CHAPTE ONE: ORGANIZATION AN STRUCTURE

ACCORDION organizational structures and responsibilities are similar to those utilized in the ACCORD trial. Seven Clinical Center Networks (CCNs) and a Coordinating Center (CoC) are contracted by the National Heart, Lung and Blood Institute to work together to successfully conduct the study. Each CCN is responsible for clinical sites within its network. In addition, there is a Central Chemistry Laboratory, and an ECG Reading Center.

Names, addresses, telephone numbers, fax numbers, and email addresses can be found using a searchable directory on the ACCORDION web site at www.accordionstudy.org.

1.1 ORGANIZATIONAL STRUCTURE

1.1.1 Clinical Center Networks and Clinical Sites

Each CCN consists of a network of clinical sites that are involved in the enrollment and follow-up of study participants. The CCNs responsible for the activities of their clinical sites and oversee clinical sites during the study on issues related to recruitment, protocol adherence, and quality control. While clinical sites interact principally through their CCNs, they will transmit their data directly to the CoC.

1.1.2 The Coordinating Center

The CoC is responsible for coordinating the writing and updating of the protocol; coordinating development and distribution of the Manual of Procedures (MOP); 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 database and web site; and analyzing all data.

During the recruitment phases of the trial, the CoC is responsible for monitoring recruitment and provides reports to the CCNs, the Executive Committee, the Steering Committee, and the NHLBI Project Office.

1.1.3 ECG Center and Central Laboratory

The ECG Center and the Central Laboratory provide central interpretation of resting ECGs, HbA1c and other blood measurements on study participants. Each core unit is responsible for development and distribution of specific measurement procedures, timely data gathering, and analysis.

1.1.4 NHLBI Project Office and Other Government Representatives

ACCORDION 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. The National Eye Institute (NEI), National Institute on Aging (NIA), National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) and the Centers for Disease Control and Prevention (CDC) are also co-sponsors of ACCORDION.

1.2 ADMINISTRATION AND GOVERNANCE

1.2.1 The ACCORDION Steering Committee

The ACCORDION Steering Committee provides the leadership for the study and establishes scientific and administrative policy. It is composed of the seven CCN Principal Investigators (PIs), the CoC PI, the NHLBI Project Officer, the Steering Committee Chair, and the Steering Committee Vice-Chair.

The Steering Committee oversees the overall conduct of the study. The committee also considers and adopts changes in study procedures as necessary during the course of the study. Voting members include the seven CCN PIs, the CoC PI, and the NHLBI Project Officer. The Steering Committee Chair, or Vice-Chair in his absence, votes only to break a tie.

There are three standing subcommittees of the Steering Committee: the Operations/Retention Subcommittee, the Morbidity and Mortality Subcommittee, and the Papers and Presentations Subcommittee. Subcommittees are responsible for monitoring specific portions of the conduct of the study and providing periodic status reports to the Steering Committee.

1.2.1.1 Operations and Retention Subcommittee

The charge of this group is to assure communication among the clinical sites with respect to overall study coordination, recruitment, and implementation of follow-up. During the recruitment phase of the study, this subcommittee monitors recruitment and screening, and assists the Clinical Center Networks experiencing recruitment difficulties. During the follow-up phases of the trial, this subcommittee monitors all aspects of participant retention, including visit adherence. The subcommittee is chaired by a CCN Coordinator and rotates annually.

1.2.1.2 Morbidity and Mortality Subcommittee

Using a representative sample of all outcomes reported in the study, this Subcommittee will review information from the clinical centers and classify each event 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.

1.2.1.3 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.

1.2.2 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, CoC personnel, Project Office personnel, one CCN PI and the current Chair of the Operations and Retention Subcommittee. The CCN PI position is rotated annually.

1.2.3 The Observational Safety Monitoring Board

An independent Observational Safety Monitoring Board (OSMB) monitors data and participant safety. Members of the OSMB, 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 CoC, and representatives from sponsoring federal agencies participate in OSMB calls as non-voting members. The OSMB meets at least once a year and will make recommendations to NHLBI regarding study continuation.

CHAPTER 2: REGULATORY RESPONSIBILITIES

As an NIH-funded study, ACCORDION will follow applicable federal regulations (45CFR46) and international guidelines (ICH/GCP) throughout the study period. Sites are expected to be familiar with, and adhere to, all applicable international, federal, state and local laws, guidelines and policies.

2.1 INSTITUTIONAL REVIEW BOARD/RESEARCH ETHICS BOARD APPROVALS

IRB/REB approval must be obtained at each clinical site, each CCN, the Central Laboratory, ECG Reading Center and Coordinating Center. Copies of IRB/REB approvals should be forwarded to the CoC as soon as they are available. Study enrollment may not begin at a local site until the local IRB/REB approval letter and copies of approved consent forms are received and reviewed by the CoC. Website access will not be granted until all necessary documents are received by the CoC.

2.2 SENDING DOCUMENTS TO THE COORDINATING CENTER

Sites are expected to send copies of the following regulatory documents to the CoC:

- Initial IRB/REB approval letter
- Blank (not signed) copies of IRB/REB-approved consent forms
- Continuing IRB/REB review approval (must be at least annually)
- IRB/REB approval letters for protocol amendments, as applicable
- IRB/REB approval letters for consent form changes, as applicable
- Local audit reports, if findings are specific to ACCORDION
- Other significant IRB/REB correspondence (e.g., withdrawal of approval, reinstatement of lapse approval, etc.)

2.3 ACCORDION REGULATORY BINDER

IRB approvals must be renewed annually and proof of all approvals/renewals must be the submitted to the ACCORDION Coordinating Center.

The Regulatory Binder serves as the regulatory record of a clinic's participation in the ACCORD study. It should be kept current and available for review by the CCN Coordinators during site visits. This book should include current copies of:

- The protocol and revisions
- Curriculum vitae for the investigators, sub-investigator and study coordinator

- IRB/REB approvals, renewals and correspondence
- Copies of IRB/REB approved informed consent document(s)
- Research participant advertisements, brochures, pamphlets, if used
- Correspondence (may keep separate correspondence file)
- Site visit log
- Enrolled participant log with pertinent identifier information (study number and acrostic)

Other study materials may be added in conjunction with local standard operating procedures.

2.4 ADVERSE EVENT REPORTING

Because ACCORDION is not an interventional trial, adverse events will not be systematically collected. In the Code of Federal Regulations, Serious Adverse Events (SAEs) are defined as being (1) unexpected, (2) serious in nature, and (3) related to study drug. Because there is no study drug in ACCORD and all three criteria must be met to qualify an event as reportable, SAEs will not be collected centrally.

Sites with local policies that do not match the federal guidelines should contact their IRB/REB for specific reporting guidelines. It is possible that events will need local reporting despite not being collected in ACCORDION.

CHAPTER THREE:

RECRUITMENT AND INFORMED CONSENT

3.1 RECRUITMENT OF STUDY COHORT

Participant recruitment is of prime importance to the success of this study. Only former ACCORD participants may be enrolled in ACCORDION. Listed below are points to consider on recruiting participants.

- The study provides a system of follow-up, which parallels the participant's private care, but does not conflict with it. Approach potential participants more than once, if necessary, unless they request no further contact.
- Emphasize the importance of the ACCORD results and, therefore, the importance of obtaining more information.
- Be courteous and pleasant, at all times.
- Be professional and show interest and enthusiasm in the study.
- Potential participants may be told, "We don't know the answers, but here is a chance to help medical science." 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.

3.1.1 Develop a Recruitment Plan

Developing a plan is vital to successful recruitment in any study. In addition to this section, sites may elect to revisit the ACCORD Survival Kit manual, for specific tips and recruitment tools that may be helpful. This manual was provided to each site as an additional reference during the ACCORD trial.

1. Identify staff involved with recruitment, review their responsibilities, and set regular meeting times.
2. Determine the number of ACCORD participants needed to contact per week in order to successfully enroll the specified amount.
3. Discuss your recruitment plan with your Project Coordinator and Network Team, as they can provide extra assistance as needed.
4. Monitor your recruitment progress and revise your plan as needed.
5. Meet weekly as a team to discuss progress. Review barriers and problems and revise the plan as necessary.
6. Maintain a log of all participants contacted.
7. Stay involved and motivated.

a. Keep your Network team informed. Share your ideas and problems.
b. Keep your staff informed of your site's progress and thank them for their support and help.

3.1.2 Recruitment Materials

Specific recruitment materials will not be distributed by the CoC. However, clinical sites are free to develop such materials and tools to be used locally. All recruitment materials should be approved by the local IRB/REB before use. (Copies are not needed at the CoC.)

3.2 ELIGIBILITY

All former ACCORD participants are eligble to participate in ACCORDION. This includes those who finished the main ACCORD trial, but did not participate in the phone-only Extension. Unless a participant has refused further contact, all living former ACCORD participants should be contacted.

3.3 OBTAINING INFORMED CONSENT

Clinical sites were given four consent documents for use in obtaining informed consent. Sites only need to submit the documents they will be using to their IRB/REB. The documents distributed were:

- Document for participation in ACCORDION
- Addendum for participation in ACCORDION Eye
- Addendum for participation in ACCORDION MIND
- Addendum for participation in ACCORDION MIND-MRI

Use of these model documents, with limited, locally-required revision only, is strongly encouraged. Significant deviations must be approved by the CoC. The ACCORDION protocol and all applicable consent documents must be approved by the local IRB/REB before enrollment can begin.

Informed consent must be obtained from the participant or his/her Legally Authorized Representative (LAR) at or prior to the first ACCORDION visit. Principles of informed consent, as detailed in ICH/GCP Guidelines, must be adhered to, including but not limited to a complete description of expectations, potential risks and benefits, and confidentiality. Potential participants should be given ample time to review the document and ask any questions. Local institutional policies regarding the consent process, including the use of an LAR, should be followed at all times.

Because approximately half of all ACCORDION participants will have a phone visit before their first in-clinic visit, local sites may consent potential participants by mail. Consenting by mail must be approved by the local IRB/REB and sites should adhere to any local policies.

Revisions to the model consent form documents, if needed, will be distributed from the CoC to all CCNs and clinical sites.

CHAPTER FOUR:
IN-CLINIC VISIT PROCEDURES

4.1 VISIT SCHEDULE OF ACCORDION STUDY ACTIVITIES – 1ST CLINIC VISIT

1. Print all appropriate visit forms prior to the participant coming into the clinic. This is done by:
    - Login to the ACCORDION website (www.accordionstudy.org)
    - Click on Data Management/Recruitment & Consent
    - Find the Participant ID number from the pick list
    - Click on Print 24 M Forms
2. This visit should occur as close as possible to the target date. For the first and last clinic visits, participants will be instructed to attend the clinic following an overnight fast (at least 8-10 hours). If a participant is not fasting the clinic should attempt to schedule a re-draw. If the participant is unwilling or unable to come back for a re-draw, all specimens should be obtained and a comment on the form should be made (i.e. Participant Non-Fasting). The HbA1c and urine ALB/Creatinine specimen are not affected by a participant's status. However, the Lipid Profile is affected because the triglycerides values will be increased. A code will be made at the Central Lab if a participant is non-fasting. The code will be reported on the results sent to the clinics.
3. For all clinic visits, participants should be instructed to bring any medications they've taken in the last two weeks with them to the clinic. They should not take their glycemia or lipid (if applicable) medications on the morning of this clinic visit but should take their blood pressure medication (with water) prior to coming to clinic. If the participant has not taken their BP 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. During the visit, the following procedures will be conducted:
4. Verify that the main study consent form has been reviewed and signed. If participant is also in the MIND and/or Eye Substudy, verify that the appropriate consent form has been obtained and signed.
5. Update the Participant Contact Information at this clinic visit and check the participant's medical release of information.
6. Inquire about any outcome events that have occurred or procedures that were performed since the last time event data were collected and record dates on the **In-Clinic Follow-up Form**. If the participant has had a reportable event, make sure that a medical release of information has been obtained in order to be able to collect the additional information to complete the **Death Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form, and/or Miscellaneous Cardiovascular Outcome Report Form.** Upon completion these forms and supporting documentation are mailed or faxed to the Coordinating Center. (Please

note: medical records are **not** required for the Miscellaneous Cardiovascular Outcome Report Form).

7. Review the Concomitant Medications list (located in the **Clinic Follow-up Form)** with participant to document medications currently taking.
8. Perform the physical exam, including weight, height, waist circumference, and foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 7, Section 7.2 and Section 7.3.3).
9. Additional procedures to be completed only at the first and last clinic visit include:
    a. Blood samples and urine samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, total cholesterol, VLDL-C, LDL-C, HDL-C, triglycerides, serum creatinine, ALT, urine creatinine and urine microalbuminuria. (See Central Chemistry Lab MOP for details).
    b. A standard 12-lead ECG will be obtained using the Heart Square and the measurements sent electronically to the ECG Reading Center. Retain a copy for the participant's research records. (See ECG MOP for details). In regard to the site PI's responsibility for "Alert" ECGs, PIs need to use good clinical practice and judgment. This process is aimed to provide a safety net for the participants during the ECG exam.
    c. Electrocardiograms for the ACCORDION study should always be transmitted to EPICARE electronically. In the rare occasion when it is not possible, the following steps should be followed by the field clinic to get the original hard copy ECG to EPICARE ECG Reading Center:
        - Immediately notify the ECG Reading Center by email (copying the CoC ( ). The reason for sending the hard copy should be stated in the email and the measures taken to prevent this from happening again in the future.
        - The field clinic should make a good copy of the ECG to keep in the participant's chart.
        - The original hardcopy ECG should be sent to the ECG Reading Center using either UPS or FedEx so shipment can be tracked to ensure the safety of the ECG's.
        - The shipment should be sent to the ECG Reading Center using the following address:

    d. Participants will be given the **Health Utilities Index Form and the HRQL form** and instructed on how to complete it. Verify that the participant completes all items before end of visit and review for suicide risk. (Refer to MOP Chapter 5, Section 5.2.2)

10. At the first clinic examination for consenting MIND participants complete cognitive test battery.
11. Obtain a medical release covering the next 12 months.
12. Schedule next 6 month contact.
13. Complete the following forms and data enter as required:
    a. **Participant Contact Information Form (as necessary)**
    b. **Encounter and Disposition Form**
    c. **In-Clinic Follow-up Form**
    d. **HUI**
    e. **HRQL**
    f. **Lab Shipment Form (send to Central Lab, no data entry necessary)**
    g. **Study Status Form (as necessary)**
14. Complete the following forms (as needed) and send to the CoC for data entry:
    a. **Death Report Form**
    b. **MI Report Form**
    c. **Stroke Report Form**
    d. **Unstable Angina Report Form**
    e. **Miscellaneous CV Event Form**

4.2 Visit Schedule of ACCORDION Study Activities – 2st Clinic Visit

1. Print all appropriate visit forms prior to the participant coming into the clinic. This is done by:
    - Login to the ACCORDION website (www.accordionstudy.org)
    - Click on Data Management/Recruitment & Consent
    - Find the Participant ID number from the pick list
    - Click on Print ## M Forms (## denotes the visit month).
2. This visit should occur as close as possible to the target date.
3. Update the Participant Contact Information at this clinic visit and check the participant's medical release of information.
4. Inquire about any outcome events that have occurred or procedures that were performed since the last time event data were collected and record dates on the **In-Clinic Follow-up Form**. If the participant has had a reportable event, make sure that a medical release of information has been obtained in order to be able to collect the additional information 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 or faxed to the Coordinating Center. (Please note: medical records are **not** required for the Miscellaneous Cardiovascular Outcome Report Form).
5. Review the Concomitant Medications list (located in the **Clinic Follow-up Form**) with participant to document medications currently taking.
6. Perform the physical exam, including weight, height, waist circumference, and foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 7, Section 7.2 and Section 7.3.3).

7. Obtain a medical release covering the next 12 months.
8. Schedule next 6 month contact.
9. Complete the following forms and data enter as required:
    a. **Participant Contact Information Form (as necessary)**
    b. **Encounter and Disposition Form**
    c. **In-Clinic Follow-up Form**
    d. **Study Status Form (as necessary)**
10. Complete the following forms (as needed) and send to the CoC for data entry:
    a. **Death Report Form**
    b. **MI Report Form**
    c. **Stroke Report Form**
    d. **Unstable Angina Report Form**
    e. **Miscellaneous CV Event Form**

4.3 Visit Schedule of ACCORDION Study Activities – 3rd Clinic Visit

1. Print all appropriate visit forms prior to the participant coming into the clinic. This is done by:
    - Login to the ACCORDION website (www.accordionstudy.org)
    - Click on Data Management/Recruitment & Consent
    - Find the Participant ID number from the pick list
    - Click on Print ## M Forms (## denotes the visit month).
2. This visit should occur as close as possible to the target date. For last clinic visit, participants will be instructed to attend the clinic following an overnight fast (at least 8 to 10 hours). If a participant is not fasting the clinic should attempt to schedule a re-draw. If the participant is unwilling or unable to come back for a re-draw, all specimens should be obtained and a comment on the form should be made (i.e. Participant Non-Fasting). The HbA1c and urine ALB/Creatinine specimen are not affected by a participant's status. However, the Lipid Profile is affected because the triglycerides values will be increased. A code will be made at the Central Lab if a participant is non-fasting. The code will be reported on the results sent to the clinics.
3. Participants should be instructed to bring any medications they've taken in the last two weeks with them to the clinic. They should not take their glycemia or lipid (if applicable) medications on the morning of this clinic visit but should take their blood pressure medication (with water) prior to coming to clinic. If the participant has not taken their BP 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. During the visit, the following procedures will be conducted:
4. Update the Participant Contact Information at this clinic visit and check the participant's medical release of information.
5. Inquire about any outcome events that have occurred or procedures that were performed since the last time event data were collected and record dates on the **In-Clinic Follow-up Form**. If the participant has had a reportable event, make sure that a medical release of information has been obtained in order to be able to collect the additional information to complete the **Death**

Report Form, Myocardial Infarction Report Form, Stroke Report Form, Unstable Angina Report Form, and/or Miscellaneous Cardiovascular Outcome Report Form. Upon completion these forms and supporting documentation are mailed or faxed to the Coordinating Center. (Please note: medical records are **not** required for the Miscellaneous Cardiovascular Outcome Report Form).

6. Review the Concomitant Medications list (located in the **Clinic Follow-up Form**) with participant to document medications currently taking.
7. Perform the physical exam, including weight, height, waist circumference, visual acuity (last clinic visit only, refer to MOP Chapter 7, Section 7.4), and foot exam. Using the appropriate technique for the Omron device, obtain blood pressure and pulse (See MOP Chapter 7, Section 7.2 and 7.3.3).
8. Additional procedures to be completed at the last clinic visit include:
    a. Blood samples and urine samples will be obtained, processed and shipped to the ACCORD Central Lab for measurement of HbA1c, total cholesterol, VLDL-C, LDL-C, HDL-C, triglycerides, serum creatinine, ALT, urine creatinine and urine microalbuminuria (See Central Chemistry Lab MOP for details).
    b. A standard 12-lead ECG will be obtained using the Heart Square and the measurements sent electronically to the ECG Reading Center. Retain a copy for the participant's research records. (See ECG MOP for details). In regard to the site PI's responsibility for "Alert" ECGs, PIs need to use good clinical practice and judgment. This process is aimed to provide a safety net for the participants during the ECG exam.
    c. Electrocardiograms for the ACCORDION study should always be transmitted to EPICARE electronically. In the rare occasion when it is not possible, the following steps should be followed by the field clinic to get the original hard copy ECG to EPICARE ECG Reading Center:
        - Immediately notify the ECG Reading Center by email ( ) copying the CoC ( ). The reason for sending the hard copy should be stated in the email and the measures taken to prevent this from happening again in the future.
        - The field clinic should make a good copy of the ECG to keep in the participant's chart.
        - The original hardcopy ECG should be sent to the ECG Reading Center using either UPS or FedEx so shipment can be tracked to ensure the safety of the ECG's.
        - The shipment should be sent to the ECG Reading Center using the following address:

    d. Participants will be given the **Health Utilities Index Form and the HRQL form** and instructed on how to complete it. Verify that the participant completes all items before end of visit and review for suicide risk. (Refer to MOP Chapter 5, Section 5.2.2).
9. Obtain a medical release covering the next 12 months.
10. Schedule next 6 month contact if there is another visit indicated on participant schedule.
11. Complete the following forms and data enter as required:
    a. **Participant Contact Information Form (as necessary)**
    b. **Encounter and Disposition Form**
    c. **In-Clinic Follow-up Form**
    d. **HUI**
    e. **HRQL**
    f. **Lab Shipment Form (send to Central lab, no data entry necessary)**
    g. **Study Status Form (as necessary)**
11. Complete the following forms and data enter as required:
    a. **Death Report Form**
    b. **MI Report Form**
    c. **Stroke Report Form**
    d. **Unstable Angina Report Form**
    e. **Miscellaneous CV Event Form**

CHAPTER FIVE: ASSESSMENT OF HEALTH RELATED QUALITY OF LIFE (HRQL) IN ACCORDION

5.1 Introduction

The goal of the ACCORDION HRQL investigation is to assess the continued impact of the ACCORD interventions on well being in all participants enrolled in ACCORDION. This assessment will address the effects on general health and well being.

5.1.1 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.

5.1.2 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 depressive symptoms with Patient Health Questionnaire.

5.2 The HRQL Instruments

Selection of the ACCORDION 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.

5.2.1 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.

5.2.2 Depression Assessment and Alert

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.

5.2.2.1 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 section 5.4).
- Once the questionnaire has been reviewed for completeness, 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 9 ("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 section 5.2.2.2 below for instructions).
- If the response to question 9 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 section 5.2.2.2 below for instructions).

5.2.2.2 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.

Notification at Data Entry
A notification system has been set up to alert site staff of emergent and non-emergent alerts. Such notifications will automatically appear at the top of the form upon saving HRQL questionnaire data in the ACCORDION 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.

5.3 Data Collection

All of the ACCORDION 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 and now being evaluated by ACCORDION. 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 Section 5.4 below for methods to conduct the interviewer administered HRQL form.

5.4 Methods For Collecting ACCORDION HRQL Data

In the ACCORDION 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. Suggestions are included below 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 truer 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 is 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 is 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.

CHAPTER SIX: OUTCOME REPORTING

ACCORDION will collect information on specific outcomes that match the ACCORD trial outcomes. These include death by any cause, stroke, MI, and miscellaneous cardiovascular events.

Clinical site personnel must be diligent in identifying events and collecting all relevant and requested data, including hospital data and information from the participant and/or friends or family of the participant. Since completion of most forms requires obtaining information from medical records, clinical sites should have each participant sign a local medical records release a each visit.

6.1 INITIAL EVENT REPORTING

6.1.a EVENTS REPORTED AT REGULARLY SCHEDULED VISITS

When any event of interest is reported at a regularly scheduled visit, th clinical sit should enter the information on the appropriate In-Clinic or Phone Follow-Up Form. Sites should indicate which event(s) the participant has experienced and the date o the event(s) o the form. In the case of multiple events, check all relevant boxes and indicate the dates of the events, even if the events occurred on the same date.

In addition to the Follow-Up Form, the appropriate, event-specific form(s), i.e., the Death, Myocardial Infarction (MI), Stroke, Unstable Angina, and/or Miscellaneous Cardiovascular (MCV) Outcomes Report Forms should be completed and data entered. Sites should collect any necessary supporting documentation for the event(s), and send these materials with the appropriate Report Form(s) to the CoC within 90 days of th date th even was discovered.

Materials may be e-mailed, faxed or mailed to the Coordinating Center. If mailed, the clinical site should photocopy the entire packet, and store the copy i the participant's study chart.

6.1.b EVENTS REPORTED BETWEEN REGULARLY SCHEDULED VISITS

When a event is reported between regularly scheduled visits, the site should complete and data enter the appropriate, event-specific Report Form(s), i.e., the Death, Myocardial Infarction (MI), Stroke, Unstable Angina, and/or Miscellaneous Cardiovascular (MCV) Outcomes Report Form. At the next regularly scheduled visit, the event should be included on the In-Clinic or Phone Follow-Up form, ensuring that the date of event matches that previously entered on the event Report Form. A second event Report Form should NOT be completed for a previously reported event.

Materials may be e-mailed, faxed or mailed to the Coordinating Center. If mailed, the clinical site should photocopy the entire packet, and store the copy i the participant's study chart.

6.2 ACCORDION DEATH REPORT FORM

An **ACCORDIO Deat Report Form** must be completed and data entered whenever a participant dies.

In addition to this form, the clinical site should send supporting clinical documentation to the CoC, with identifying information blacked out and the participant ID on each page. As applicable, documentation should include:

- Death Certificate
- Hospital discharge summary
- Hospice notes
- Admission history and physical
- Emergency room notes
- Autopsy/coroner reports

If the participant dies outside the hospital and there are available medical records that would assist the Morbidity & Mortality Subcommittee members in classifying the cause of death, these records should be sent with the Death Report Form. For example, if a participant known to have cancer died at home, documentation of the cancer diagnosis should be sent. This documentation could include previous hospital discharge summaries, progress notes or patholog notes.

Please see section 5.1.a of the ACCORD Protocol for specific definitions of death classifications and the Death Report Form QxQs for specific instructions regarding form completion.

6.3 ACCORDION MYOCARDIAL INFARCTION REPORT FORM

For event classification purposes, myocardial infarction (MI) in ACCORDION 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). Each of these classifications is further defined in the ACCORD Protocol, section 5.1.b.

An **ACCORDIO Myocardial Infarction Report Form** must be completed and data entered whenever a participant has an MI (heart attack). In addition to the MI Report Form, the clinical site should send copies of supporting clinical documentation, with identifying information blacked out and the participant ID/Acrostic on each page. As applicable, documentation should include:

- Emergency room notes
- Admission history and physical
- Cardiology consults
- Relevant ECGs
- Hospital discharge summary
- Cardiac enzyme data (indicate normal troponin and/or CKMB values) – *the mention of cardiac enzymes elsewhere is not adequate. Actual lab reports are needed and will be requested.*
- Cardiac procedure reports

Please see the Myocardial Report Form QxQs for specific instructions regarding form completion.

6.4 ACCORDION STROKE REPORT FORM

For event classification purposes, stroke in ACCORDION will be defined as either: 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. Each of these classifications is further defined in the ACCORD Protocol, section 5.1.c

An **ACCORDIO Stroke Report Form** must be completed and data entered whenever a participant has a stroke, including a stroke that was not primarily due to a vascular cause (e.g., a tumor). In addition to the Stroke Report Form, the clinical site should send copies of supporting clinical documentation, with identifying information blacked out and the participant ID/ Acrostic on each page. As applicable, documentation should include:

- Emergency room notes
- Admission history and physical
- Hospital discharge summary
- Neurology consult notes
- C scan reports
- MRI reports

Please see the Stroke Report Form QxQs for specific instructions regarding form completion.

6.5 ACCORDION UNSTABLE ANGINA REPORT FORM

For event classification purposes, Unstable Angina in ACCORDION will be defined as new onset exertional angina, accelerated or rest angina, o both. Further definitions are located i the ACCORD Protocol, section 5.3.b.

An **ACCORDION Unstable Angina Report Form** must be completed and data entered whenever a participant has an episode of unstable angina. In addition to the Unstable Angina Report Form, the clinical site should send copies of supporting clinical documentation, with identifying information blacked out and the participant ID/Acrostic on each page. As applicable, documentation should include:

- Emergency room notes
- Admission history and physical
- All relevant ECGs
- Cardiac enzyme lab reports (troponin and/or CKMB values) *the mention of cardiac enzymes elsewhere is not adequate. Actual lab reports are needed and will be requested.*
- Cardiac procedure reports
- Cardiology consult
- Hospital discharge summary

Please see the Unstable Angina Report Form QxQs for specific instructions regarding form completion.

6.7 ACCORDION MISCELLANEOUS CARDIOVASCULAR OUTCOMES REPORT FORM

Th **ACCORDION Miscellaneous Cardiovascular Outcomes Report Form** must be completed whenever participant experiences a therapeutic cardiovascular procedure, or hospitalization for congestive heart failure. Please note that procedures should be therapeutic in nature, NOT diagnostic and include the following:

- PTCA (balloon)
- PTCA (with stent only)
- CABG Surgery
- Carotid angioplasty with stent
- Carotid endarterectomy
- Peripheral angioplasty with o without stent
- Peripheral vascular surgery, including aortic aneurysm repair
- Limb amputation: including partial or digit amputation due to vascular disease

Please see the Miscellaneous Cardiovascular Event Report Form QxQs for specific instructions regarding form completion. Supporting documentation is NOT required for these events unless they are accompanied by an MI, UA, Stroke, or Death.

6.8 OUTCOME EVENT TRACKING

Specific reports for outcome tracking are available on the ACCORDION website to assist with management of clinical events. These reports detail what paper documentation has been received at the Coordinating Center, and what remains missing.

If required documentation is not available, the clinic should send written explanation—including documented attempts at obtaining information—to the Coordinating Center before the event will be cleared on the tracking report.

CHAPTER SEVEN: MEASUREMENT PROCEDURES

7.1 ANTHROPOMETRY

7.1.1 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 participant 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 participants 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.

7.1.2 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.

7.1.3 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.

7.1.4 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.

7.1.5 Waist Circumference (WC)

Equipment: The measuring tape should be made of material that is not easily stretched such as fiberglass.

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 10th 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.

7.2 Blood Pressure/Pulse

7.2.1 Background and Rationale

A standard automated blood pressure measurement device and a specific protocol in ACCORDION for the measurement of BP and pulse will be utilized.

7.2.2 Definition

Seated BP and pulse are measured three times at each clinic visit. The seated BP and pulse readings for ACCORDION 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.

7.2.3 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.

If an OMRON HEM-907 is non-functional and a replacement is not available, a manual (preferably mercury) manometer can be used to obtain a BP measurement.

<u>Equipment</u>

- 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 nor 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 In-Clinic Follow-up Form.

7.2.3.1 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 7.3.2)

Arm measurement:

The proper size cuff must be used to obtain accurate blood pressure (BP) readings. See the table above 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 nor 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.

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.

7.3 GUIDELINES FOR PROPER USE AND MAINTENANCE OF EQUIPMENT

7.3.1 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.

7.3.2 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.

7.3.3 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. For any technical questions in regard to OMRON devices, sites can call Consumer and Professional Services at 877-216-1336.

In the event that sites need to order replacement cuffs or a replacement OMRON HEM 907XL (which is the newer model as the older device is no longer available), sites can call directly, and they can help sites with their need. Sites are responsible for the replacement costs.

7.4 EYE EXAM

7.4.1 Visual Acuity Measurements in ACCORDION

7.4.1.1 Introduction

The measurement of visual acuity is an important endpoint in the ACCORDION Study. The visual acuity will be performed at last in-clinic visit for all participants in the study. Since changes in visual acuity are important endpoints, it is essential for the visual acuity to be measured using the following standard protocol.

7.4.2 Measurement of Visual Acuity

This technique should be used at the last in-clinic visit by the ACCORDION clinical coordinator or qualified staff member at each clinical site. Training for the protocol procedure for clinical site staff that has not been trained previously can be conducted via a teaching video located on the ACCORDION website under the "Videos" link.

Participants should be instructed to bring their current glasses with them for the final in-clinic visit. All participants will be assessed for their "habitual vision" with their usual correction for the distance. Visual acuity will be assessed utilizing the participant'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 that can be printed form the website. The visual acuity score can be recorded on the Visual Acuity data entry page.

7.4.2.1 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. 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.

7.4.2.2 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.

7.4.2.3 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.

7.4.2.4 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.

7.5 TESTING of "HABITUAL" VISUAL TESTING

7.5.1 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.

7.5.2 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.

7.5.3 Scoring Best-Corrected Visual Acuity

The examiner records each letter identified correctly by circling the corresponding letter on the Visual Acuity Worksheet. A slash (/) can be used for letters read incorrectly and letters for which no guesses are made. 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.

7.5.4 Referral of Participant with Visual Acuity Score 70 or Less

Participants whose visual acuity score is 70 or less (less than 20/40), should be referred to an ophthalmologist.

7.6 ACCORDION NEUROPATHY EXAMINATION FORM (FOOT EXAM)

As part of the physical examination at the in-clinic follow-up visits, 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: amputation/foot inspection, 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.

7.6.1 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 participant, whose eyes are closed, is asked to respond 'yes' if he or she 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.

7.6.2 Scoring the ACCORDION 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.

Chapter (16)

Electrocardiography Assessment Manual

ACCORD Follow On Study
(ACCORDION)

The ACCORDION Central ECG Reading Center (CERC)
Epidemiological Cardiology Research Center (EPICARE)
Division of Public Health Sciences
Wake Forest University School of Medicine
Winston Salem, NC

March 22, 2011- Version 2

Table of Contents

I. INTRODUCTION

The Epidemiological Cardiology Research Center (EPICARE) is the ACCORDION Central ECG Reading Center (CERC). It is located at Wake Forest University Health Sciences, Winston Salem, NC. The CERC main contacts are listed in Appendix A.

II. BACKGROUND AND PURPOSE

A standard 12-lead ECG will be obtained for ACCORDION participants at the first and last of the three in-clinic visits and the ECGs will be sent electronically to the ECG Reading Center. Along with the information regarding Q-waves, ST depression, ST elevation, and T-waves, ascertainment of the occurrence of a silent (unrecognized) MI will be identified. The ACCORDION CERC will use the Minnesota ECG classification as basis for detection of myocardial infarction, myocardial ischemia, left ventricular hypertrophy, arrhythmias, and conduction defects. A number of continuous ECG measurements that are known to be associated with a poor prognosis will be also detected from the study ECGs.

III. FIELD CENTER PROCEDURES

The field center procedures include ECG acquisition (section III.1) and local ECG reading by the clinic physician (section III.2).

III.1. ECG ACQUISITION PROCEDURES

At each ACCORDION ECG examination visit, a 12-lead ECG will be recorded for each participant in the fasting status (similar to ACCORD). That is, the ECG must be recorded after an overnight fast (and checking this history in the clinic) and before any snack is given. The ECGs should be transmitted to the CERC at least twice weekly.

III.1.1 Electrocardiograph

The electrocardiograph to be used for ECG recording and transmission in the ACCORDION study is the GE MAC 1200 electrocardiograph which is the same machine used previously in ACCORD. The MAC1200 is a portable device and can easily be moved from one location to another.

- Each machine will be configured specifically for the ACCORDION study ECG acquisition and transmission.
- The MAC1200 is to be used for resting ECG recording only.
- It is not intended for use as a vital signs physiological monitor.
- The MAC1200 has a customized menu specific to the ACCORDION study.
- Appendix B includes the instructional charts that outline the SETUP for the ACCORDION MAC 1200 ECG machines.
- All of the ACCORDION ECG technicians should become familiar with the GE MAC 1200 Operator's Manual.

III.1.2. Supplies

Table 1 summarizes the equipment and supplies needed for recording and transmitting ECGs. Always order supplies in advance.

Table 1

- GE MAC1200 Electrocardiograph
- Telephone jack cable
- Scissors
- HeartSquare
- Felt tip non-toxic washable markers
- The CERC contact list (Appendix A)
- Reference guides for “Patient Data Entry” (Table 2)
- Reference guide for “Transmission of ECG” (Appendix C)
- GE MAC1200 operation manual
- ECG paper
- Disposable silver chloride electrodes
- Alcohol swabs and gauze pads
- Cotton surgical tape
- Examining table disposable paper

III.1.3 Preparation for ECG recording

- Participant should be relaxed and comfortable in supine or semi-recumbent position.
- Examination table/bed should be adequate to comfortably accommodate the participant.
- Supply drape for exposed upper torso.
- An additional covering may be needed to prevent the participant from becoming chilled.
- Make sure ankles and wrists are accessible for electrode application.
- ECG electrode placement should be performed with the technician standing to the participant’s left side.
- Reference guide for “Participant Data Entry” instructions should be available to insure accuracy.
- Supplies needed for ECG acquisition should be assembled and arranged efficiently.

III.1.4 Location of the ECG electrodes

III.1.4.1 Location of limb electrodes (Figure 1)

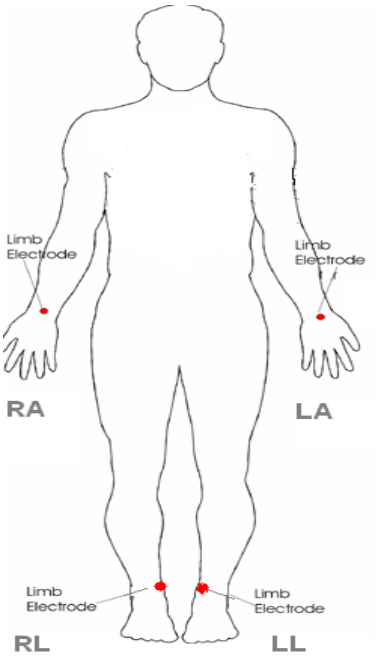
RIGHT LEG (RL) and LEFT LEG (LL):

- On the inner side of the right leg (RL), above the ankle, rub briskly an area about 1-2 inches in diameter with an alcohol swab using firm, circular motions
- Mark the position to place the electrode later.
- Repeat this procedure for the left leg (LL).
- In amputees, the leg lead electrode may be placed higher up on the torso.

RIGHT ARM (RA) AND LEFT ARM (LA):

- Rub the inner side of the right arm (RA) above the wrist similar to what you did with the right and left legs.
- Mark the position to place the electrode later.
- Repeat the process for the left arm (LA).
- In amputees, the arm electrode may be placed on the shoulder, below the clavicle.

FIGURE 1



III.1.4.2 Location of chest electrodes

V1 and V2:

- First, locate the sternal angle about the width of your 3 middle fingers below the sternal notch (Figure 2). Mark a dot over the sterna angle.
- 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. While feeling the sternal angle, move your fingers to the left side of the sternum and feel the 2nd rib between your fingers 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 the reference level for V1 and V2. Mark their locations at the right and left sternal border (Figures 2 and 3).

FIGURE 2

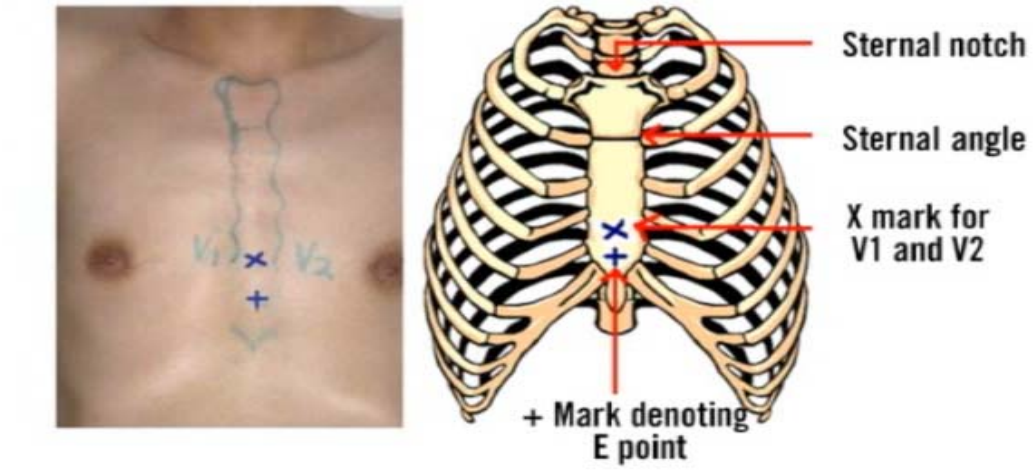
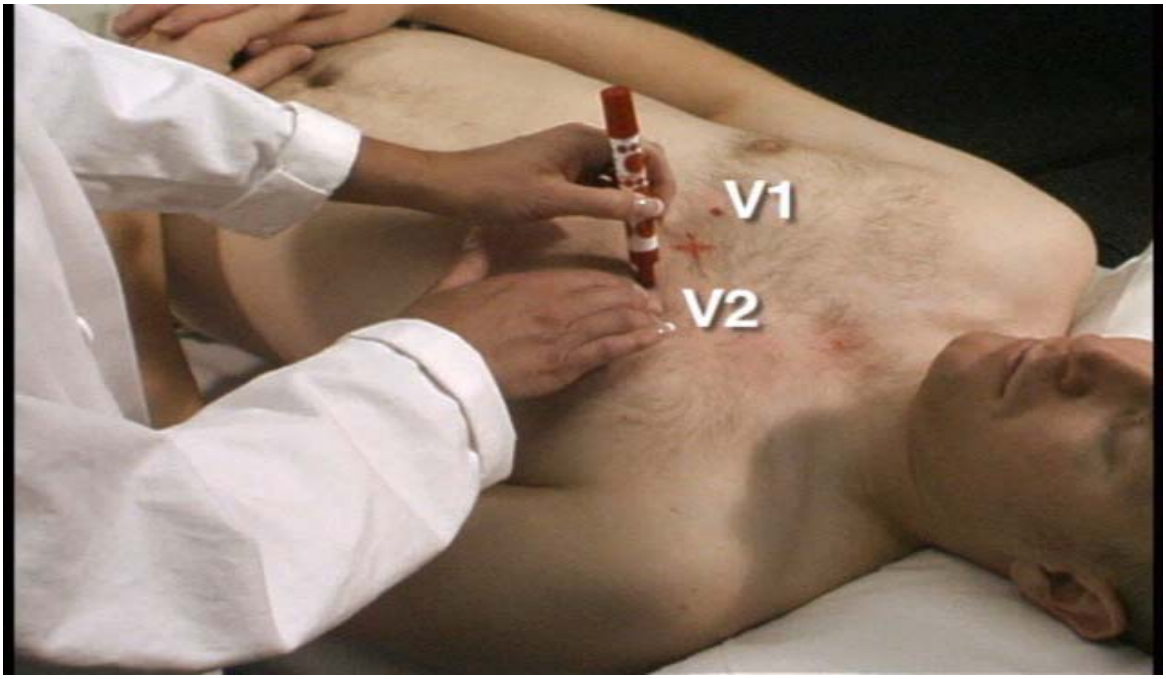


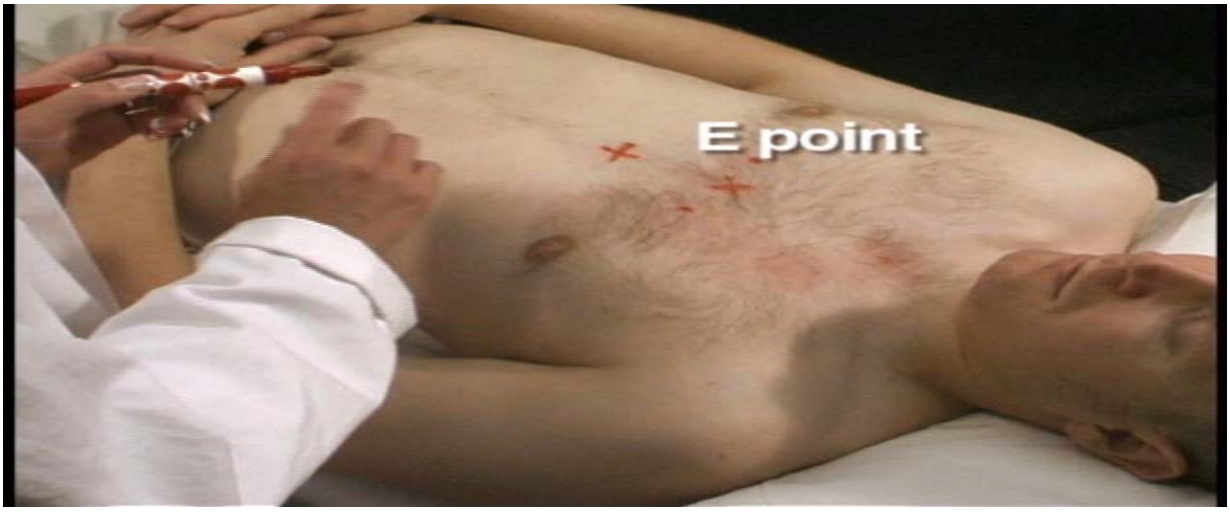
FIGURE 3



V4 and V6

- From the location of V2, palpate with the middle finger of your right hand the 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 then feel the 5th intercostal space with your index finger.
- At the level of the 5th intercostal space, mark a **+** sign at the midsternal line below your **x** mark for V1-V2 level. This **+** is the reference level "E" for V4, V5, and V6 (Figure 2 and Figure 4).
- In overweight persons and in women with tender breast tissue, it is often difficult to locate the 5th intercostal space. In such a case, mark the **+** sign for E point 1 ¼ in (3 cm) below your reference level **X** for V1 and V2 (in smaller adults, 1 inch (2.5 cm) is enough).

FIGURE 4



APPROXIMATE LOCATION OF V6

- Move the left elbow laterally without moving it anteriorly or posteriorly, while observing the anterior and posterior axillary folds. The left elbow must be supported properly.
- Follow a line exactly in the vertical midplane of the thorax (mid-axillary line - Figure 5) down where the line meets the horizontal plane of E point. Using your marker, make a vertical 1-2 inch long line there as an approximate location of V6 (Figure 6).

FIGURE 5

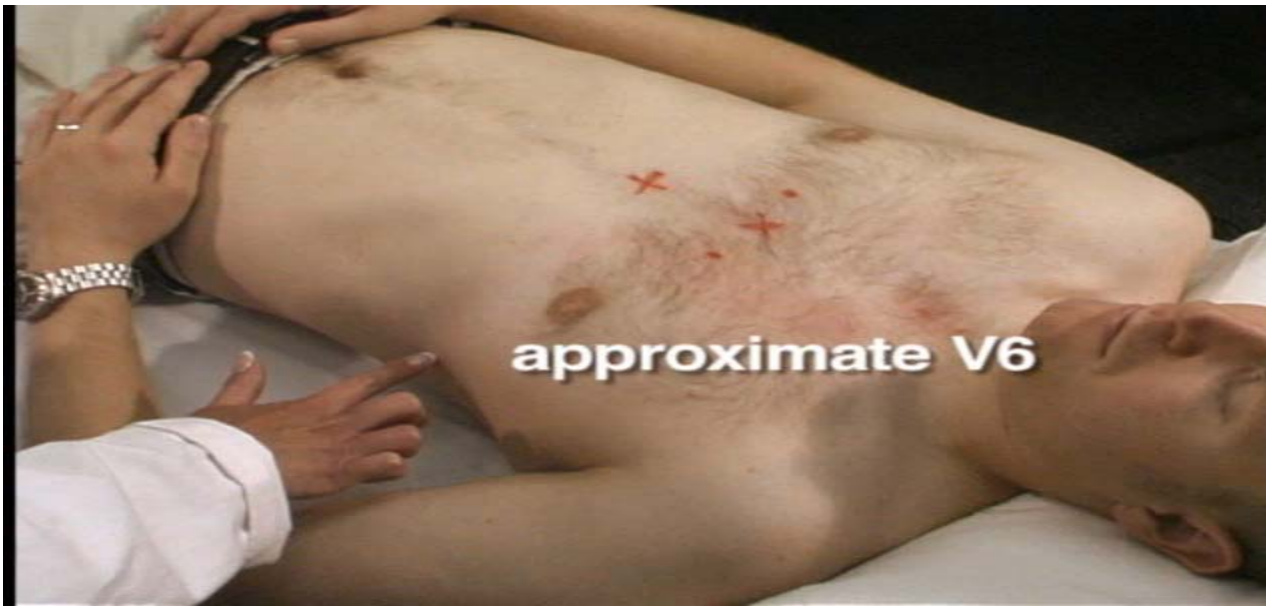
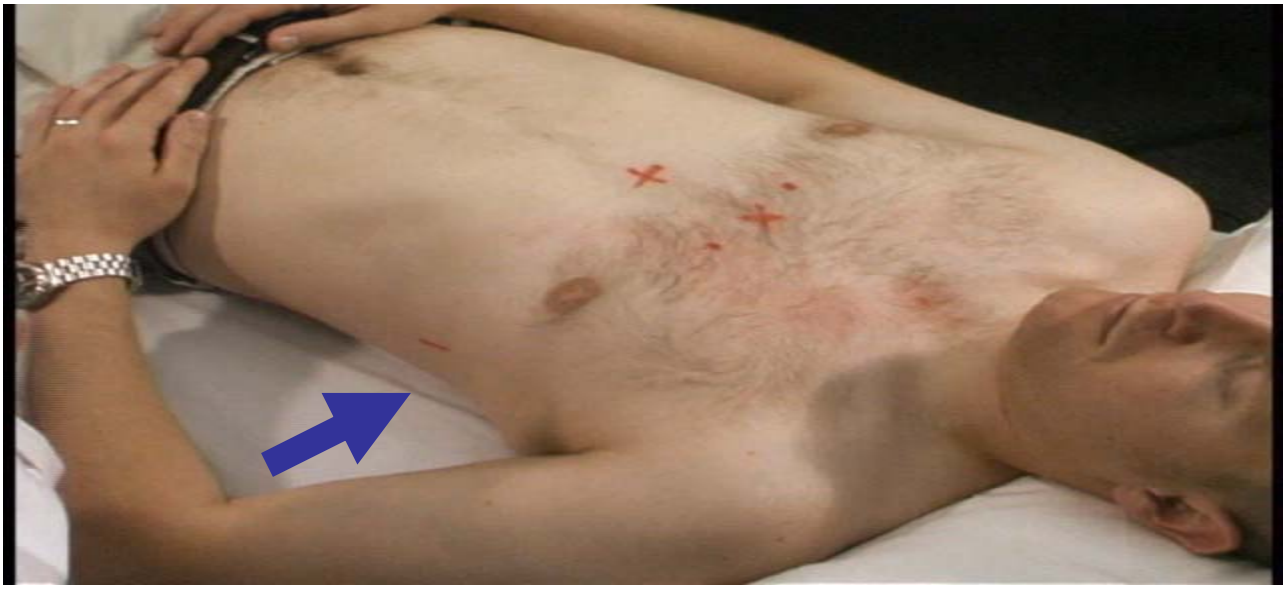


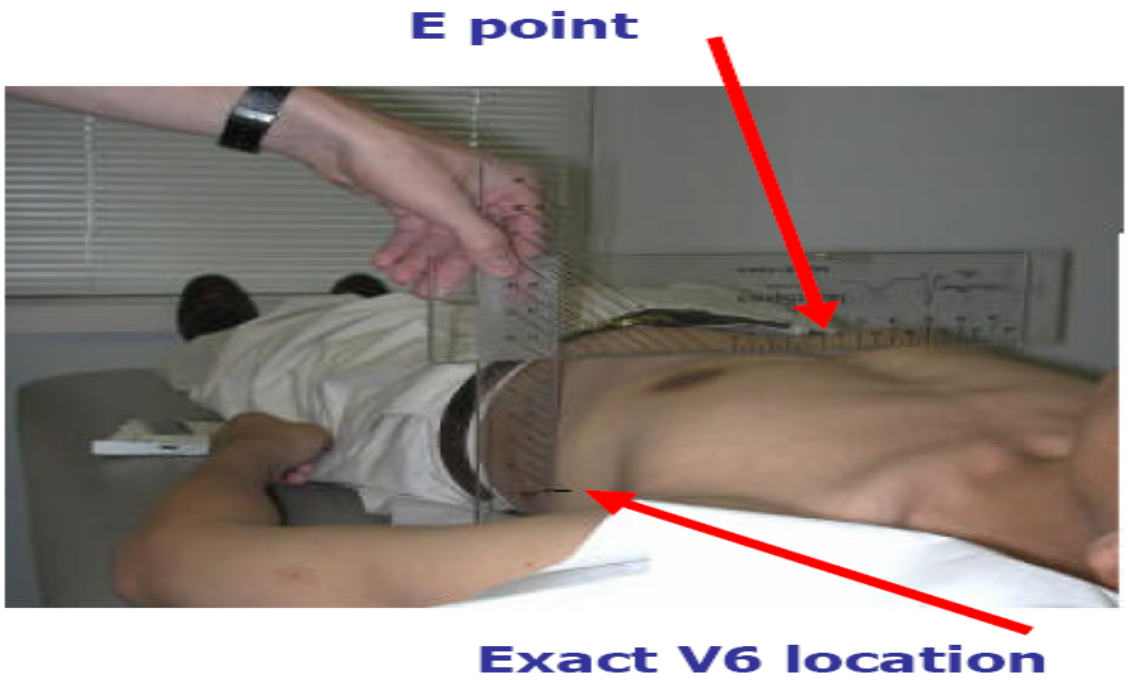
FIGURE 6



EXACT LOCATION OF V6

- Exact location of V6 is determined by using the HeartSquare.
- Place the HeartSquare horizontally with the wider arm (E arm) at level e point (Figure 7).
- Slide the V6 arm of the HeartSquare towards the midaxillary line until the arrow points to the mark at the midaxillary line. Mark the exact location of V6 at the level of the arrow on the V6 arm. Mark the exact location of V6

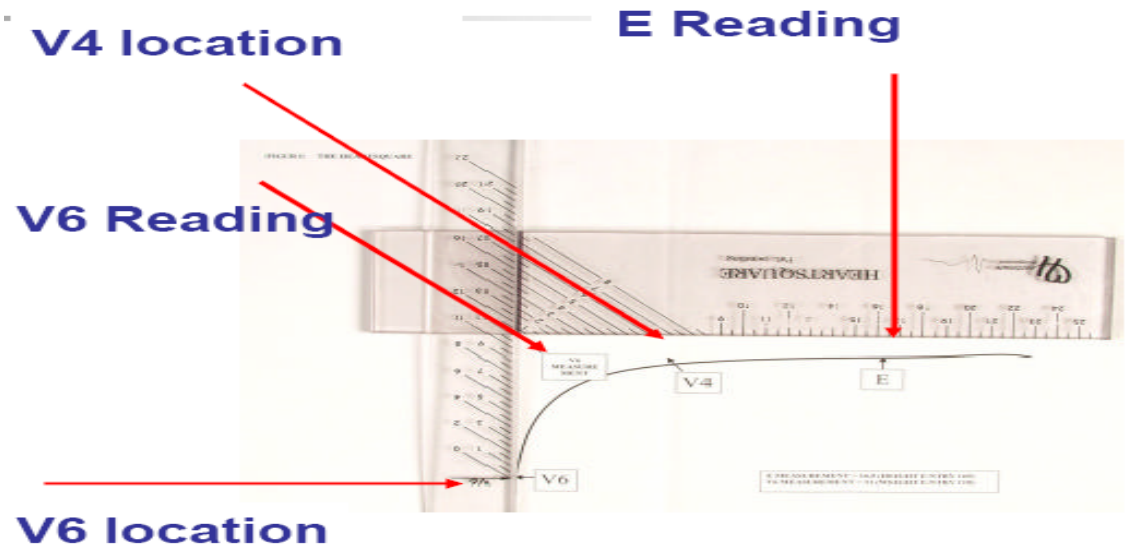
FIGURE 7



EXACT LOCATION OF V4

- While keeping the HeartSquare in the horizontal position with the arrow on the V6 arm pointing toward the V6 position, observe the reading at E point. (Figure 7)
- Use this e reading on the centimeter scale on the V6 arm, and follow this same E reading along the 45 degree lines towards the torso to locate the exact position of V4.
- Now that you have located V6 and V4, secure the V6 arm with your thumb to prevent it from sliding. Note the V6 reading which is the distance from the arrow on the V6 arm to where this arm intersects the E arm at right angles. You may then remove the HeartSquare.
- Enter the E and V6 measurements as three digits. Figure 8 shows that the E entry is 160 and the V6 entry is 120 for the readings of 16.0 cm and 12.0 cm, respectively. Enter the 160 for E in the height field of your Mac 1200 and 120 for the V6 measurement in the weight field. (DO NOT ENTER THE HEIGHT AND WEIGHT OF THE PARTICIPANT).
- If the HEARTSQUARE is too small for participant, enter 000 as the E and V6 measurements

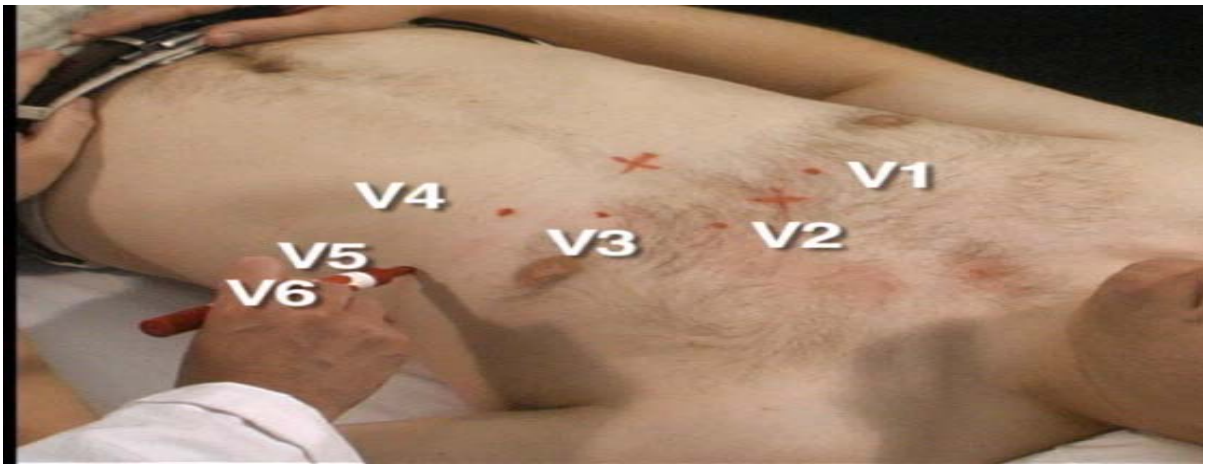
FIGURE 9



LOCATIONS OF V3 and V5

- Mark V3 exactly halfway between V2 and V4 (Figure 10).
- Mark V5 exactly halfway between V4 and V6 (Figure 10).

FIGURE 10



III.1.4.3 Attaching the electrodes:

- After you have marked electrodes positions and rubbed them with alcohol swabs, you may apply the electrodes.
- Lower limb electrodes should be facing up, while upper limb electrodes could be facing up or down
- Do not place electrodes directly over bone.
- Attach lead wires in the same, correct order every time to establish routine and to eliminate lead swaps.
- Position the MULTI-LINK on the participant's abdomen.
- Grasp each lead at the MULTI-LINK attachment point.
- Follow lead wire to the electrode attachment end.
- Attach wire to electrode, making sure clip is not in contact with electrode adhesive.
- Make sure lead wires have some slack and are hanging loosely.
- You may secure the lead wire to the skin by applying paper tape 1-inch below the clip, especially if the ECG shows baseline noise despite careful preparation.

III.1.5. ECG recording

- Turn on the MAC1200.
- Allow the machine to go through the "self-test." Do NOT press "R."
- Press "Pat info" key to enter the participant information
- Use the participant data entry sheet as a reference guide (Table 2).
- Press the START/STOP key to return to the ECG screen on the ECG machine.
- Press the START/STOP key again to record the ECG.

Table 2 Participant Data Entry into the MAC1200 for the ACCORDION Study

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
FIRST NAME*	Enter Visit Code (will be provided to you)
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	No action required
TECHNICIAN	Use other and enter defined Tech. ID #
LOCATION	No action required

* Do not enter participant's name

III.2. Local ECG reading (Alert ECGs)

The computer statements on the clinic ECGs are often overstated i.e. 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." If the ECG says, "nonspecific ST-T abnormalities," "bundle branch block," "junctional rhythm," "low voltage QRS," or perhaps a few other items, the technician may 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:

a) Atrial fibrillation (Figure 11)
b) Atrial flutter (Figure 12)
c) Ventricular tachycardia (Figure 13)
d) Acute myocardial infarction (Figure 14)
e) Ventricular preexcitation/Wolff-Parkinson-White (WPW) ECG pattern (Figure 15)
f) Complete atrioventricular block (Figure 16)
g) Any statement which includes a reference to **acute** injury or ischemia

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.

Figure 11 Atrial fibrillation

Diagnosis key points: irregular QRS complexes (heart rate) and absence of the P wave

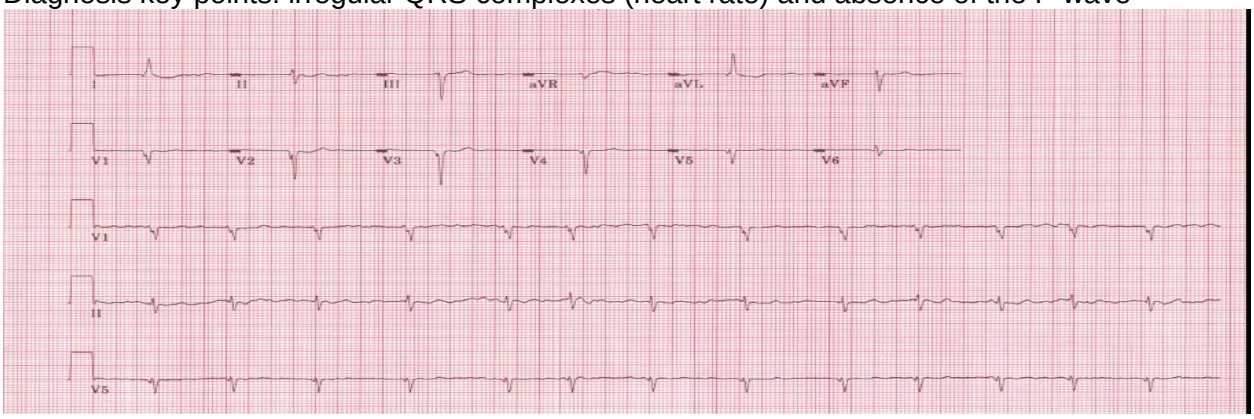


Figure 12 Atrial flutter

Diagnosis key points: multiple P waves; saw-teeth pattern (as in V1), mostly regular but could be irregular with a certain pattern (regular irregularity)

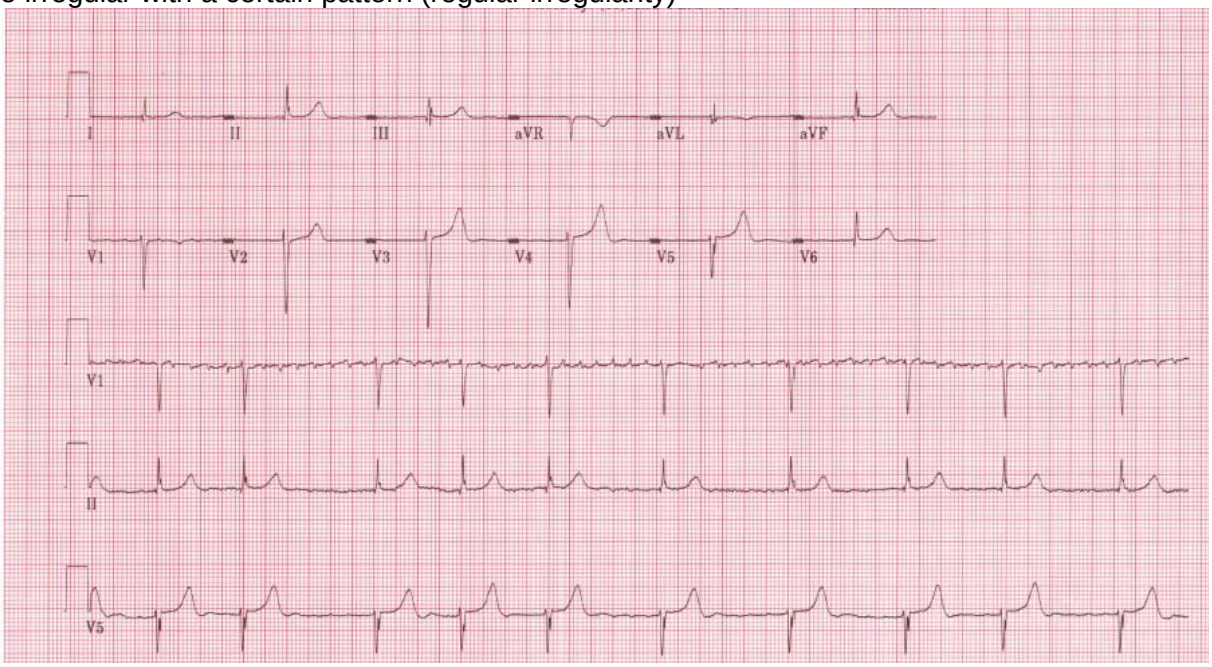


Figure 13 Ventricular tachycardia

Diagnosis key points: Wide complex tachycardia (HR≥110) with QRS not preceded by P wave. The participant will be mostly restless

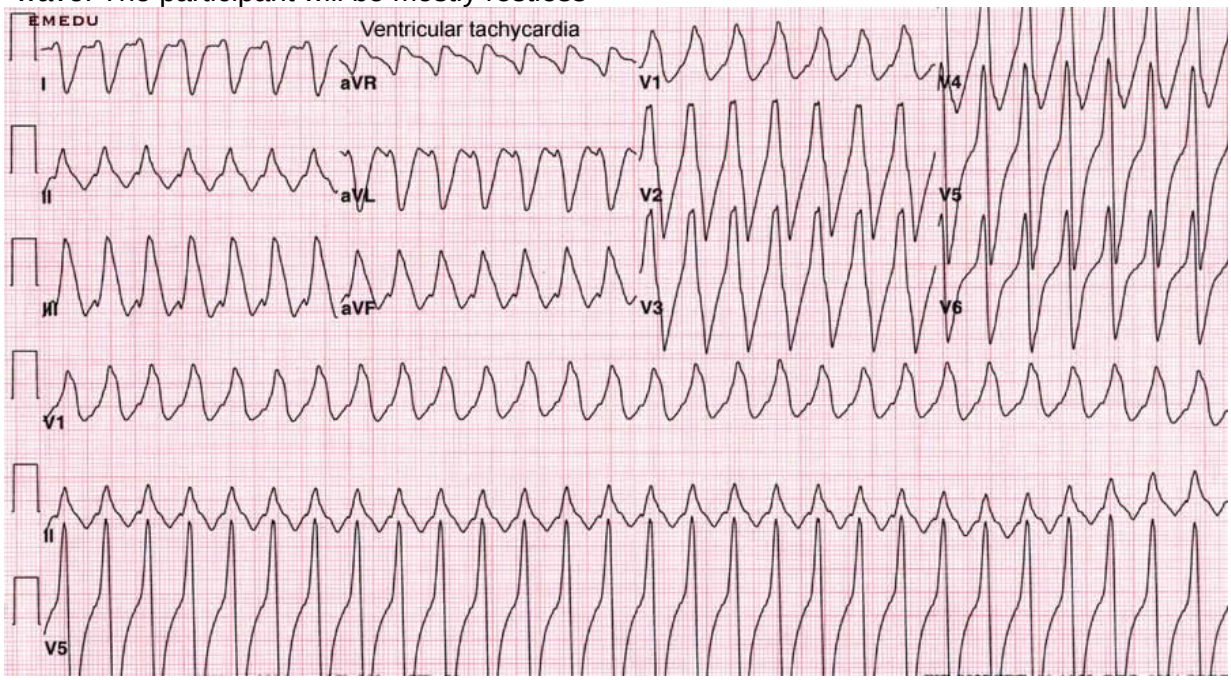


Figure 14 Acute inferior (upper panel) and acute anterior (lower panel) myocardial infarction

Diagnosis key points: Elevated ST segment in a group of adjacent leads with or without Q waves and with or without ST depression in other leads. Patients usually will have chest pain

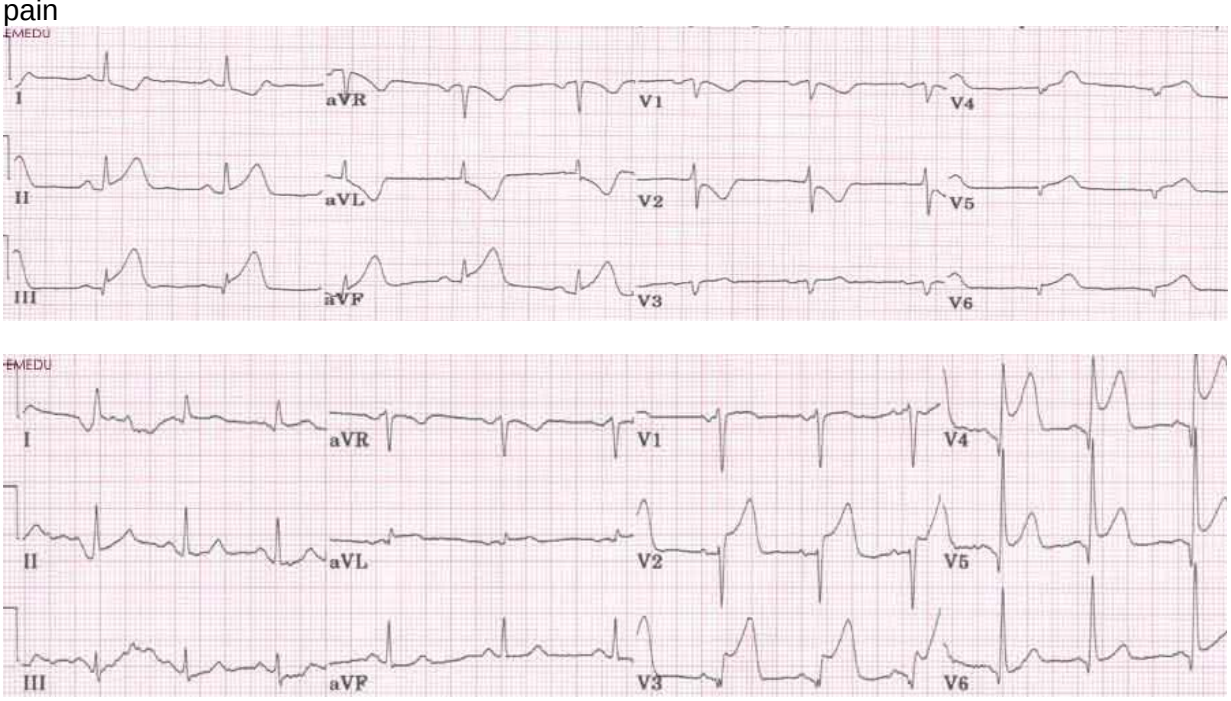


Figure15. Wolf Parkinson White Syndrome

Diagnosis key points: Short PR interval (below 120 ms), slurred upstroke of the R wave (delta wave) with wide QRS complex (mostly above 110 ms)

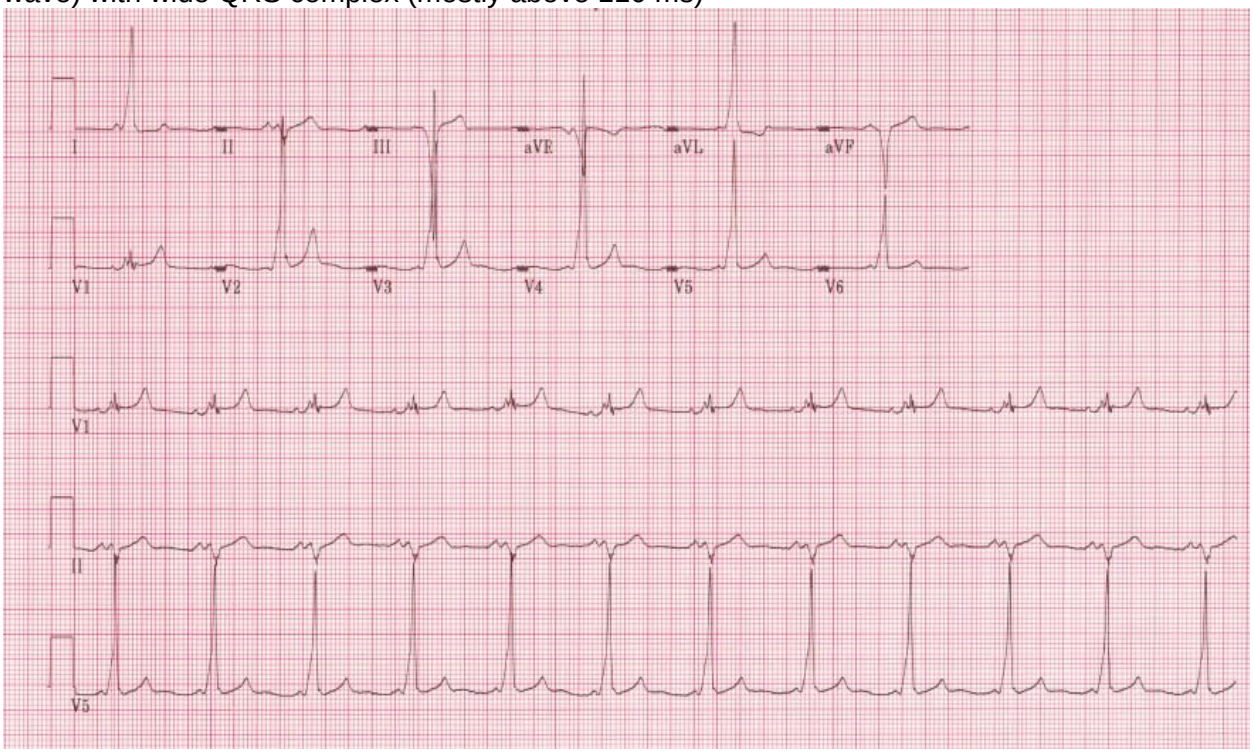
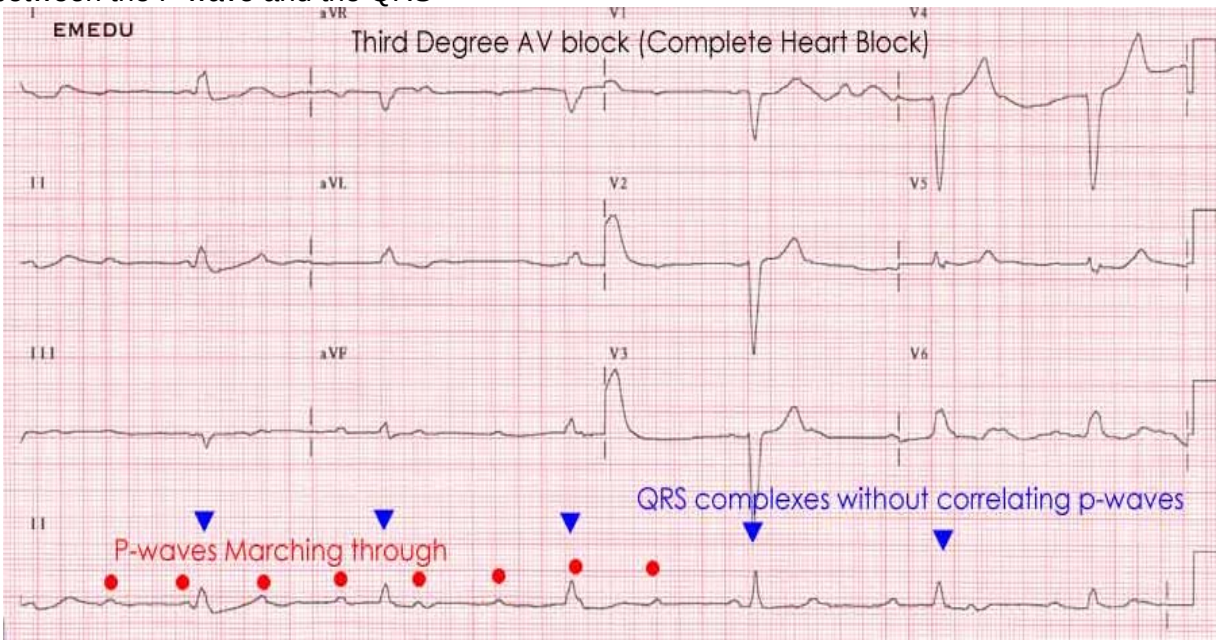


Figure 16 Complete (3rd degree) atrioventricular block
Diagnosis key points: Slow heart rate (around 40 beats per minute) with no relation between the P wave and the QRS



III.3. Data management procedure

III.3.1 Communications setup for transmission

Internal set up of the ECG machines must be done according to the instructions established by the CERC. Correct internal set up should enable the clinics to transmit the study ECGs via a phone line to the reading center. Adding 9 (or other number) to get an outside line and/or adding an access code for long distance are taken into consideration. [NOTE: Contact the CERC any time with questions]

III.3.2 Before transmitting ECGs to the CERC

- Ensure that all previously transmitted ECGs are deleted.
- Check to ensure that all IDs are valid.

III.3.3 Transmitting ECGs to the CERC

- 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.
- Plug one end of the phone cable into the connector marked "**LINE**" on the rear of the modem and the other end into any "**analog**" (fax) phone line**.**
- Start at the 12-lead screen. While holding the "Shift" key down, press the "Store/Retrieve" key. Press the down arrow 3 times and then hold the shift key and the down arrow together to get to the desired ECG to be transmitted. The screen will show black squares on the right and left sides of the ECG selected for transmission.
- To skip an ECG press the down arrow without using the shift key.

- Repeat this procedure until all ECGs that are to be transmitted have been selected.
- Once selections are made, press the “Enter” key. This will return you to the top of the screen.
- Use the right arrow to highlight “Send” and press the “Enter” key.
- Another screen will appear which states “to start transmission, press enter”. Once transmission is complete, press the “Start/Stop” key, located on the far bottom right of the keyboard, to return to the 12-lead screen.
- Delete transmitted ECGs ONLY after you have received email or verbal confirmation of receipt of ECGs from the ECG center.

III.3.4 Directory management

Keep your directory correct and current by doing the following:

- BEFORE TRANSMISSION: Delete all unwanted ECGs like those with flat lines, poor quality or duplicates. Correct any errors in participant data entry like ID numbers
- AFTER TRANSMISSION: Delete transmitted ECGs ONLY after confirming that EPICARE has successfully received the ECGs.

VI. READING CENTER TECHNICAL DETAILS

Set-up of the machines is ONLY allowed to be done at the CERC or with assistance of one of the CERC staff or an authorized study personnel if it has to be done at the clinic. It may be necessary to re-program the machine after the start of the study if a malfunction occurs, or the battery has been allowed to become dead. The machine set-up and programming instruction are listed in Appendix B. All ACCORDION ECGs will be electronically transmitted to CERC. The digital ECGs are stored in an electronic database at the ACCORDION CERC, in a Marquette measurement matrix, by participant ID. This database will remain unaltered. Additionally, a second and third database will be created after technician editing of correct onset and offset of the waveforms. These two databases are then transformed into Minnesota Code and Novacode categories by the EPICARE ECG coding program for later reporting. The format and route of data transfer will be determined by agreement between the Coordinating Center (CC) and the CERC. Monthly reports will be sent from the CERC to the CC. All electronic ECGs will be processed and reported within 30 days from receipt.

V. QUALITY CONTROL PROCEDURES

V.1 Quality grades

The ECG reading centre evaluates and ranks the ECG quality through an automated system with visual confirmation if needed. There are 5 grades from 1 to 5. The best grade is 1 and the worst is 5. Generally, grades 1 and 2 are difficult to separate visually and they are considered good. Grades 3 and 4 are given to ECGs that have correctable problems i.e. the ECG problems could be adjusted for on reading them. Grade 5 ECG are given for the ECGs that there have major problems which make it difficult to read them

V.2 Certification/Recertification procedures

- All ECG technicians **must go through the certification** process before they are allowed to acquire study ECGs.
- Each technician must acquire and successfully transmit 3 good quality ECGs.
- The 3 ECGs should be approximately 20 minutes apart or recorded from 3 different volunteers.
- After evaluation of certification ECGs by EPICARE staff, the technicians will be notified of their certification status.
- Recertification process (required every 2 years) is the same as the certification process.
- The participant data entry should be done according to the instructions in table 3 after pressing the “pat info” key on the MAC 1200 keyboard

Table 3 Entry into the MAC1200 for certification of technicians **ONLY**

Category	**Entry**
New Patient	YES
Last name	Enter technician’s last name
First name	Enter technician's first name
Date of birth	Enter volunteer’s birth date (MM/DD/YY)
Participant ID	Enter 999999999 (Press “Shift” key to enter numbers)
Secondary ID	Enter 999999999 (Press Shift key to enter numbers)
Pacemaker	YES or NO
Gender	M or F
HEIGHT	E Measurement of HeartSquare (e.g., if E=16.0, enter 160)
WEIGHT	V6 Measurement of HeartSquare (e.g., if V6=12.0, enter 120)
Race	Choose “Other” and choose defined race codes
Referring physician	No action required.
Technician	Choose “Other” and select technician’s last name
Location	No action required.

V.3. Examples of common ECG quality problems and possible solutions

- EXCESSIVE BASELINE DRIFT (**Figure 17**): This occurs if the participant is moving around or there is tension on the lead wires. Ask the 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 significant drift.

- EXCESSIVE MUSCLE NOISE (**Figure 18**): The participant is either tense due to lack of body support or may be cold. Use a wide bed and blanket to cover the participant.

- BASELINE DRIFT DUE TO TANGLED WIRES (**Figure 19**): 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 (not a cross loop) with the electrode wires, i.e., the wire should not cross but remain open like a U; never crossover wires.

- LOOSE ELECTRODE CONNECTION (**Figure 20**): Loose electrode connection may cause a wavy baseline in some ECG leads. Check each electrode to ensure that it is secure.

- SIXTY HZ NOISE (**Figure 21**): Periodic 60 HZ noise is sometimes visible in the record. This may be caused by AC interference from a nearby machine. Make a visual check of this before recording the ECG. Unplug any unnecessary surrounding electric equipment *Note:* Jewelry does not cause 60 HZ noise.

- MISSING LEADS AND LEAD REVERSAL (**Figures 22-24**): To minimize the chances of having lead reversal and missing leads, always make sure that there are no flat lines in the ECG recording and/or mainly positive QRS in aVR lead. Also, always have a second look at the connections before recording

Figure (17) Excessive baseline drift due to sudden movement of the participant

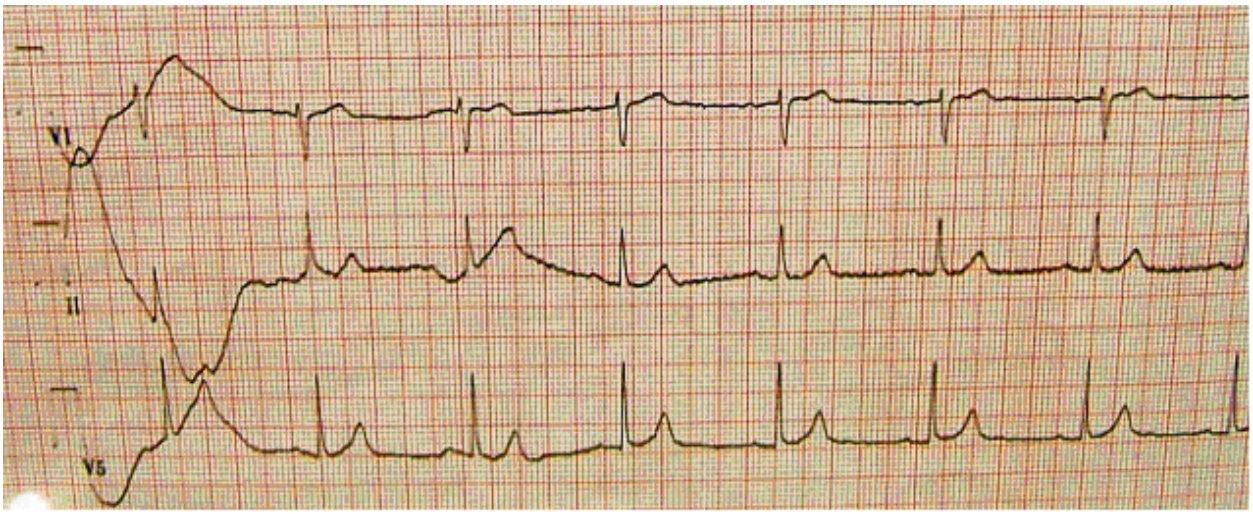


Figure (18) Excessive muscle noise

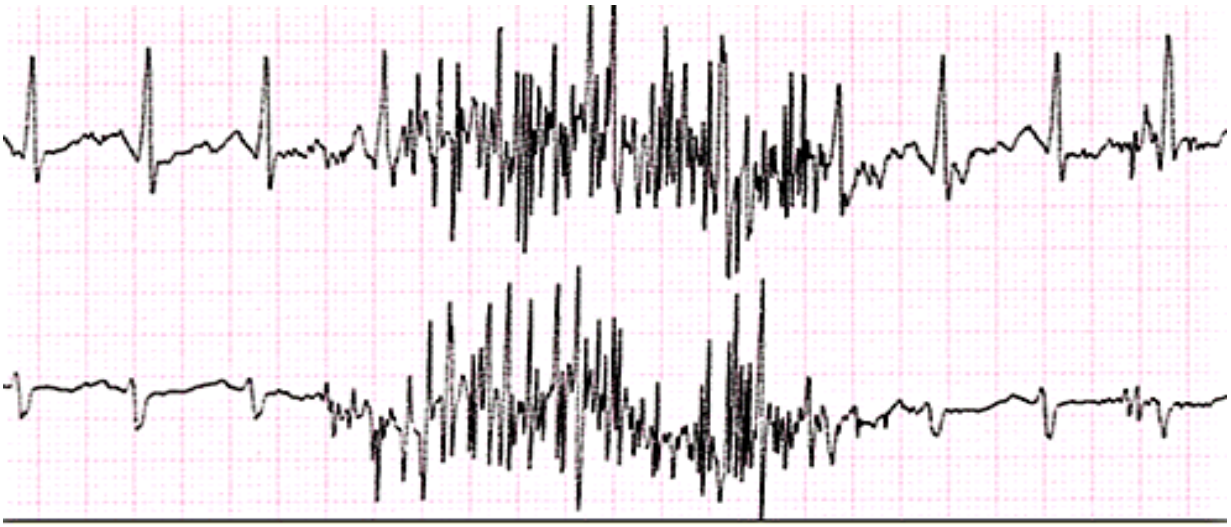


Figure (19) Baseline drift due to tangled wires

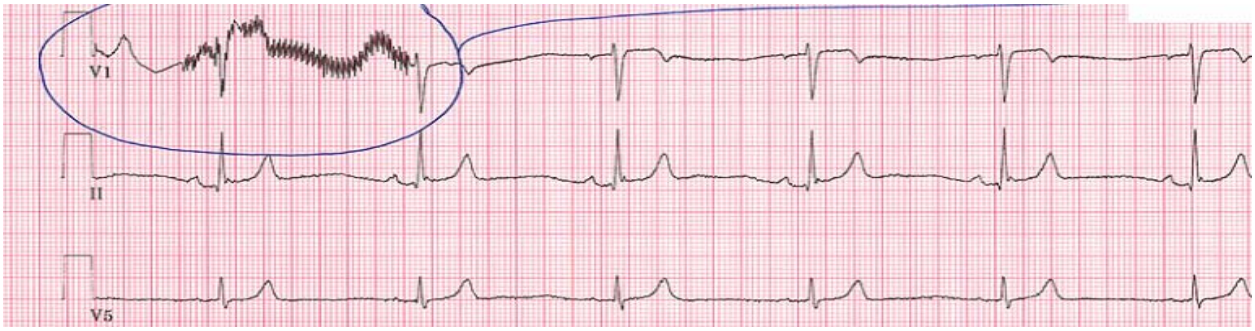


Figure (20) Wavy V1 baseline due to loose electrode

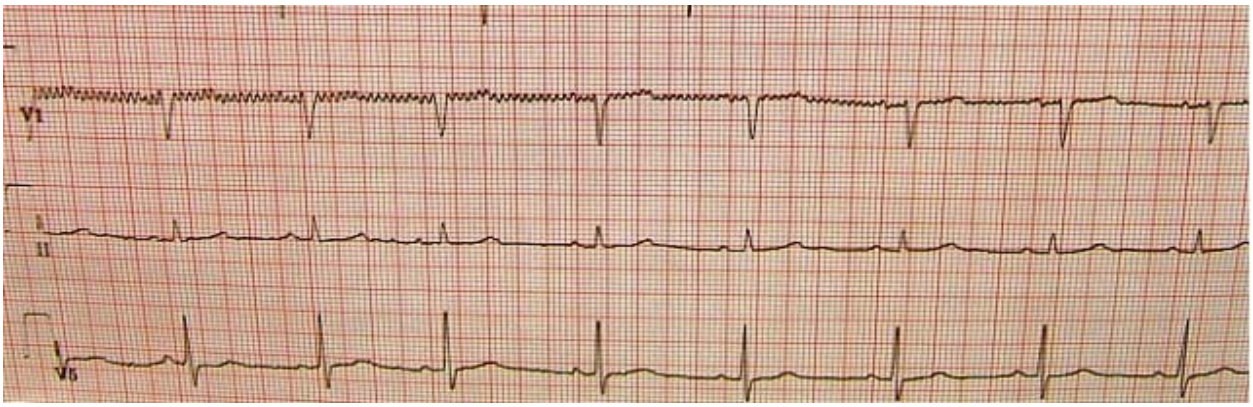


Figure (21) Sixty Hz electrical interference

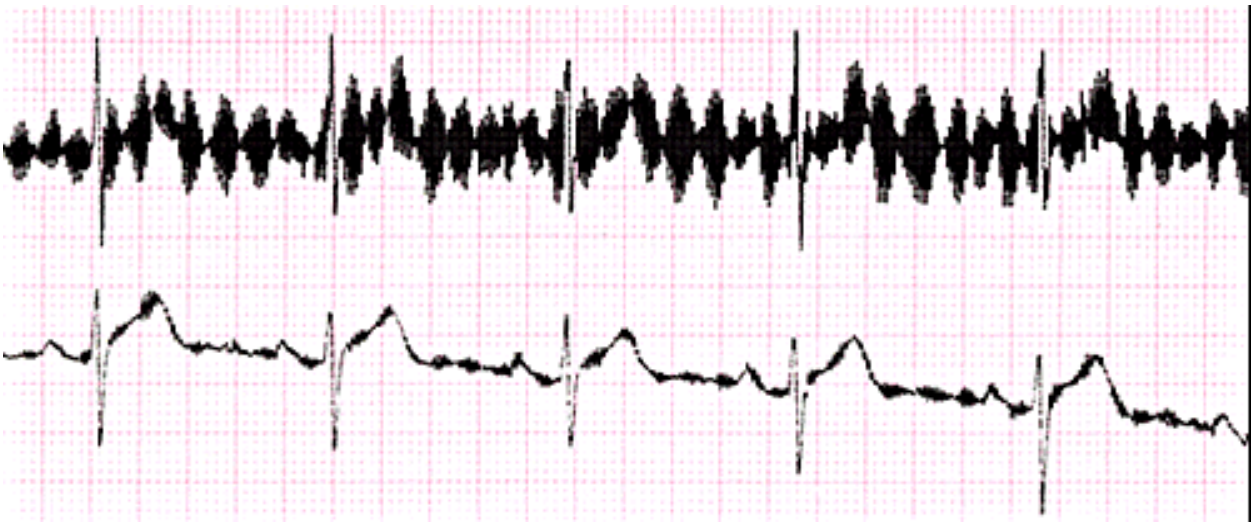


Figure (22) Flat line due to missing V1 lead

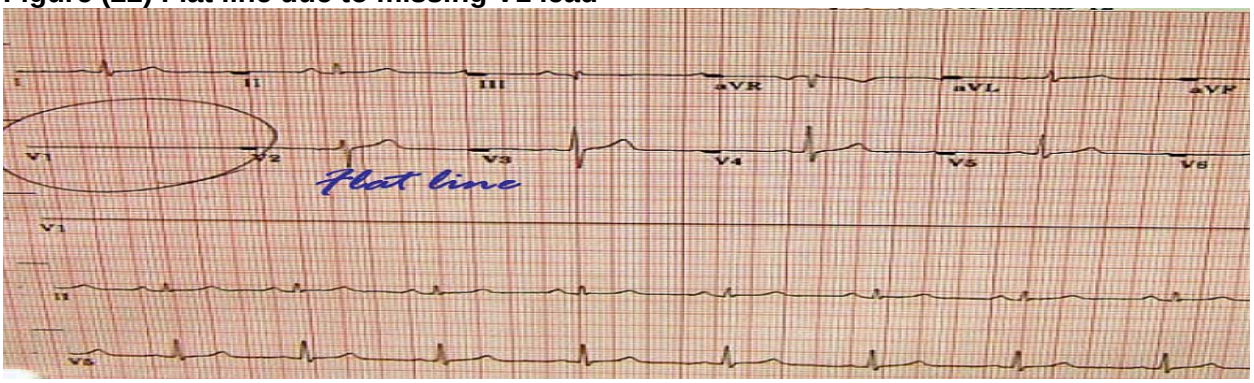


Figure (23) Lead reversal denoted by positive aVR (upper panel) **compared to the normal** (lower panel)

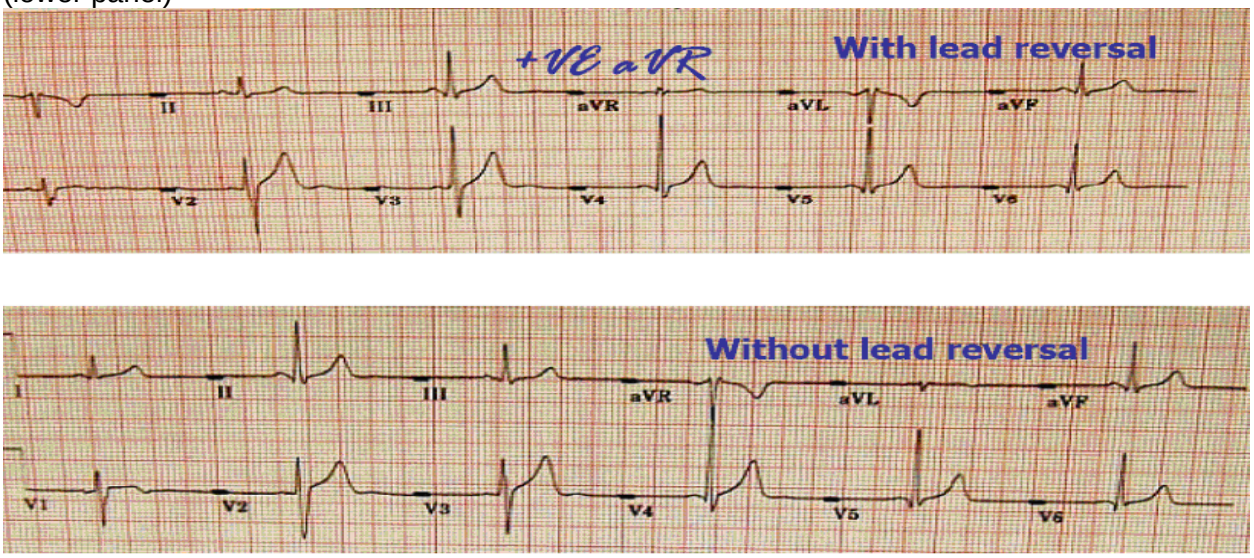
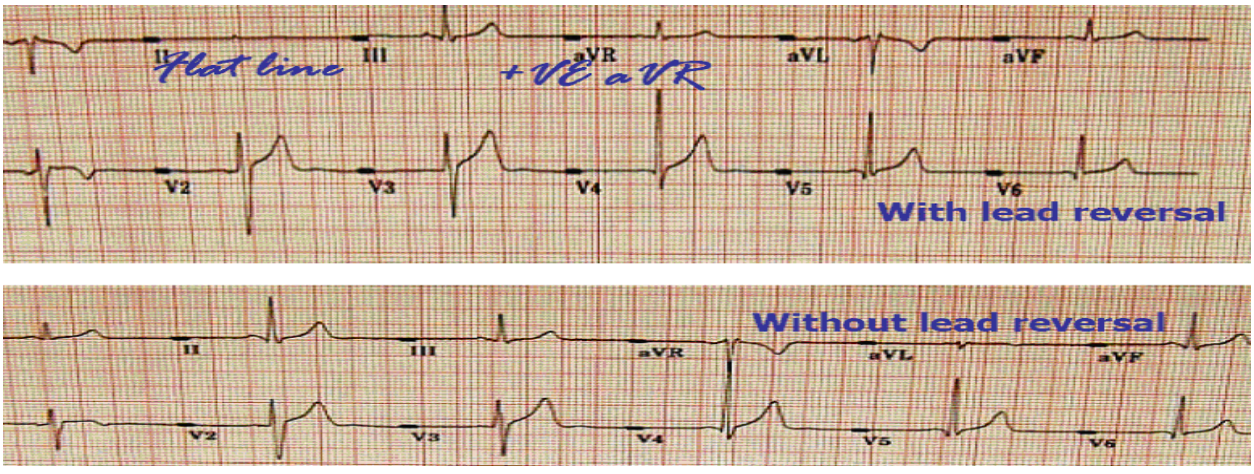


Figure (24) Lead reversal denoted by flat line in one of the limb leads (upper panel) **compared to the normal** (lower panel)



Appendix B

MAC 1200 PROGRAMMING AND SETUP

Minor changes in the set up below may occur during the course of the study- Call EPICARE for assistance

In order to setup a MAC1200 for the ACCORDION study, turn the ECG machine ON. After the self-test completes, the ECG machine will be at the 12-lead screen (3 flat lines). Press the "Setup" key. Press "Enter" to select either12-lead setup, system setup, communication setup, participant data setup, or code setup. To make a selection, use the four arrow keys to highlight any selection and press "Enter".

12-Lead Setup

CATEGORY	SELECTION
REPORT SEQUENCE	[STANDARD]
RHYTHM LEADS	[II]
GAIN	[10]
REPORT FORMAT	[4x2.5R1]
DETAILED RESULTS	[NO]
MUSCLE FILTER	[NO]
MUSCLE FILTER FREQUENCY	[40 Hz]
AC FILTER	[YES]
MANUAL COPY TO	[HOST]
NO. OF COPIES	[1]
DELETE ECG AFTER TRANSMISSION	[NO]
AUTOSAVE ECG	[YES]
USE SCREENING CRITERIA	[NO]
SUPPRESS NORMAL STATEMENTS	[NO]
SUPPRESS ABNORMAL STATEMENTS	[NO]
INTERPRETATION	[YES]
PRINT INTERPRETATION	[YES]
OVERRIDE FUNCTION	[YES]

When finished, press the STOP key

Press the Down Arrow key to highlight System Setup, and press ENTER.

System Setup

CATEGORY	SELECTION
ORDERING PHYSICIAN	No
REFERRING PHYSICIAN	Highlight OTHERS press ENTER. Press ENTER until the cursor is under the LAST NAME; type ACCORDION. Press ENTER until the cursor is under the FIRST NAME; type the ACCORDION field unit location and number. (2-03 Seattle)
TECHNICIAN	Choose OTHERS, press ENTER. Press ENTER until the cursor is under the LAST NAME; type the technician's LAST NAME then press ENTER. Type the technician's FIRST NAME then press ENTER. Press the Stop key.
INSTITUTION NAME	ACCORDION 2-03 (for ACCORDION field unit 2-03)
CART NUMBER (ACCORDION clinic #)	# for assigned Clinic (Ex: 203) **MUST BE NUMERIC**
SITE NUMBER	ENTER **4.** This is EPICARE's Study Number for ACCORDION
LOCATION NUMBER	Assigned Cart ID (2-03)
DATE (mm/dd/yyyy)	ENTER the correct date using the mm/dd/yyyy format.
TIME (hh:mm)	ENTER the correct time in the hh:mm format.
LEAD FAIL BEEP	[NO]
HIGH HR BEEP	[NO]
LEAD LABELS	[AAMI]
PACE ENHANCEMENT	[NO]
BASELINE ROLL FILTER	[0.08]
DATE	[MM/DD/YYYY]
TIME	[24]
UNITS	[Cm, Kg]
MAINS	[60 Hz]
LCD LIGHT OFF AFTER	[5 MINS]- Time Out Mechanism
LOW BATTERY BEEP	[0 sec]
DEFAULT MODE	[12 LEAD]
LANGUAGE	[ENGLISH]
ENABLE PASSWORD	[NO]
TEST DATA	[NO]
RESTORE DEFAULTS	[NO]
PRINT SETUP LISTS	[NO]

When finished, press the STOP key

Press the Down Arrow key to highlight Communication, and press ENTER.

Communication Setup

CATEGORY	SELECTION
BAUD RATE (PC)	[9600]
PROTOCOL	[CSI]
MODEM	MultiTech 56k
DIAL MODE	TONE
PHONE NO.	**13367161248** If an Access code is required to dial a long distance number, enter the access code and the transmission telephone number at EPICARE, the same way you would dial a long distance number from your institution (using your Access code), e.g.: • If the Access Code is needed AFTER entering the transmission number, enter: 133613367161248,,,123456789 where 123456789 is the Access Code • If the Access Code is needed BEFORE entering the transmission number, enter 123456789,,, 13367161248 where 123456789 is the Access Code **Note:** Access codes are separated from the EPICARE transmission telephone number by three commas. This allows the MAC1200 to pause before another telephone number is entered.
OUTSIDE LINE	If you need an outside line to obtain dial tone, enter that digit here, e.g. 9

When finished, press the STOP key

Press the Down Arrow key to highlight Patient Data Setup, and press ENTER.

Participant Data Setup

CATEGORY	SELECTION
NEW PATIENT	[YES]
PACEMAKER	[YES]
GENDER	[YES]
HEIGHT	[YES]
WEIGHT	[YES]
RACE	[YES]
SYSTOLIC BP	[NO]
DIASTOLIC BP	[NO]
ORDERING PHYSICIAN	[NO]
REFERRING PHYSICIAN	[YES]
TECHNICIAN	[YES]
PHONE NO.	[NO]
MEDICATION	[NO]
COMMENTS	[NO]
ID REQUIRED	[YES]
PATIENT ID LENGTH	9
SECONDARY ID	[YES]
SECONDARY ID REQUIRED	[YES]
LAST NAME (Required)	[YES]
FIRST NAME (Required)	[YES]
LOCATION #	[NO]
ROOM #	[NO]
ORDER NUMBER	[NO]
EXTRA QUESTIONS	[Leave Blank]

When finished, press the STOP key. Press the STOP key once again to exit the Setup menu. The Option Code Setup requires NO action.

Appendix C

Transmission of ACCORDION study ECGs to the CERC

Before transmitting ECGs to the CERC

1. Ensure that all previously transmitted ECGs are deleted only after confirmation of receipt by the CERC.
2. Check to ensure that all IDs are valid.
3. You can correct any variable from your participant data information by doing the following:
    a. While holding the “Shift” key down, press the Store/Retrieve key,
    b. Move the cursor to the ID in question,
    c. Select ECG
    d. Press “Enter” to return to top screen
    e. Highlight “change/edit”
    f. Proceed to correct information

Transmitting ECGs to the CERC

1. Plug one end of the phone cable into the connector marked “LINE” on the rear of the modem and the other end into any “analog” (fax) phone line.
2. Start at the 12-lead screen.
3. While holding the “Shift” key down, press the “Store/Retrieve” key.
4. Use arrow keys to move the cursor to the ECG to be transmitted. While holding down uppercase key, use up or down arrow key to select more ECGs (Black box will appear at either side of a selected ECG). Repeat this process until all ECGs that are to be transmitted have been selected.
5. Press the enter key to start the transmission
6. Once transmission is complete, press the “Start/Stop” key, located on the far bottom right of the keyboard, to return to the 12-lead screen.
7. You will receive email confirming receiving the ECGs. Never delete an ECG before confirmation of receipt. Call the ECG center for confirmation anytime

ACCORDION
ACCORD TRIAL FOLLOW-UP STUDY

Central Chemistry Laboratory

Manual of Procedures

Specimen Collection
Processing
Shipment

NORTHWEST LIPID METABOLISM AND DIABETES RESEARCH LABORATORIES
University of Washington School of Medicine

March 2010

ACCORDION
ACCORD TRIAL FOLLOW-UP STUDY

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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 Santica Marcovina, PhD, ScD, 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:

ACCORDION - Action to Control Cardiovascular Risk in Diabetes Follow-Up
AIM – HIGH - Atherothrombosis Intervention in Metabolic Syndrome
CARDIA - Coronary Artery Risk Development in Young Adults
CIT - Clinical Islet Transplantation Consortium
DPPOS - Diabetes Prevention Program Outcome Study
ITN018, 027, 028, 041 & 045AI - The Collaborative Network for Clinical Research in Immune Tolerance
LABS - Longitudinal Assessment of Bariatric Surgery
Look AHEAD - Action for Health in Diabetes
NSABP - Breast Cancer Prevention Trial (BCPT)
SEARCH III - Search for Diabetes in Youth
SEARCH CVD - Cardiovascular Disease in Youth
SNAS - Nutrition and Metabolic Status in Youth with Type 1 DM: SEARCH Ancillary
TEEN LABS - Adolescent Bariatric: Assessing Health Benefits and Risks
TODAY2 - Studies to Treat or Prevent Pediatric Type 2 Diabetes
Trial Net - Natural History/Oral Insulin/CTLA4-Ig/Metabolic Control/GAD/NIP/AntiIL-1Beta

Vision Statement

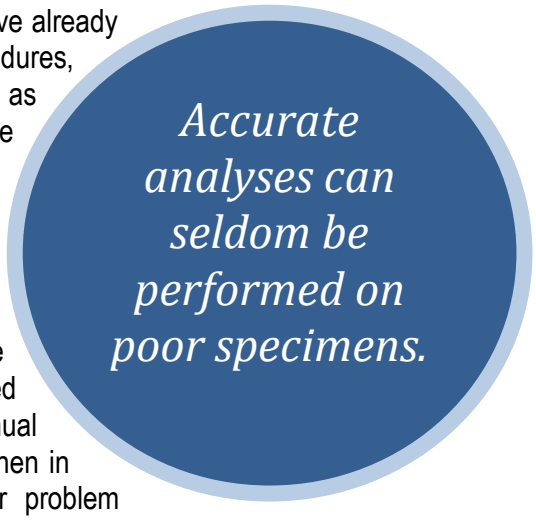
To be a model organization, thriving in a dynamic environment and respected as a leader in quality laboratory services with a strong commitment to continuous quality improvement.

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 ACCORDION Follow-Up Study.



This detail is provided for a reason: submission of proper specimens under optimum conditions is very important. 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.

SUPPLIES

Supplies Provided by the CCL

Specimen collection materials will be provided in "bulk" shipments for the ACCORDION study. The first bulk shipment will be made to the sites prior to the start of the study. Additional supply shipments will be made at the site's request, by using the ACCORDION Supply Request Form.

Your order should have enough collection tubes to last 6 months, because these tubes typically have a 6 month expiration date.

For Blood Collection:

- 8.5 mL tiger-top SST (with inert gel separator)
- 2.0 mL purple-top (EDTA anticoagulant)

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

EXEMPT HUMAN SPECIMEN

Equipment, Supplies & Facilities Provided By Clinical Sites

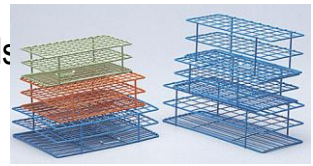
These are suggested supplies only; clinics may use equivalent substitutions, if desired.

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:

- ✓ 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 set to 4˚C
- ✓ 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 Occupational Safety & Health Administration

http://www.niehs.nih.gov National Institutes of Health NIEHS National Institute of Environmental Health Sciences ~ Your Environment is Your Health ~

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 re-contaminate 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.

Note: Urine collections for female participants should be re-scheduled if the participant is menstruating.

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.

COLLECTION CHART

Follow the study protocol to determine which assessments must be made at each of the visits and use the tables below as a reference guide for specimen collection.

VISITS: FU1 & FU2

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 • Ship fresh
Lipids S. Creatinine ALT	Chem/DBQ	Fasting	8.5 mL Tiger-top SST		• 20 - 30 Minutes at Room Temperature. • Centrifuge • Ship fresh
Urine Albumin & Creatinine	Urinalysis	Non-fasting acceptable	Urine Cup & 10mL transfer vial		• Transfer 5.0mL urine into 10mL transfer tube. • Ship fresh

SPECIMEN COLLECTION

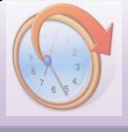
Blood specimens collected will be shipped fresh to the CCL on cold pack refrigerant in their collection Vacutainers via **Federal Express Overnight Courier Services**, within 24 hours of blood draw. Urine specimens are shipped in transfer tubes along with the blood. Keep all specimens in a refrigerated state prior to shipment. To the right is a brief sequence of this process.

TRANSFERING SERUM TO 10ML TUBE

Some sites may elect to transfer the serum from the tiger-top collection tube into a 10mL screw cap transfer vial after the specimen is centrifuged. When this is done the 10mL screw cap transfer vial must be labeled with the participant ID specific barcode label for the Chem/DBQ sample. A blank label should be used for the collection tube. The participant's ID number will have to be hand written on this label by the site.

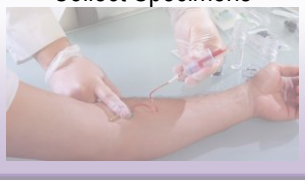
After the serum has been transferred to the 10mL vial, the cap should be tightly screwed onto the vial to avoid possible leakage during transit.

Verify that the participant has reported as fasting for at least **8 hours**.



Label specimen vacutainers and urine collection cups.

Collect Specimens



Centrifuge SST Tiger-top vacutainers

Transfer urine in appropriately labeled 10 mL plastic tubes.

Refrigerate specimens if not shipped immediately.

Complete shipment form and ship specimens to the CCL.

SPECIMEN LABELING

The CCL will provide participant ID pre-printed labels. Draw date information must be handwritten on the labels in the space provided with a permanent marker.

Affix the appropriate label to each of the collection tubes and specimen transfer tubes.

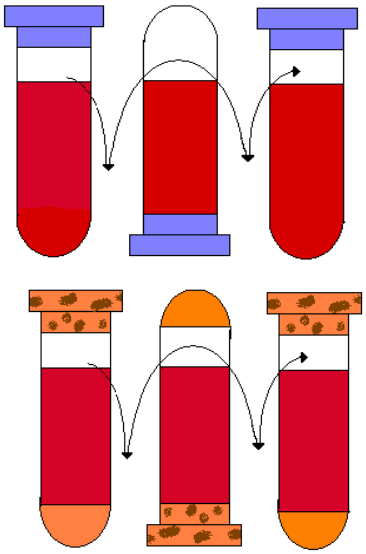
Label orientation is important for proper scanning of the barcode. Please affix labels to collection tube and transfer tubes as shown here, with the barcode number running vertically.

Fine point Sharpies are recommended for writing the draw date on labels.

These labels utilize barcode technology and are linked to one another as visit sets. DO NOT mix label sets. If, for some reason, a label becomes unusable, such as by an accidental breakage of a tube, use a provided blank label (which does not contain a barcode) and hand-write the analysis and participant id on the label. The lab will manually enter that sample.

SPECIMEN PROCESSING

As stated earlier, we presume that all personnel performing this work have been trained in proper blood collection procedures. Listed below are some important reminders.



= 1 inversion

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) tube 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.

Urine Specimen:

- Instruct the study participant in the proper procedure for urine collection, and provide him/her with the necessary collection materials.
- Obtain the 10mL screw-cap vial labeled Urinalysis and use a clean transfer pipette to transfer at least 5mL of urine from the collection cup into the screw-cap vial. Screw the cap on tightly and refrigerate at 4˚C unitl you are ready to prepare the shipment.
- Any remaining urine in the collection cup should be discarded in the toilet and the collection cup and lid discarded in a biohazard waste container.

Due to the possibility of blood contamination during collection, participants who are menstruating should not be asked to provide a urine sample.

SPECIMEN CENTRIFUGTION

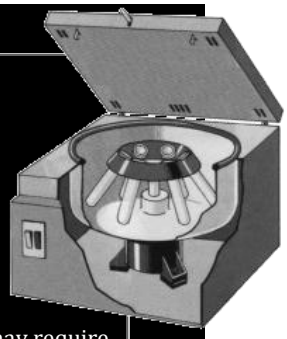
After 20 to 30 minutes from sample collection, transfer the tiger-top vacutainer to the centrifuge, loading it according to the manufacturer's instructions.

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 to 4˚C or prepare the tubes for shipment.

Leaving blood samples in a non refrigerated centrifuge or at room temperature will compromise the accuracy of analysis.

Non-refrigerated Centrifuge

If using a non-refrigerated centrifuge, it is imperative that the blood tubes not be allowed to sit in the centrifuge after rotation has ceased. Heat can build up in non-refrigerated centrifuges and cause hemolysis if specimens are not removed immediately after rotation has ceased. We recommend that a timer pinned to the lab coat be used to alert you when tubes need to be 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 tube gently several times; the gel barrier is good if the red cells are not contaminating the serum. If the gel barrier appears to be compromised, aliquot the serum to a transfer tube, centrifuge again, transfer the clean serum to another tube and ship to the laboratory.

PREPARING SPECIMENS FOR SHIPMENT

Specimens collected for ACCORDION will be shipped fresh on cold packs to the CCL, 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 and 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 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

Regulations implemented by the International Air Transport Association are for the packaging and shipping of diagnostic specimens. The International Air Transport Association 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 CCL will provide you with shipping materials that meet the 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 C 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 freeze cold packs in a 70°C freezer. Doing this may cause freezing of the blood during transport.

Shipping Schedule

Shipments should be made **Monday through Thursday** using, ***Federal Express Priority Overnight Service***. Please keep this in mind when scheduling participant appointments for blood collection. Specimens should be shipped on the day of specimen collection to assure quality results using fresh specimens. No provisions for Saturday Delivery have been included for this study. Specimens collected on Friday must be stored in a refrigerator set at 4˚C until shipments can be made on the following Monday.

Air bills

The CCL will provide each site with FedEx shipping air waybills. The air bills will have the CCL's address and specific billing information pre-printed. It is the clinical sites responsibility to fill in their contact name, return address and telephone number in the spaces provided on the air bill. Under no circumstances should a clinic use the FedEx account number on these air bills to make shipments to any location that is not the CCL.

Ship Specimens To

ACCORDION-CCL
Northwest Lipid Metabolism and Diabetes Research Laboratories

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.

- **Fax the completed form**

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 delay we will receive the samples on Saturday. 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.

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 delay we will receive the samples on Wednesday.

Federal Holiday	2011	2012	2013
New Year's Day	Fri, December 31	Mon, January 2	Tue, January 1
MLK Jr's Birthday	Mon, January 17	Mon, January 16	Mon, January 21
President's Day	Mon, Feruary 21	Mon, February 20	Mon, February 18
Memorial Day	Mon, May 30	Mon, May 28	Mon, May 27
Independence Day	Mon, July 4	Wed, July 4	Thurs, July 4
Labor Day	Mon, Septmenber 5	Mon, September 3	Mon, September 2
Veterans Day	Fri, November 11	Mon, November 12	Mon, Nov. 11
Thanksgiving	Thurs, November 24 Fri, November 25	Thurs, November 22 Fri, November 23	Thurs, November 28 Fri, November 29
Christmas Day	Mon, December 26	Tue, December 25	Wed, December 25

ATTACHMENTS - FORMS

A: **Fax Notification**
B: **Supply Request**
C: **Shipping Guidelines (for reference only)**

FAX

Northwest Lipid Metabolism & Diabetes Research Laboratories
University of Washington

TO: **Specimen Processing**
FAX:
Phone:

FROM: _____

Phone: _____

Email: _____

PLEASE BE ADVISED OF THE FOLLOWING SHIPMENT ARRIVAL:

Clinical Site: _____

Number of boxes shipped*:* _____

Date specimens shipped: _____

Fed Ex Tracking Numbers: _____

_____

Comments:

SUPPLY REQUEST FORM

ALL REQUESTS FOR SUPPLIES SHOULD BE MADE AT LEAST *TWO WEEKS* PRIOR TO THEIR ANTICIPATED NEED

Site Number: _____ 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)

SUPPLY	QUANTITY DESIRED	QUANTITY SHIPPED	QUANTITY PENDING
Specimen Collection/Processing			
8.5mL Tiger-top SST			
2.0mL Purple-top			
Urine Collection Cup			
Antiseptic Towlette			
Disposable Pipette			
10mL Transfer tube			
Specimen Shipment			
Polyfoam Tube Holder with cardboard sleeve			
Biohazard Bag			
Polyfoam Shipping Container			
Cold Packs			
Ziploc Bags			
FedEx Air Waybill			
Participant Tube Labels Pat. ID = _____			
Other (specify):			

Request Instructions:

1. Fill in the amount of each item desired in the table to the left.
2. Fax the completed for to the lab:
3. Your order will be processed and shipped to you with a copy of this form enclosed.
4. Insure that the contents of your shipment exactly match the supplies specified on this form.
5. If there are no discrepancies, sign the form and fax back to the lab.

If you have any questions, please call:

Comments:

_____

_____

I have reviewed the contents of my shipment and confirm that all supplies listed have been received.

Signed: _____ Date:_____

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:

Specimen must meet the following definition:

ecimens 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.

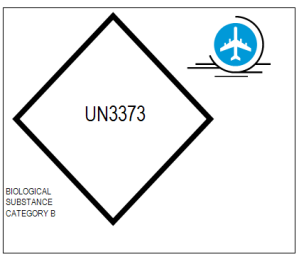
2. DO NOT use the "Biological Substance, Category B UN3373" label on the outer container unless you ARE aware the specimen contains a pathogen.

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.



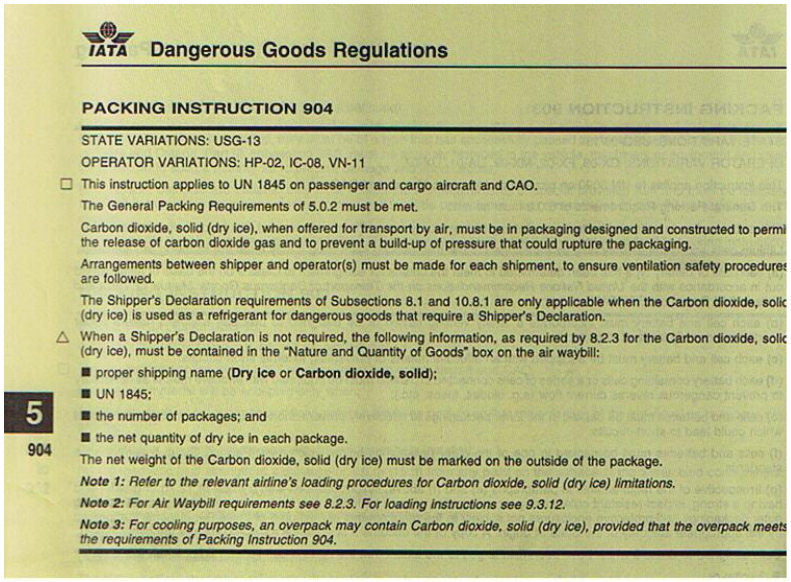
SHIPPING DRY ICE REFRIGERATING A NON-DANGEROUS COMMODITY[1]

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 over pack, provided the over pack 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.

5

904

The net weight of the Carbon dioxide, solid (dry ice) must be marked on the outside of the package.

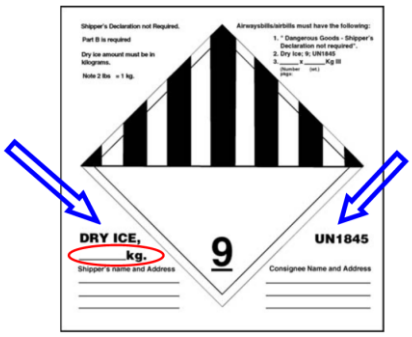
Note 1: *Refer to the relevant airline's loading procedures for Carbon dioxide, solid (dry ice) limitations.*

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.*

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.

[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.