sulfonylurea (a type of drug that lowers blood sugar) with certain other drugs should be avoided. Your study doctor will make sure that you do not take these kinds of medicines together.

Researchers also know that using statins and fibrates together may increase the chance for certain side effects such as liver problems and muscle pain and inflammation. These side effects are rare, but are more likely at higher statin doses. If your dose of simvastatin is increased to 40 mg per day, your chance of side effects may be increased. Many doctors use simvastatin and fenofibrate together, and the ACCORD trial will use caution whenever you are given this combination. Additionally, the ACCORD clinic will be checking your blood to make sure that the study medications are not harming your liver or muscles. These tests will be done at 1, 4, 8, and 12 months after you begin the medications, and every year after that. If your study doctor thinks that the statin and fibrate medicines are causing problems for you, then he/she may take you off one or both these medicines.

If you are eligible to be in the lipid portion of ACCORD and if you are on warfarin (also called Coumadin), your personal doctor will be informed both by phone and in writing that you may be on fenofibrate. Because the use of fenofibrate generally means that your dose of warfarin should be reduced to avoid excessive risk of bleeding, you will be tested to see how fast your blood clots. This blood test can be done by either the ACCORD clinic or by your private doctor. You will not be randomized until the ACCORD clinic staff speaks with your private doctor about monitoring the appropriate dose of warfarin for you. If you are placed on warfarin during the study, you will need to make sure that your private doctor is reminded that you may be on fenofibrate.

POTENTIAL BENEFITS

What are the possible benefits? The ACCORD treatment may or may not be of personal benefit to you. The information gathered from the study will be very important for the treatment of diabetes in the future. There will be no charge to you for any of the required tests and procedures performed during your participation in this study. Clinic visits, physical exams, laboratory tests, electrocardiograms and any other procedures associated with the research aspects of this study are paid for by the study. In addition, your medications for the blood sugar control as well as for the blood pressure control portion or blood lipid control portion of ACCORD (whichever part you are in) will be provided to you free of charge. You will not be paid for your participation in this study.

ALTERNATIVE TREATMENTS

If you chose not to participate, what other options do you have? You do not have to participate in this research study in order to receive treatment. A number of treatments are available for diabetes, high blood pressure, or high cholesterol. These treatments include drugs, diet, exercise, and weight loss. If you decide to stop

participating in this study, your personal doctor should manage your medical care.

NEW INFORMATION

What if we learn about new risks during the study? You will be given any new information gained during the course of the study that might affect your health, welfare, or willingness to stay in the ACCORD study. Results of your laboratory tests and clinical measurements will be provided to you to share with your personal physician.

PRIVACY

How will your privacy be protected? Any information obtained about you during this study will be treated as strictly confidential to the full extent permitted by applicable law. To ensure confidentiality, a code number will be assigned to you. Your name and any other potentially identifying information will not be used on any data or samples you provide. However, your name and Social Security and Medicare numbers will be recorded and stored centrally to help the study keep track of any illnesses you may experience. Also, in order to receive supplies (glucose strips) to measure your own blood glucose during the trial, you will need to provide the information that will permit billing for Medicare (if you are covered) and/or other insurance you may have (if you have it.) You will not be identified in any report or publication about this study.

Your records for this study may be reviewed by authorized representatives from the National Heart, Lung, and Blood Institute, the Food and Drug Administration (FDA) and monitoring personnel from the _____ Clinical Center Network Office for the study at _____and by the committee in charge of protecting research participants at_____.

At the end of the study, all forms with your name or other identifying information will be kept in a locked room for a period of five years. Only your study doctor or co-workers assisting the doctor will have access to these forms. After five years, the forms will be destroyed.

Also at the end of the study, the Coordinating Center will provide the National Heart, Lung, and Blood Institute (NHLBI) data from the study, without personal identifying information such as your name, address, Social Security number, or Medicare number. Blood, urine, and/or tissue samples or other materials taken from you during the study will be considered donated by you to medical research. These materials may also be provided to the NHLBI at the end of the study, again without personal identifying information. The data and/or materials may be shared with other scientists who meet NHLBI requirements including treating the data or materials as medically confidential, obtaining approval from their Human Subjects review boards, and agreeing not to share the data or materials with other parties. Drug companies that have contributed drugs, and in some cases money, to the ACCORD study also will be provided study data without any personal identifying information.

U.S. Federal Certificate of Confidentiality. It is particularly important to you to know that ACCORD has been granted a Certificate of Confidentiality from the United States Federal Government to make sure we can best protect your privacy. This certificate means that the ACCORD researchers cannot be forced to tell anyone not connected with the study about your participation. This includes courts and police. The researchers will only release information if you request it.

There are some limits to the researcher's ability to maintain your confidentiality. If we learn that keeping information private would immediately put you in danger, or put someone else we know about in danger, then we will have to tell the appropriate agencies to protect you or the other person.

INJURY

What will happen if you become ill during the study or suffer a complication related to the treatment that you are receiving as part of the study? While it is not likely that you will suffer major health problems as a result of your participation in this study, the medical treatment that is a part of this study carries a small risk of serious health problems. Of course, should a problem occur, or should you need emergency medical help, necessary emergency care would be provided and the investigator working with you would help you find a doctor to continue your care if needed. Any cost of medical care that results from such a health problem will be your responsibility and will not be paid for by the National Heart, Lung, and Blood Institute, the study investigators, or the hospital or clinic conducting this study.

QUESTIONS ABOUT THE STUDY AND YOUR RIGHTS

What if you have questions about this study? For questions about the study or in the event of a research-related injury, contact the study investigator, _____, at _____ [INCLUDE AFTER-HOURS NUMBER].

What if you have questions about your rights as a participant? For questions about your rights as a research participant, you may contact the Chairman of the Institutional Review Board, which is a group of people who review the research to protect your rights as a research participant, at _____. You will be given a copy of this consent form.

What if you want to stop before your part in the study is complete? Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your study doctor also has the right to stop your participation in this study at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

GENETIC STUDIES

What is the goal of the genetic studies? One goal of ACCORD is to examine your genetic material (DNA) and its relationship to the effects of the treatments. If you volunteer to participate in the genetic studies you will be asked for a sample of blood (about 1 teaspoon) to obtain DNA from your blood cells. Information gained from research on your DNA may be used to develop new ways to detect or treat major diseases.

Will the DNA samples be shared with other institutions? If you agree to participate in the genetics portion of the study, the ACCORD Central Laboratory may share DNA samples with researchers participating in ACCORD. If you give permission, samples may also be shared with other research laboratories studying the genetics of type 2 diabetes and the development of heart and blood vessel diseases, other major diseases, health conditions, or risk factors. The scientists from these laboratories would be given the DNA without any information to identify you.

How will genetic information be kept private? Only the ACCORD Central Laboratory will have access to the samples. No other individual, including your spouse, parents, children, physician or employer will have access to the stored sample or information gained from your stored sample. At the end of the study, your samples may be provided to other investigators under certain conditions, without any personal identifying information (See Privacy section above).

How long will the DNA samples be kept? Your sample may be kept until it is no longer of scientific value. If, at any time during the study, you decide that you do not wish to have your DNA sample stored any longer, notify your ACCORD study coordinator and the sample will be destroyed.

Who owns the samples? By checking "yes" at the end of this document, you volunteer to provide genetic samples for medical research purposes. Your DNA will not be sold to anyone or to institutions or companies for financial gain or commercial profit without your consent. Also, neither you nor your heirs will receive money from any discoveries or inventions made using the information and/or specimens you provide. There is no cost to you or your insurance company for the storage and use of the samples.

Will you receive study results of research involving your samples? You will not be informed of the results of the research performed on your genetic blood sample, although genetic tests may be developed after a study of samples in the ACCORD study. If there is any new information about genetic testing for type 2 diabetes and its relationship to heart and blood vessel diseases or other health conditions, you will be informed by your study doctor if this information may be important to you or your family.

PARTICIPANT'S AGREEMENT FOR THE GENETIC PORTION OF ACCORD

*Please check **one** of the following choices:*

____ **Yes**, I agree to participate in the genetic portion of ACCORD

____ No, I do **NOT** agree to participate in the genetic portion of ACCORD

If you agreed to participate in the genetic portion of ACCORD, please check one of the following regarding diseases to be studied:

____ I agree to allow my genetic sample to be studied for genes related to any major disease or health condition or risk factors.

____ I agree to allow my genetic sample to be studied **ONLY** for genes related to diabetes, blood pressure, blood cholesterol abnormalities, heart disease, other cardiovascular diseases, kidney diseases, or other risk factors for heart disease or for diabetes.

If you agreed to participate in the genetic portion of ACCORD, please check one of the following regarding investigators who will have access to the genetic samples:

____ I agree to allow my genetic samples to be used for research by ACCORD investigators as well as by other researchers who meet NHLBI standards and procedures.

____ I agree to allow my genetic samples to be used **ONLY** for research by ACCORD investigators.

PARTICIPANT'S AGREEMENT FOR ACCORD STUDY

I have read the information provided above. I voluntarily consent to participate in the ACCORD study.

_____ _____

Participant's signature Date

_____

Printed name of participant

_____ _____

Signature of person obtaining consent Date

_____

Printed name of person obtaining consent