Action to Control Cardiovascular Risk in Diabetes

Protocol

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Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial
Protocol

ABSTRACT

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

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

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

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

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

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

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

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

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

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

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

Chapter 1
Introduction and Background

Patients with type 2 diabetes mellitus die of cardiovascular disease (CVD) at rates two to four times higher than nondiabetic populations of similar demographic characteristics. They also experience increased rates of nonfatal myocardial infarction and stroke. Diabetes is a complex metabolic disorder with abnormalities in carbohydrate, lipid, and protein metabolism, often accompanied by other CVD risk factor abnormalities, such as elevated blood pressure. The combination of diabetes with hypertension and/or dyslipidemia confers a much higher risk than each one alone. Diabetes increases the risk of cardiovascular events two-to-three-fold at every level of blood pressure (BP) and total serum cholesterol, and in diabetic patients there is a graded increase in risk across the ranges of BP and total serum cholesterol. In addition, patients with type 2 diabetes often have low plasma HDL-cholesterol levels, putting them at increased risk for CVD, and there are data supporting a role for lowering triglycerides and raising HDL-cholesterol levels for primary and secondary prevention of CVD in diabetic patients.

With the growing prevalence of obesity in the United States, CVD associated with type 2 diabetes is expected to become an even greater public health challenge in the coming decades than it is now. Expected increases in event rates will be associated with a concomitant rise in suffering and resource utilization. Despite the importance of this health problem in the North American population, there is a lack of definitive data on the effects of intensive control of glycemia and other CVD risk factors on CVD event rates in diabetic patients. Scientists on three panels convened or sponsored by the National Institutes of Health since 1997 concluded a trial was needed to determine the effects on macrovascular disease of aggressive glycemic, lipid, and/or blood pressure control in type 2 diabetic patients.

The overall goal of the *Action to Control Cardiovascular Risk in Diabetes* (ACCORD) trial is to address this problem by testing three complementary medical treatment strategies for type 2 diabetes to enhance the options for reducing the still very high rate of major CVD morbidity and mortality in this disease. The design is a randomized, multicenter, double 2 X 2 factorial design in 10,000 patients with type 2 diabetes mellitus. The trial is designed to test the effects on major CVD events of intensive glycemia control, of treatment to increase HDL-cholesterol and lower triglycerides (in the context of good LDL-C and glycemia control), and of intensive blood pressure control (in the context of good glycemia control). All 10,000 participants will be in the overarching glycemia trial. In addition, one 2 X 2 trial will also address the lipid question in 5,800 of the participants and the other 2 X 2 trial will address the blood pressure question in 4,200 of the participants. Thus each participant will be in a 2 X 2 trial testing 2 treatment strategies of 2 interventions, one of which is always glycemic control and the other is either lipid or blood pressure control.

The primary outcome measure for the trial is the first occurrence of a major cardiovascular event, specifically nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Participants will be recruited over two non-contiguous periods (described in Sections 1.6 and 7.1) and followed for about 4 to 8 years (approximate mean of 5.6 years).

The three primary ACCORD hypotheses are to determine if the rate of major cardiovascular events in type 2 diabetic patients at increased risk for CVD can be reduced by:

(1) Intensive glycemic control compared with standard glycemic control

(2) Lipid control through drug treatment to raise HDL-C and lower triglyceride levels in the context of LDL-C treatment compared to LDL-C treatment alone.

(3) Intensive blood pressure control compared with standard blood pressure control

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

If more than one of the more intensive treatment groups experience significantly lower major CVD event rates than the respective control groups, clinicians' choices may be further guided by 1) effects on secondary clinical outcomes, including microvascular disease, adverse effects, and quality of life; 2) subgroup analyses of effects in combined versus single factor approaches; 3) resource requirements, including medical care costs; and 4) patient acceptance and tolerance of various classes of medications.

1.1 Diabetes and Glycemia

1.1.a Diabetes and Cardiovascular Disease

Diabetes mellitus is a common disorder that is frequently misunderstood and poorly treated. Although usually thought of in terms of the acute symptoms and long-term consequences associated with elevated glucose levels, diabetes is a complex metabolic disorder with abnormalities in carbohydrate, lipid, and protein metabolism. It is not a single disease and although common forms of diabetes are associated with an increased risk of CVD, the type of diabetes may have implications for the approach to preventing its cardiovascular complications. Current recommendations for CVD prevention generally apply to both type 1 and type 2 diabetes. In the United States, approximately 10 percent of diabetic patients have type 1 diabetes (previously called insulin-dependent diabetes, or IDDM) while approximately 90 percent have type 2 diabetes (previously called non-insulin-dependent diabetes, or NIDDM). The optimal treatment for the young, type 1 diabetic patient with severe, labile hyperglycemia may not be the best treatment for the older, type 2 diabetic with mild, stable glucose elevations. Type 1 diabetes is characterized by severe insulin deficiency, and restoration of normal glucose levels by intensive insulin therapy may be more successful in reducing risk of all chronic complications of this disorder. Type 2 diabetes, a more complex disease with generally elevated levels of insulin resistance and variable levels of circulating insulin, is often accompanied by multiple other CVD risk factor abnormalities, such as elevated blood pressures and lipids. While glucose control also appears important for type 2 patients, it is critical not to overlook treatment of these other CVD risk factors, which may have a greater or lesser effect than glucose control on prevention of CVD complications. Nevertheless, several recent studies indicate that in clinical practice neither hyperglycemia nor other CVD risk factors are adequately controlled in patients with diabetes (Savage 1998).

Declines in CVD mortality in the United States in the past 30 years have been smaller among diabetic patients than among non-diabetic patients. Compared to their non-diabetic counterparts, the relative risk of CVD for men with diabetes is 2 to 3, and for women with diabetes is 3 to 4 (Stamler 1993, Kannel 1979, Fuller 1983, Barrett-Connor 1991, Goldbourt 1993, Manson 1991). Population-based studies suggest that approximately 45% of white adults with diabetes have coronary heart disease compared to 25% in non-diabetic individuals (Wingard 1995). The annual risk of fatal and nonfatal CVD in middle-aged diabetic individuals is 2 to 5% (Stamler 1993, Morrish 1991, ETDRS Investigators 1992, Damsgaard 1992, Neil 1993). This risk is independent of the risk associated with other risk factors such as hypercholesterolemia, smoking, and hypertension (Stamler 1993). Diabetic patients with other CVD risk factors are at greater risk than non-diabetic individuals. Data collected in the recent Heart Outcomes Prevention Evaluation Study (HOPE 2000) confirm these high risks and show that they apply even in 1999, despite the use of therapies proven to reduce CVD risk. (At baseline, 56% of placebo patients were on aspirin, 20% on diuretics, 29% on beta-blockers and 22% on lipid lowering agents.) In this large multicenter trial, 1769 high-risk people with diabetes but without clinical CVD who were randomized to placebo experienced a 4.5-year rate of myocardial infarction, stroke or cardiovascular death of 19.8% (4.4%/year).

Patients with diabetes also have an even worse prognosis following a cardiovascular event. Prospective studies report that the relative risk of mortality following a myocardial infarction is 2 to 3 times higher in diabetic compared to non-diabetic individuals (Behar 1997, Mak 1997). This higher risk also applies to diabetic patients with unstable angina. In a recent unpublished analysis of data from the international OASIS registry (Yusuf 1998) of hospitalized unstable angina patients (21% with diabetes), the relative risk for MI, stroke, or CVD mortality within 2 years of admission was two-fold higher (RR=1.8; 95%CI 1.6-2.2) in diabetic patients compared to non-diabetic patients; the absolute rate in diabetic patients was 16.9% (versus 9.7% in non-diabetic patients).

1.1.b   Glucose as a Continuous Risk Factor for Cardiovascular Disease

Diabetes is a metabolic disease characterized by hyperglycemia, in which the defining glucose cutoffs are those that predict a high subsequent risk of eye and kidney disease (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997). As noted above, people with diabetic-range hyperglycemia are also at high risk for CVD. This suggests that hyperglycemia is also a risk factor for CVD. Indeed, large prospective epidemiologic studies (summarized in Table 1.1) have consistently shown that in patients with diabetes, the higher the glucose, the higher the incidence of CVD (Moss 1994, Kuusisto 1994, Andersson 1995, Gall 1995, Agewall 1997, Turner 1998, Wei 1998, Hadden 1997, Fu 1993). Taken together, these studies suggest that the risk of a CVD event rises approximately 10-30% for every 1% increase in HbA1c. This estimate is supported by the UKPDS observational results showing that the incidence of MI rose 14% per 1% rise in HbA1c (Stratton 2000).

As the diagnostic thresholds for diabetes were not chosen on the basis of predicting a high CVD risk, there is no *a priori* reason that the glucose-CVD risk relationship should not extend below these microvascular risk cutoffs that characterize diabetes. Indeed, recent epidemiologic studies have clearly shown that this relationship extends well below diabetic glucose thresholds and may extend down to normal fasting and postprandial levels (Coutinho

1999, Gerstein 1999, Gerstein 1996, Gerstein 1997, Balkau 1998, Bjornholt 1999, Haffner 1998). These observations strongly support the hypothesis that lowering glucose to levels within the normal, non-diabetic range may prevent CVD. The mean normal fasting and 2-hour post-load plasma glucose levels are 92 mg/dl (5.11 mmol/l) and 97 mg/dl (5.39 mmol/l), respectively (Cowie 1995).

Table 1.1: Relationship Between Glycemia and Risk of CVD in type 2 Diabetes								
Study	**N**	**Age**	**F/U, yrs**	**Glycemia**	**Outcome**	**Rate (%)**	**Relative Risk**	**RR / 1% HbA1c Increase**
Andersson (1995)	411	66	7.4	SMBG$\geq$ 7.8 mmol/l (140.4 mg/dl) vs <7.8 mmol/l	Death	44 vs 32	1.4	N/A
Kuusisto (1994)	229	68	3.5	HbA1c$\geq$7 vs <7 HbA1c$\geq$7 vs <7	CHD Death All CHD	12 vs 3 20 vs 13	4.3 1.6	N/A
Gall (1995)	328	56	5.3	HbA1c$\geq$7.8 vs <7.8	CV Death	10.4 vs 4.6	2.2	1.3
Agewall (1997)	94	67	6.3	N/A	CV Death	N/A	N/A	1.54
Lehto (1997)	1059	58	7.2	HbA1c$\geq$10.7 vs<10.7	CHD Death	N/A	1.4	N/A
Wei (1998)	4875	52	7.5	FPG 8-11.5 mmol/l (144 –207 mg/dl) vs <8 mmol/l	CV Death	6.3 vs 2.8	2.9	N/A
Turner (1998)	3055	52	7.9	HbA1c >7.5 vs <6.2	Fatal MI Any MI/angina	N/A	1.72 1.52	N/A 1.11
Moss (1994)	1780	66.6	8.3	N/A	IHD Death Stroke Death	N/A	N/A	1.1 1.17
Fu (1993)	479	61.2	4	HbA1c>8.4 vs <6.3	ECG MI/angina	30.8 vs 20.3	1.5	1.17

N: sample size; FPG: fasting plasma glucose; IHD: ischemic heart disease; F/U: follow-up; RR: relative risk; SMBG = self monitoring of blood glucose.

1.1.c   Glucose Reduction to Lower the Risk of Cardiovascular Disease

The possibility that blood glucose level may be a modifiable CVD risk factor is supported by the above epidemiologic data. It is also supported by a growing body of data from clinical trials (Table 1.2). The UKPDS is the first trial to show that a policy of intensive glycemic control using oral agents or insulin can reduce clinical outcomes in patients with type 2 diabetes. In the main study of 3867 individuals with newly diagnosed type 2 diabetes, a fasting plasma glucose <6 mmol/L (108mg/dl) was targeted by initial therapy with either a sulfonylurea (SU) or insulin.

Other agents were added when needed. Using this approach, the intensive group achieved a median HbA1c of 7.0% (interquartile range 6.2-8.2%) over a 10-year period and experienced a 25% relative risk reduction (RRR) in microvascular outcomes and a 12% RRR in all diabetes-related endpoints compared to a policy that achieved a median HbA1c of 7.9% during this period (UKPDS 1998a). There was a strong trend towards a reduced risk of MI with an observed RRR of 16% (95%CI 0%-29%;P=0.052). This 16% RRR for MI per 0.9% decrease in median HbA1c over 10 years is consistent with the 18% RRR in MI per 1% decrease in HbA1c observed in the UKPDS and other epidemiologic analysis (Section 1.1 and Table 1.1). As noted in Table 1.2, the results for the group initially randomized to insulin were similar to the results for the intensive group as a whole.

Unfortunately, stable degrees of glucose control in either of the randomized groups could not be maintained. Therefore, the median HbA1c in the intervention group was 6.6% (IQR 5.9-7.5%), 7.5% (IQR 6.6-8.8%) and 8.1% (IQR 7.0-9.4%) in the first, second and third 5-year intervals respectively. The median HbA1c in the conventional group during these 3 periods was 7.4%, 8.4% and 8.7% respectively. Expressed differently, 50% of newly diagnosed UKPDS participants in the intensive group had HbA1c values >7.0% during the first 10 years of follow-up, and 25% had values >8.2% during this period. In essence, the UKPDS showed that delaying the rise in HbA1c by 5 years and maintaining good control for at least the first 5 years led to clinically important differences in CVD events.

A separate randomization of 1704 obese participants in 15 UKPDS centers allocated 342 participants to intensive control with metformin, 951 to sulfonylureas or insulin and 411 to conventional control (UKPDS 1998). The median HbA1c was 7.4% in the metformin/other intensive group and 8.0% in the conventional group during the first 10 years of follow-up. Despite a more modest separation in HbA1c, the metformin group had a 32% risk reduction in any diabetes-related endpoint, a 42% risk reduction in diabetes-related death, a 36% risk reduction in all-cause mortality, and a 39% risk reduction in MI. There was a nonsignificant 29% reduction in microvascular outcomes. Conversely, intensive therapy with sulfonylureas or insulin did not significantly reduce outcomes. Indeed, the metformin group had statistically better outcomes than the other intensive groups for any diabetes-related endpoint, all-cause mortality, and stroke. However, if the results of the metformin arm are combined with the sulfonylurea/insulin arm, the results support the cardiovascular benefit of glucose lowering. In this analysis, the risk of myocardial infarction or stroke in the metformin intensive group would be 19.3% and the risk in the conventional group would be 23.4% (relative risk reduction = 18%). Similarly, the relative risk reduction for the combined outcome of myocardial infarction, stroke, and cardiovascular death (assuming that cardiovascular death accounted for 80% of all deaths) was 21.5%. As noted above, the observed median difference in HbA1c was 0.6% (UKPDS, 1998b).

Despite the impressive results with the obese patients in the metformin study, another randomization of obese and non-obese intensive group participants in which metformin was added to a sulfonylurea if the fasting plasma glucose was 6.1-15 mmol/l (109.8–270 mg/dl) led to 96% increase in diabetes-related deaths, and a 60% increase in all-cause mortality. This surprising observation was not apparent after a combined analysis with the treatment group starting with metformin and with epidemiologic analysis of the data, and remains unexplained.

Nevertheless, it increases uncertainty regarding the best treatment approach for patients with type 2 diabetes.

Taken together these UKPDS reports show that a policy of improving glycemia in patients with type 2 diabetes reduces clinically important outcomes. The benefit is especially clear for microvascular disease, although there is a trend towards reduced macrovascular disease. In light of strong epidemiologic evidence that the risk of CVD rises as the glucose level rises, and the results of the UKPDS, it is likely that the CVD outcomes would have been reduced to a greater degree had stable tight glycemic control been achieved in the intervention group. This hypothesis clearly requires testing in prospective trials of high-risk patients followed for several years, and is the primary basis for the ACCORD Trial.

In addition to the UKPDS, other trials of tight glycemic control in patients with diabetes further support the hypothesis that tight glycemic control is cardio-protective (Table 1.2). The Kumamoto study of insulin-mediated intensive control in thin patients with type 2 diabetes reported a CVD event rate of 0.6/100 patient-years in the intensive group and 1.3 in the conventional group (Ohkubo 1995) (i.e. a nonsignificant RRR of 46%). In the DIGAMI study of insulin-mediated glycemic control after a myocardial infarction, a HbA1c of 7.1% vs 7.9% after 1 year of therapy was associated with a 29% lower mortality rate (Malmberg 1995). In the variable insulin dose arm of the UGDP study, there was also a nonsignificant trend in favor of reduced CV deaths (Genuth 1996). This controversial study reported an increased CVD mortality in a tolbutamide arm after 6 years, which was therefore discontinued. Finally, a recent meta-analysis of all intervention studies in patients with type 1 diabetes showed that intensive therapy with insulin reduced macrovascular events by 45% (95%CI 22%-65%) (Lawson 1999) and the development of a first event by 28% (P=NS). Although these studies were not powered to detect an effect of tight control on CVD outcomes, the results of this meta-analysis also support the hypothesis that glucose-lowering may prevent CVD outcomes.

In contrast to the evidence cited above, the possibility that intensive glycemic control may worsen CVD outcomes was raised by the feasibility phase of the VACS-DM trial, in which the intensively treated group had a nonsignificant increase in the risk of CVD events (Abraira 1997). This observation remains unexplained, but may have been related to the short duration of the trial, the use of a sulfonylurea-class drug in the intensive group but not in the conventional group (or of the sulfonylurea used, glipizide), or the relatively few events. Nevertheless, the results highlight residual uncertainty regarding the potential CVD benefits of glycemic control, and the importance of testing if glycemic control with various strategies prevents CVD events.

Study	Yrs	HbA1c (Intense)	HbA1c (Control)	Therapy	Outcome	Relative Risk Reduction (RRR) (CVD)	RRR (micro)
Table 1.2: Glucose Lowering Trials and CVD in People with Diabetes							
UKPDS [(1998)]	10	7.0% (113%)	7.9%(127%)	Insulin/SU	MI	16% (0,29)	25%
UKPDS [(1998)]	10.7	7.4%(119%)	8.0% (129%)	Metformin	MI	39% (11,59)	29%(NS)
Kumamoto (Ohkubo 1995)	6	7.1% (111%)	9.4%(147%)	Insulin	CV Events	46% (NS)	65%
VACSDM (Abraira 1997)	2.3	7.1% (116%)	9.3% (152%)	Insulin/SU	CV Events	-40% (5,-108)	N/A
DIGAMI (Malmberg 1995)	1	7.1% (range)	7.9%(range)	Insulin	Mortality	29% (4,51)	N/A
UGDP[(IVAR)]* (Genuth 1996)	12.5	FPG 130-146 (7.2-8.1 mmol/l)	FPG 170-186 (9.4-10.3 mmol/l)	Insulin	CV Deaths	9% (NS)	9%(NS)
Type 1 DM** (Lawson 1999)	2-7	7.6%	8.7%	Insulin	Any Event	45% (22,65)	not calculated
Type 1 DM** (Lawson 1999)	2-7	7.6%	8.7%	Insulin	First Event	28% (-17,56)	

SU: sulfonylurea; micro: microvascular disease; NS: not significant in the report; DM: diabetes mellitus
*From the variable insulin dose arm of the UGDP in which a fasting plasma glucose of 130-146 mg/dl (7.2-8.1 mM) was achieved. Results are expressed as the reported value and the % above the upper limit of normal for the assay used (different assays were used in different sites in DIGAMI). Results for surrogate markers are shown (eye exam, poor visual acuity or severe retinal changes).
**From a meta-analysis of all studies of tight control in type 1 diabetes

1.1.d   Glucose Reduction and Adverse Events

The risks of glucose reduction are mainly those of hypoglycemia and weight gain, and in randomized trials of people with type 2 diabetes these risks are highest in insulin-treated individuals. Table 1.3 lists the actual risks in major trials that suggest that between 2-3% of patients with type 2 diabetes who achieve close to optimal glycemic control with intensified insulin therapy will have a severe hypoglycemic reaction annually. This rate may change with newer approaches to therapy and with increased self-management education.

In addition to the risks of glucose-lowering *per se*, adverse effects due to the agents used to lower glucose may also occur. These effects include the possibility that SUs may increase the risk of arrhythmias, especially in an ischemic myocardium (Smits 1995), that metformin increases the risk of lactic acidosis and gastrointestinal symptoms, and that thiazolidinediones increase the risk of liver toxicity and are associated with mild anemia and edema (DeFronzo 1999).

Table 1.3 : Risks of Tight Control with Insulin in Patients with type 2 Diabetes				
Study	**HbA1c**	**Hypoglycemia**		**Mean Weight Gain**
		Severe	**Any**	
UKPDS [(1998)]	7.1% (115%)*	1.8%/yr	28%/yr	4 kg > control (10 yrs)
Kumamoto (Ohkubo 1995)	7.1% (111%)	0%	1.9%/yr	BMI incr 20.5 - 21.2 (6 yrs)
VACSDM [(Abraira 1997)]	7.3% (120%)	3%/yr	41%/yr	Same as control
DIGAMI [(Malmberg 1995)]	7.0%	Control	N/A	1 kg/yr
UGDP[(IVAR)] (Genuth 1996)	FPG 6.7 mmol/l (120.6 mg/dl)	3.2%	N/A	0.2%/yr

NB: severe hypoglycemia is defined as an episode requiring third party assistance; *HbA1c in the group randomized to initial therapy with insulin; not different from control rate (Malmberg et al, personal communication); variable insulin group in the University Group Diabetes Program; fasting plasma glucose at the end of the study (mmol/l); BMI: body mass index

1.1.e Rationale for a Trial of Glucose Lowering to Prevent Cardiovascular Disease

Epidemiologic and clinical trial evidence strongly support the hypothesis that glucose is a modifiable risk factor for CVD in people with diabetes, and that achieving near-normal glycemia will prevent CVD events. Unfortunately, the clinical trial data are insufficient to prove the hypothesis and definitive conclusions regarding the results of a therapy cannot be made from epidemiologic analyses alone because they do not correct for the possibility that outcome and glycemic control may be confounded with other unmeasured variables. Possible reasons for a failure to demonstrate a statistically significant benefit of glucose control on CVD risk in the UKPDS include low MI event rates. For example, the rates of MI in the control and intervention group in the UKPDS were 17.4 and 14.7/1000 patient-years respectively (UKPDS 1998a); the 3867 patients would have been sufficient to detect a 20% risk reduction (but not a lower reduction) with approximately 80% power. The fact that normal glucose levels were not maintained throughout the study in the intervention group is also a limitation.

Support for the benefits of glucose lowering are balanced by several concerns: a) aggressive glycemic lowering has clear risks (see Section 1.1.d), b) there is no definitive clinical trial evidence for CVD benefits of glucose lowering, c) there is no definitive clinical trial evidence of microvascular benefits for HbA1c levels below 7-7.5%, d) the largest clinical trial (the UKPDS) was done in relatively low-risk newly diagnosed individuals, and e) few data are available regarding the CVD effect of glycemic control on high-risk older individuals with well-established diabetes. These considerations strongly support the need to determine definitively the CVD efficacy and risks of intensive glycemic control in people with type 2 diabetes.

ACCORD participants will be randomized to two targeted levels of glucose control. Participants randomized to the intensive group will have a HbA1c target of < 6.0%. Patients

randomized to the conventional group will have a HbA1c target of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%).

1.1.f   Key Methodologic Questions

1.1.f.1 Can We Achieve a HbA1c Target of 6% in the ACCORD Intensive Group?

Prior to the ACCORD Vanguard, the answer to this question for middle-aged patients with established diabetes was unknown, and attempts to achieve this target have not been reported. Reasons for this include the following: a) the continuous relationship between hyperglycemia and CVD in people with type 2 DM was not clearly described until after 1995; b) until the UKPDS was published, there were concerns (from the UGDP, VACSDM and biologic data) that tight glycemic control in people with type 2 diabetes, with insulin, SU or metformin could increase the risk of CVD, hypoglycemia and weight gain, and there was considerable debate over whether or not it would decrease the risk of microvascular disease; c) until recently, the value of combining oral agents and insulin was unknown and discouraged, and there were few data in support of such a strategy - for example the UKPDS and VACSDM were both designed as monotherapy trials in which a second agent was added after the first one failed - indeed in the UKPDS, a second agent was added only when the fasting plasma glucose exceeded 270 mg/dl (15 mmol/l); d) only SUs were available in the United States until metformin was introduced - several other oral agents have been introduced since then; e) there was no point-of-care HbA1c testing available in earlier trials; f) the intensity of follow-up in large trials may have been inadequate to achieve tight metabolic control - for example, participants in the UKPDS intensive group only attended clinic visits every 3-4 months and had HbA1c measured only every 6 months (UKPDS 1998a), and in the Kumamoto study participants were seen only every 6 months (Ohkubo 1995); g) postprandial glucose levels were not explicitly targeted - for example in the VACSDM study intensive therapy participants were asked to do twice daily capillary blood sugar testing before meals and once weekly 3 am testing (Abraira 1995); h) normal HbA1c values were not always targeted - the goal of therapy in the Kumamoto study was a HbA1c < 7% (Ohkubo 1995).

The above shows that most large studies have been able to achieve good mean HbA1c values of 7% using relatively simple monotherapy-based approaches with modest follow-up protocols. Whether better levels can be achieved by the comprehensive intensive protocol discussed above remains unknown and required testing in the Vanguard Phase of ACCORD. At least 2 small studies have shown that normal HbA1c levels can be achieved in people with type 2 DM using insulin alone. In one study of 14 obese individuals (mean age 59; BMI 31 kg/m^2) with a mean HbA1c of 7.7%, twice daily insulin injections (without oral agents) reduced this value to 5.1% within 4 months (Henry 1993, Henry 1996). During this time, no severe (and only minimally mild) hypoglycemic episodes occurred. However, mean weight increased by 9% (8.7 kg). In another small study of 14 individuals (mean age 50; mean glycated Hb 13%), continuous subcutaneous insulin for a 3 week period achieved a normal glycated Hb of 8.1% (normal range was 6.3%-8.2% in this assay) (Garvey 1985). In ACCORD, eligibility criteria have been selected to enhance the likelihood of being able to achieve this target (see Section 2.1.a). The ACCORD Vanguard Phase established the feasibility of achieving HbA1c levels less than 6.0%

in a substantial portion of patients when this level is the goal and there is the ability to use multiple medications.

1.1.f.2 Is it Ethical to Target a HbA1c of 7.0 to 7.9% in the ACCORD Standard Group and What is the Risk-Benefit Relationship?

The UKPDS reported that for newly diagnosed obese and non-obese people, a policy of tight glycemic control over a median of 10 years reduced clinically important diabetes-related endpoints and microvascular events by 12% and 25% respectively (UKPDS 1998a). The absolute risk reductions for these outcomes were approximately 5% and 3% respectively over the 10-year period.

The HbA1c in that trial rose over the duration of follow-up; the median HbA1c during the 10-year period was 7%, and 1 out of 4 patients had a value >8.2%. The median and 75th percentiles of HbA1c during the 1st, 2nd and 3rd 5-year follow-up period are noted in Table 1.4.

The UKPDS also showed that for obese individuals, a policy of tight control starting with metformin (which achieved a median HbA1c of 7.4% during a median follow-up period of 10.7 years) reduced the risk of diabetes-related endpoints, diabetes-related death, and MI by 32%, 42% and 39% respectively (compared to a HbA1c of 8%). The approximate absolute risk reductions were 13%, 5%, and 7% respectively for these outcomes (UKPDS 1998b).

ACCORD will utilize a treatment protocol that will introduce metformin early and will target a HbA1c of 7.0 to 7.9% (inclusive) in the standard group. This value is consistent with the intervention group's values in the UKPDS analysis of the effect of metformin in obese people (which showed a large absolute benefit on clinical endpoints). It is also consistent with a substantial portion of the intervention group's values in the UKPDS analysis of the effects of sulfonylurea and insulin in obese and non-obese people (Table 1.4). Moreover, it is lower than the HbA1c usually achieved in most people with type 2 diabetes and lower than the median HbA1c noted at baseline in the ACCORD Vanguard Phase. Therefore, people in the ACCORD standard group will have a drug and HbA1c treatment policy that is consistent with what was proven effective in the UKPDS.

With this background, it is expected that participants in both the intensive and standard group will be experiencing reductions in HbA1c levels in ACCORD and would thus be expected to derive microvascular benefits from participating.

Table 1.4: UKPDS HbA1c Values			
Population (Drug)/Period	Median HbA1c (%)	25th - 75th %-ile HbA1c cut-points	% of participants above 7.5%
Obese/Non-obese (SU & Insulin)/	7.0	6.2-8.2	>25%
1st 5 yrs	6.6	5.9-7.5	25%
2nd 5 yrs	7.5	6.6-8.8	50%
3rd 5 yrs	8.1	7.0-9.4	>50%
Obese (Metformin)/	7.4	N/A	N/A
1st 5 yrs	6.7	N/A	N/A
2nd 5 yrs	7.9	N/A	N/A
3rd 5 yrs	8.3	N/A	N/A

For the standard group, the challenge is to minimize the risks of severe hypoglycemia, while at the same time lowering glucose sufficiently to reduce the risk of microvascular events from the risk which that group would have otherwise incurred if they had continued on their pre-ACCORD glycemic therapy. Therefore, if there is no CV benefit to intensive glycemic control, the risks of being treated intensively will likely outweigh the benefits; if there is a CV benefit of intensive glycemic control, the risks of being treated conventionally may outweigh any benefits.

Table 1.5 lists estimated relative and absolute risks and benefits for various degrees of glycemic control (i.e. HbA1c levels) that will be achieved in the standard group and is based on several assumptions:

a) The baseline (pre-randomization) HbA1c will be 8.5% (which it was in the Vanguard).

b) The annual absolute risk of severe hypoglycemia will be greater than 2.5% per 1% fall in HbA1c from baseline. Thus this estimate represents the minimum risk.

c) The microvascular benefits for ACCORD standard participants will be as noted in the UKPDS epidemiologic analysis (Stratton 2000): a 37% relative risk reduction for every 1% fall in HbA1c.

d) There is a linear relationship between HbA1c and both risk and benefit within the HbA1c range of 7.0% to 8.5%.

These estimates facilitate a comparison of the impact of 2 different final conventional group HbA1c levels and illustrate the risk-benefit trade-off within the HbA1c range of 7.1% to 7.9%. As noted in Figure 1.1 that was derived from these estimates, the risk of severe hypoglycemia (even when minimum estimates are used) clearly rises more steeply than the fall in the risk of microvascular events. Thus, a final standard group median HbA1c of 7.7% versus 7.5% would lead to a 5-year absolute risk of microvascular events (i.e. mainly laser therapy) of 8% versus 7%. This 1% absolute risk reduction over 5 years would be countered by a 2.5% absolute risk increase of severe hypoglycemia (i.e. 10% versus 12.5%) over 5 years.

Table 1.5: Effect of the Degree of Fall in HbA1c in Standard ACCORD Participants							
Absolute HbA1c fall from 8.5%	Final HbA1c	Microvascular Events				Severe Hypoglycemia	
		RRR	Annual ARR	Absolute Risk		Absolute Risk	
				Annual	5 yr	Annual	5 yr
None	8.5%	0	0	~ 2.3%*	11.5%	N/A	N/A
0.8%	7.7%	30%	0.7%#	1.6%	8%	>2%	>10%
1%	**7.5%**	**37%****	**0.9%****	**1.4%****	**7%**	**>2.5%**	**>12.5%**
1.2%	7.3%	44%	1%	1.3%	6.5%	>3%	>15%
1.4%	7.1%	52%	1.2%	1.1%	5.5%	>3.5%	>17.5%

RRR – relative risk reduction; ARR – absolute risk reduction; *The actual risk may be greater for the older, high cardiovascular risk people in ACCORD than in the UKPDS. # calculated as (2.3-1.6); ** from Stratton 2000.

Figure 1.1:
Projected Microvascular versus Severe Hypoglycemia Risks
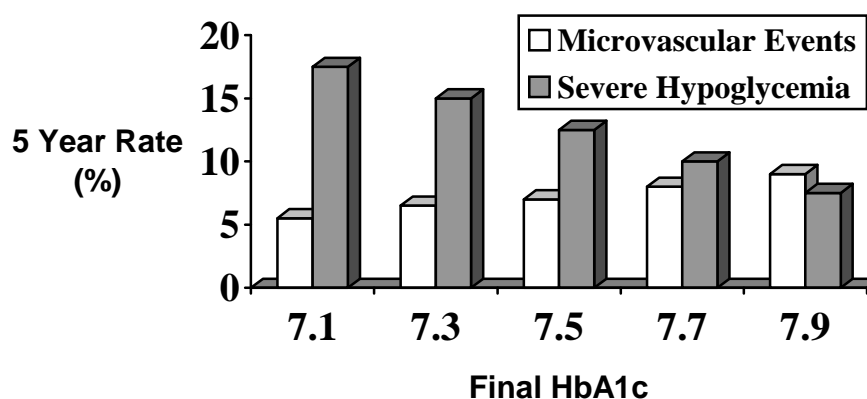
1.1.f.3 Can ACCORD Achieve and Maintain an Absolute HbA1c Difference Approaching a Target 1.5% Between the Intensive and Standard Groups?

Given the currently available data, a HbA1c difference of approximately 1.5% is estimated to be a conservative target that would lead to a 15% or greater reduction in CVD events. Although review of the UKPDS data of obese participants suggests that a lower differential of 1% may be adequate, sufficient uncertainty regarding these estimates exists to justify the 1.5% differential. Other trials such as the UKPDS (UKPDS 1998a, UKPDS 1998b), Kumamoto study (Ohkubo 1995), VACSDM (Abraira 1997), UGDP (Genuth 1996) and DIGAMI (Malmberg 1995) study have successfully achieved and maintained separation of the HbA1c using different protocols with less flexibility and choice of therapy.

Targeting a between-group difference in HbA1c that is lower than 1.5% may jeopardize ACCORD's chance of achieving an adequate HbA1c difference. In light of the high importance of achieving and maintaining a HbA1c difference that is sufficient to test the research question, ACCORD has adopted a delta of 1.3% as an alert level. Greater separations are, however, expected in response to the novel approaches to glycemic control that will be employed for both treatment groups (see Section 3.2). Nevertheless, if the HbA1c separation falls below 1.3% in participants with at least 2 years of follow-up, the progress of the trial will be carefully scrutinized by the investigators, and actions will be taken to increase the separation. The Data Safety and Monitoring Board will also monitor the HbA1c levels and separation.

1.2 Diabetes and Dyslipidemia

1.2.a Type 2 Diabetes and Dyslipidemia

One of the goals of ACCORD is to determine if more aggressive control of diabetic dyslipidemia, specifically raising HDL-cholesterol and lowering triglycerides (TG), in the context of desirable levels of LDL-cholesterol, will provide greater benefit than only having desirable levels of LDL-cholesterol. The reason for choosing to address this question is that a dyslipidemia characterized by low HDL-cholesterol and high TG levels, with average LDL-cholesterol levels, is typical of type 2 diabetes mellitus. Albrink and coworkers first reported links between hypertriglyceridemia and insulin resistance (Davidson 1965), but it was the work of Reaven and Farquhar and their colleagues that clearly defined this link (Reaven 1967, Olefsky 1974). Since then, numerous investigators conducting either small, detailed physiologic studies or larger epidemiologic studies have confirmed the relationship between type 2 diabetes, insulin resistance and increased blood levels of very low density lipoprotein (VLDL) TG (Olefsky 1974, Albrink 1980, Laws 1997, Howard 1998, Bonora 1998). *In vivo* studies of lipoprotein metabolism have indicated that insulin resistant states are associated with increased assembly and secretion of apoprotein B100 (apoB)-containing lipoproteins. Thus, increased secretion of both VLDL TG and apoB (Sigurdsson 1976, Kissebah 1982, Ginsberg 1982, Howard 1983) is a central abnormality in individuals with insulin-resistance/type 2 diabetes. It is believed that increased free fatty acid flux to the liver in insulin-resistant individuals drives TG synthesis and assembly of VLDL. Reduced activity of the key enzyme in triglyceride removal from plasma, lipoprotein lipase (LpL), is also important. LpL is an insulin regulated enzyme in muscle and fat, and has been shown to be modestly reduced in many patients with type 2 diabetes (Taskinen 1987). In patients with type 2 diabetes, hyperglycemia may contribute to increased VLDL

secretion as well, although correction of blood glucose levels seems to only partly reverse the dyslipidemia (Ginsberg 1991).

Patients with type 2 diabetes have low plasma HDL-cholesterol levels, and this does not seem to be related to either glycemic control or mode of treatment (Hollenbeck 1986, Gordon 1977). A consistent finding has been the inverse relationship between plasma insulin (or C-peptide) and HDL- cholesterol levels (Uusitupa 1986). The degree of insulin resistance also appears to be related inversely to HDL-C concentrations (Laakso 1990). Increased secretion of apo B-containing lipoproteins could result in increased cholesterol ester transfer protein (CETP)-mediated transfer of HDL cholesteryl esters to those lipoproteins (Tall 1986, Bagdade 1993), and this would explain the reduced levels of plasma HDL-cholesterol in patients with type 2 diabetes. The finding of triglyceride-enriched HDL-C particles in patients with this disorder supports this scheme. Increased hepatic lipase (HL) activity may also contribute to the development of low HDL-cholesterol (Horowitz 1993, Lamarche 1999). ApoAI and AII levels are reduced consistently as well, and fractional catabolism of apoAI is increased in type 2 patients with low HDL-C (Golay 1987), as it is in nondiabetic patients with similar lipoprotein profiles (Le 1988, Nicoll 1980, Brinton 1991).

Small dense LDL-C are commonly present in patients with type 2 diabetes and is most likely an integral part of the dyslipidemia of insulin resistance (Feingold 1992, Reaven 1993). Thus, increased plasma levels of VLDL TG can stimulate CETP-mediated transfer of LDL cholesteryl esters to VLDL in exchange for TG. The TG-enriched LDL-C is then modified by LPL and/or HL, producing small dense LDL-C.

1.2.b Evidence that LDL-Cholesterol Lowering Reduces Cardiovascular Events

Several primary and secondary prevention trials have demonstrated remarkable reductions in CHD events and mortality in high-risk patients, and the issue for ACCORD is how to apply this evidence to LDL-C treatment goals in the lipid portion of the trial. Beginning with the landmark Coronary Primary Prevention Trial in which cholestyramine was used (Lipid Research Clinics Program 1984), and continuing through the secondary prevention trials of HMG CoA-reductase inhibitors (or "statins") such as 4S (Scandinavian Simvastatin Survival Study Group 1994), CARE (Sacks 1998), LIPID (LIPID 1998) and the primary prevention statin trials such as WOSCOPS (Shepherd 1995) and AFCAPS/TEXCAPS (Downs 1998), treatment to lower LDL-C has resulted in consistent reductions in cardiovascular events. The data from the trials validate the algorithm for cholesterol treatment suggested by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III that sets initiation and treatment targets for cholesterol lowering in patients with various levels of risk. The rationale of the NCEP panel was that those at the highest risk would benefit the most and warrant the most aggressive treatment. Characteristics of the landmark statin trials published through 1998 are summarized in Table 1.6.

Table 1.6: Landmark Statin Trials						
			LDL-Cholesterol (mg/dl)			
Population	Trial	N	Eligibility	Mean On Placebo	Mean On Statin	Agent
Primary Prevention						
HIGH LDL-C	WOSCOPS	6595	>155 (4.03 mmol/l)	191(4.97 mmol/l)	140 (3.64 mmol/l)	Pravastatin
LOW LDL-C	AFCAPS*	6605	> 125 (3.25 mmol/l)	156 (4.05 mmol/l)	115 (2.99 mmol/l)	Lovastatin
Secondary Prevention						
HIGH LDL-C	4S	4444	>155 (4.03 mmol/l)	186 (4.84 mmol/l)	121 (3.15 mmol/l)	Simvastatin
LOW LDL-C	CARE	4159	>115 (2.99 mmol/l)	135 (3.51 mmol/l)	98 (2.54 mmol/l)	Pravastatin
LOW LDL-C	LIPID	9014	>115 (2.99 mmol/l)	150 (3.9 mmol/l)	113 (2.94 mmol/l)	Pravastatin

N: sample size   *AFCAPS participants were particularly healthy: no unstable hypertension; diabetic patients with HbA1c > 20% upper limit of normal excluded.

Table 1.7 summarizes events in the major primary and secondary prevention statin trials.

Table 1.7: Event Rates in Statin Trials.					
			Event Rate		
Population	Trial	N	Placebo	Statin	Event Definition
Primary Prevention					
HIGH LDL-C	WOSCOPS	6595	248/3293=7.9%=1.6%/yr	174/3302=5.5%=1.1%/yr	Fatal CHD + NFMI
LOW LDL-C	AFCAPS	6605	183/3301=5.5%=1.1%/yr	116/3304=3.5%=0.7%yr	Fatal + NFMI, USA, sudden death
Secondary Prevention					
HIGH LDL-C	4S	4444	622/2223=28%=5.2%/yr	431/2221=19%=3.5%yr *	Fatal CHD + NFMI
LOW LDL-C	CARE	4159	274/2078=13%=2.6%/yr	212/2081=10%=2%/yr	Fatal CHD + NFMI
LOW LDL-C	LIPID	9014	715/4502=15%=2.6%/yr	557/4512=12%=2%/yr	Fatal CHD + NFMI

N: sample size; MFMI: nonfatal MI; USA: unstable angina
* = 2%/yr for the 40% of 4S participants whose LDL-C was <95 mg/dl (2.47 mmol/l) on treatment

1.2.c Evidence that LDL-Cholesterol Lowering Reduces Cardiovascular Events in People with type 2 Diabetes

In several of the secondary prevention studies there were small numbers of individuals with type 2 diabetes. Subgroup analyses show very high rates of CHD events and mortality in patients with type 2 diabetes, and demonstrate substantial reductions in outcomes in the treated groups consistent with overall results of these trials. (LIPID 1998, Goldberg 1998, Haffner 1999). The results of those subgroup analyses are presented in Table 1.8.

		# Diabetic Patients	Event Rate		Event Definition
Table 1.8: Event Rates in Diabetic Patients in Statin Trials					
	Trial		Placebo	Statin	
Primary Prevention					
HIGH LDL-C	WOSCOPS	70	---	---	
LOW LDL-C	AFCAPS	155	6/71 = 8.4% = 1.6%/yr	4/84 = 4.8% = 0.9%/yr	Fatal + NFMI, USA, sudden death
Secondary Prevention					
HIGH LDL-C	4S	202	44/97=45% = 8.4%/yr	24/105=22%= 4.2%/yr	Fatal CHD + NFMI
LOW LDL-C	CARE	602	112/304=37%= 7.4%/yr	81/282=29%= 5.8%/yr	Fatal CHD + NFMI +revasc
LOW LDL-C	CARE*		3.9%/yr	3.1%/yr	Fatal CHD + NFMI*
LOW LDL-C	LIPID	782	88/386=23% = 3.8%/yr	76/396=19%= 3.1%/yr	Fatal CHD + NFMI

Abbreviations are in Table 1.7. *Data from CARE are corrected assuming that the proportion of events attributable to revascularizations in diabetic patients equals that in non-diabetic patients. CARE and 4S data for diabetic patients have been published separately (Goldberg 1998, Haffner 1999). Rates in WOSCOPS too small to report.

1.2.d Evidence that Going Beyond LDL-Cholesterol Lowering to Raise HDL-Cholesterol and Lower Triglycerides May Lead to Further Reductions in Cardiovascular Events in People with Type 2 Diabetes

The evidence presented above indicates clearly that lowering LDL-cholesterol levels is beneficial for non-diabetic patients and people with diabetes. However, the event rates in the treated diabetic subgroups are similar to the rates observed in the non-diabetic placebo groups. That is, the risk among diabetic patients is not "normalized". This raises the question about the potential benefit of going beyond simple LDL-cholesterol-lowering. One option would be to treat the lipid abnormalities characteristic of diabetes patients. In fact, there are data supporting a role for lowering triglycerides and raising HDL-cholesterol levels in primary and secondary prevention trials. In the Helsinki Heart Study, gemfibrozil lowered LDL-C modestly but also lowered triglycerides and raised HDL-C, and the reduction in cardiac events in that primary prevention trial was linked by multiple regression analysis to the rise in HDL-cholesterol. There were too few diabetic patients in that study to observe a significant benefit in that group, although a trend toward benefit was seen (Frick 1987).   The recent VA-HIT trial (Rubins 1999) indicated that in men with CHD and LDL-cholesterol levels of about 110 mg/dl (2.86 mmol/l), treatment with gemfibrozil reduced new events by 22% over a five-year period. Gemfibrozil treatment was associated with a 25% lowering of triglycerides, a 7% increase in HDL-cholesterol, and no change in LDL-cholesterol. About 25% of the 2500 men in the trial had diabetes, and this group appeared to have both a much higher event rate in the placebo group (37% over five years) and a similar 22% reduction in events in the gemfibrozil treated group. The results of VA-HIT are summarized in Table 1.9.

Table 1.9: Event Rates in VA-HIT				
Population	**N**	**Event Rate**		**Event Definition**
		Placebo	**Fibrate**	
Overall	2531	275/1267=22%=4.3%/yr	219/1264=17%=3.3%/yr	CHD Death, NFMI, stroke
Diabetic Participants	627	116/318=36%=7%/yr	88/309=28%=5.5%/yr	CHD Death, NFMI, stroke

A key fact to note regarding VA-HIT was that the initial LDL-C level was in a range considered to be near target. However, even with a near target LDL-C, the placebo group rates for the diabetic patients were almost twice as high as the rates for the nondiabetic patients. More importantly, VA-HIT has demonstrated that increasing HDL-C and lowering TG can provide significant additional benefits for patients with a near target LDL-C. To extrapolate from the VA-HIT study, it could be hypothesized that even after statin therapy (with lowering of LDL-cholesterol from an average level of about 140 mg/dl (3.64 mmol/l) [the expected level of LDL-C in a diabetic population] to a target LDL-C of about 115 mg/dl (2.99 mmol/l)), the addition of a fibrate could further reduce event rates significantly. This is the basis for the ACCORD lipid intervention hypothesis.

1.2.e Rationale for Trial of Fibrate + Statin vs. Placebo + Statin.

As noted above, the very high five-year event rates in VA-HIT participants with diabetes in the placebo group (36%) and in the fibrate treated group (28%) indicate a need to answer the question as to whether combined therapy with statin and fibrate would provide greater benefit than therapy with statin alone.

Regarding trials in diabetic patients, there is only one completed fibrate-only trial and only one fibrate-only trial underway. The Diabetes Atherosclerosis Intervention Study (DAIS) was an angiographic trial in which 418 patients with diabetes (mean HbA1c=7.5%) and coronary artery disease were randomized to fenofibrate or placebo and followed for a mean of about 40 months. The fenofibrate group had a statistically significant smaller increase in percent diameter stenosis and a statistically significant smaller decrease in minimum lumen diameter. Although not powered for clinical events, there were fewer cardiac events in the fenofibrate group (38 versus 50) (DAIS 2001). The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study is a clinical event trial of 8,000 diabetic patients largely without coronary artery disease that will not be completed for several years.

The only other trial attempting to address the issue of therapy with statin plus a fibrate in patients with diabetes was the Lipid Diabetes Study (LDS), which was using fixed doses of cerivastatin and fenofibrate (vs placebos) in a 2 X 2 factorial design in a primary prevention setting. However, this trial was recently terminated after cerivastatin was removed from the market. Therefore, ACCORD is now the only trial addressing this important issue. Also, the ACCORD protocol differs from the original LDS protocol in that ACCORD includes both primary and secondary prevention groups and evaluates lipid treatment in the context of protocol-specified glucose control.

Other strategies that could be used to obtain better outcomes in diabetic patients beyond average or near target LDL-cholesterol levels are improved risk stratification and achievement of lower LDL-cholesterol levels. Improved risk stratification implies the ability to better identify those individuals at highest risk than is now feasible. Approaches to this include measurement of serum markers (e.g. C reactive protein) or direct non-invasive quantification of vascular disease (e.g. with coronary calcium screening). Data supporting this approach, while intriguing, are tentative at the present time.

A strategy of achieving lower LDL-cholesterol than currently recommended is an attractive one, but there are 2 large clinical trials ongoing that will address this question, although not exclusively in diabetic patients. The Treating to New Targets (TNT) trial will randomize 8600 patients with coronary heart disease to high or low-dose atorvastatin and follow them for clinical events. The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial is a similar trial with high vs low dose simvastatin in 12,000 patients with coronary heart disease.

An additional rationale for studying the efficacy of combined therapy with a statin and fibrate is that this is an increasingly used combination that must be proved safe as well as effective. Data from a number of small clinical trials suggests that the incidence of myositis, defined as muscle pain and plasma CPK level greater than 10 times upper limit of normal, is about 1%. In those small, tightly controlled trials, there were no cases of rhabomyolysis. This purported safety profile must be confirmed in a large trial and placed in the context of the hypothesized additional benefit achieved by the combined treatments.

1.2.f   Justification for Use of Simvastatin in Lipid Trial Participants

ACCORD is a trial of a high-risk diabetic population, one with prevalent vascular disease, evidence of subclinical disease, or the presence of multiple CVD risk factors. The data presented above, as well as national guidelines, support the use of statins for such patients. Thus, in each of the trials noted above, the diabetic subset had much higher event rates than the overall group. Even after treatment with a statin, the diabetic patients had event rates in the range of 3.1-4.2% per year. In AFCAPS/TEXCAPS, a primary prevention trial of relatively low risk individuals, the diabetic subgroup on lovastatin had an event rate that was 50% greater than the overall trial population (Downs 1998). In the Heart Protection Study (Heart Protection Study [HPS] Collaborative Group 2002), patients with diabetes without prior CHD events who were on simvastatin had a 2.8% yearly event rate.

Although the NCEP guidelines define diabetes as a CHD-equivalent (and has LDL-C > 130 mg/dl as the initiation for pharmacologic treatment and the goal at 100 mg/dl), and an update of the guidelines states that an LDL-C goal of <70 mg/dL is a therapeutic option for patients with existing cardiovascular disease (Grundy 2004), the guidelines also note that drug treatment is optional for CHD patients with an LDL-C between 100 and 129 mg/dl, inclusive, and that clinical judgment may call for deferring drug therapy in this subcategory because of limited data identifying the exact levels for either initiation or goals. As noted above, placebo treatment in the three major statin trials was associated with the following event rates and corresponding on-treatment LDL-C: 4S 5.2%/year, 186 mg/dl; LIPID 2.6%/year, 150 mg/dl; CARE 2.6%/year, 135 mg/dl. Thus a 20% lower LDL-C in LIPID compared to 4S was associated with an event

rate that was half a great. However, a 10% lower LDL-C in CARE compared to LIPID was associated with no fewer events. Similarly, pooled analysis of CARE and LIPID data showed no benefit of treatment at the lowest quintile of baseline LDL-C (median of 117 mg/dl [3.04 mmol/l], Sacks 1999). On the other hand, the results from the Heart Protection Study (HPS) demonstrate benefit of lowering LDL-C in a high risk group even when baseline LDL-C levels are low. Specifically, five-year CHD event rates were reduced from 22.2% to 17.6% in subjects who had a baseline LDL-C less than 116 mg/dl. Further, five-year CHD event rates were reduced from 21.0% to 16.4% in subjects with baseline LDL-C levels less than 100 mg/dl. More recently, the Treating to New Targets (TNT) trial of persons with existing CHD found that lowering LDL-C levels to an average of 77 mg/dL using atorvastatin 80 mg/day, compared with an average of 101 mg/dL using atorvastatin 10 mg/day, resulted in a significant 22% reduction in major cardiovascular events over a median of 4.9 years of follow-up [LaRosa 2005]. Thus, based on the HPS results and other evidence such as TNT, ACCORD will treat all primary prevention participants in the lipid portion of the trial with 20 mg/day simvastatin and all secondary prevention participants with 40 mg/day. In addition, the dose of simvastatin will be increased from 20 mg/day to 40 mg/day in participants who begin the trial as primary prevention who then have a cardiovascular event during the course of the trial or whose LDL-C is consistently greater than 100 mg/dl (2.59 mmol/l). The estimated in-trial mean LDL-cholesterol level of participants in the lipid component of ACCORD is estimated to be approximately 82 mg/dl (2.12 mmol/l) (see Section 3.3.c).

(It is to be noted that under the Vanguard Protocol [dated September 13, 2001], participants in the lipid trial were titrated from 0 to 20 mg of simvastatin for the purpose of achieving an LDL-C of approximately 100 mg/dl [2.6 mmol/l]. Under this main trial protocol, all lipid trial participants, including those randomized during the Vanguard who provide consent, will be assigned 20 or 40 mg simvastatin, depending on their CVD status.)

Available data from the major secondary prevention trials published prior to HPS indicate that when individuals have baseline LDL levels greater than 120 mg/dl, lowering LDL-C to below that level is associated with benefit that is similar regardless of the exact LDL-C concentration that is achieved. Thus, recurrent event rates related to the average on-treatment LDL-C in the active treatment groups were: LIPID 2%/year, average 113 mg/dl; POSCH 2%/year, 111 mg/d; CARE 2%/year, 97 mg/dl; and for the 40% subset of participants in 4S who lowered their LDL-C to < 100 mg/dl, 2%/year, 95 mg/dl. These studies had similar event rates for on-treatment LDL-C that ranged from 95 mg/dl to 113 mg/dl. On the other hand, in HPS, benefit of simvastatin treatment was observed even when baseline LDL-C levels were less than 100 mg/dl. We believe that the ACCORD lipid trial protocol, in which we will treat all primary prevention participants with 20 mg simvastatin and all secondary prevention participants with 40 mg, regardless of baseline LDL-cholesterol levels, is consistent with all of the published trial results. Because 40 mg of simvastatin may increase the risk for adverse events, particularly in the patients receiving fenofibrate, participants will be followed closely and CPK regularly measured. LDL-cholesterol levels will be monitored by the Coordinating Center and any participant who is on 40 mg of simvastatin and whose LDL-cholesterol is consistently greater than 120 mg/dl will be unmasked and treated appropriately.

1.3   Diabetes and Hypertension

1.3.a   Diabetes and Cardiovascular Disease

Diabetes mellitus increases the risk of cardiovascular events two-to-three-fold at every level of SBP or diastolic BP (DBP) and in diabetic patients there is a graded increase in risk across the entire range of blood pressure levels (Stamler 1993).   Therefore, diabetes and hypertension combined confer a much higher risk than either one alone.   In part because of this higher risk, even at high normal levels of BP, JNC VI recommended beginning drug treatment in diabetic patients if the SBP is >130 mm Hg or the DBP is >85 mm Hg, and BP goals are <130/85 mm Hg (JNC VI 1997).   However, at the time these recommendations were made, there were no completed clinical trials supporting the recommendations.

1.3.b   Trials of Reducing Blood Pressure in Diabetic Patients

Table 1.10 describes the clinical trials of blood pressure lowering in diabetic patients.   In the 583 participants with type 2 diabetes mellitus in SHEP, major cardiovascular disease events were reduced by 34% (Curb 1996).   Although this was the same risk reduction as in nondiabetic participants, the absolute risk reduction was twice as great for diabetic participants.   The SHEP BP entry criterion was a SBP 160-219 mm Hg; the treatment goal was <160 mm Hg and at least 20 mm Hg reduction from baseline.   Systolic BP was reduced from 170 to 143 mm Hg.

Subsequent to JNC VI, the Hypertension Optimal Treatment (HOT) study reported that in the diabetic subgroup (n=1,501) major cardiovascular events were reduced by 51% (P=0.005) in those randomized to a DBP goal of <80 mm Hg compared to a goal of <90 mm Hg: 12 versus 24 events/1000 patient-years (Hansson 1998).   However, this was a *post hoc* analysis and the number of events was relatively small.   The achieved BP for the more intensive group in the diabetic patients has not been reported, but for all hypertensive patients it was 140/81 mm Hg. There were no differences in cardiovascular events between randomized groups in the entire 18,790 hypertensive patients in HOT.   In the United Kingdom Prospective Diabetes Study (UKPDS 1998), 1,148 hypertensive type 2 diabetic patients were randomized to either tight BP control (<150/85 mm Hg) or less tight BP control (<180/105 mm Hg).   In that trial, diabetes related endpoints were reduced by 24% (P=0.005), deaths related to diabetes by 32% (p=.019), strokes by 44% (p=.013), and microvascular endpoints by 37% (p=.009) after a median follow-up of 8.4 years (UKPDS 1998a).   Although not statistically significant, all-cause mortality was reduced by 18% and MI by 21%.   Average BP over 9 years was 144/82 mm Hg and 154/87 mm Hg in the tight and less tight BP control groups, respectively, for a BP difference of 10/5 mm Hg. In a placebo-controlled trial of treatment of isolated systolic hypertension, the Systolic Hypertension in Europe (Syst-Eur) Trial, the 492 patients with diabetes were reported in a *post hoc* analysis to have significant reductions in CVD mortality, all CVD events, and stroke with the mean SBP reduced from 175 to 153 mm Hg (Tuomilehto 1999).   Entry criteria were similar to SHEP (SBP 160-219 mm Hg), and the goal was to reduce SBP at least 20 mm Hg to <150 mm Hg.   The Appropriate Blood Pressure Control in Diabetes (ABCD) Trial, a prospective, randomized, masked trial in 470 hypertensive diabetic patients (type 2), compared the effects of moderate control of BP (target DBP 80-89 mm Hg) with those of intensive control of BP (DBP

75 mm Hg) on the incidence and progression of diabetic nephropathy, retinopathy, cardiovascular disease and neuropathy (Schrier 1996, Estacio 1998). The results of the microvascular outcomes of the ABCD trial BP comparison have recently been reported (Estacio 2000). The mean blood pressure achieved in the intensive group was 132/78 mm Hg and was 138/86 mm Hg in the moderate control group. There were no differences in any microvascular endpoints for the 2 BP goals (and no microvascular differences between nisoldipine vs enalapril in the more intense group). The BP delta was 6/8 mm Hg, although the goals were just for DBP. The intensive therapy group had a lower mortality rate, 5.5% vs 10.7% (p=0.037), but there were no statistically significant differences in MI, cerebrovascular events, or CHF to account for the mortality difference (Estacio 2000).

Table 1.10: Clinical Trials of Blood Pressure Lowering in Diabetic Patients							
Trial	N	Duration	Mean BP, less intense	Mean BP, more intense	Initial Therapy	Outcome	Risk Reduction
SHEP (Curb 1996)	583	5 years	155/72*	143/68*	Chlorthalidone	Stroke CVD events CHD	22% (ns) 34% 56%
Syst-Eur (Tuomilehto 1999)	492	2 years	162/82	153/78	Nitrendipine	Stroke CV events	69% 62%
HOT (Hansson 1998)	1,501	3 years	144/85*	140/81*	Felodipine	CV events MI Stroke CV mortality	51% 50% 30% (ns) 67%
UKPDS (UKPDS 1999a)	1,148	8.4 years	154/87	144/82	Captopril or atenolol	Diabetes-related endpoints: deaths: Strokes Microvascular	34% 32% 44% 37%
ABCD (Estacio 2000)	470	5.3 years	138/86	132/78	Nisoldipine or enalapril	C_{Cr} Albuminuria Retinopathy Neuropathy Mortality MI, CVA, CHF	nc nc nc nc 49% ns

BP = blood pressure, ns = not significant, nc = no change
* BP in diabetic + non-diabetic population, since BP not reported for diabetic patients alone

Therefore, the HOT and UKPDS studies provide the most definitive clinical trial evidence to date and support BP goals in diabetic hypertensive patients of <150/85 mm Hg (UKPDS) and DBP <80 mm Hg (HOT). Based on these goals, as well as achieved BP levels in other trials, including SHEP, all of the trials are consistent with SBP goals of 140 mm Hg in diabetic patients and none, including ABCD, have confirmed benefit to lower goals than this.

The ALLHAT study was begun in 1994 and includes more than 15,000 diabetic patients (Davis 1996). It is primarily designed to compare 4 different classes of antihypertensive drugs. The BP goal of therapy is at least <140/90 mm Hg. Neither this trial, nor others in progress, will provide data on the added effect on CVD morbidity and mortality of BP-lowering on top of glycemic control in diabetic patients. ACCORD will address this issue and should also provide

the first clinical trial data on the possible benefit of treating to more aggressive BP goals (compared with the UKPDS, for example) in preventing CVD in diabetic patients.

1.3.c   Trials Regarding Choice of Antihypertensive Drug

Ongoing trials, such as ALLHAT, will clarify whether there are important differences in CVD outcomes among various classes of antihypertensive agents in patients with type 2 diabetes mellitus and hypertension (Davis 1996, Cutler 1998). Results from the 15,000+ diabetic hypertensive participants within ALLHAT (randomized to receive chlorthalidone, amlodipine, lisinopril, or doxazosin in a double-masked design) should give more definitive direction for antihypertensive drug therapy for ACCORD, although the projected end of follow-up for ALLHAT is not until 2002. In early 2000, however, the doxazosin arm of ALLHAT was stopped because of a significantly higher incidence of cardiovascular events in the doxazosin group versus the chlorthalidone group (ALLHAT 2000). In the diabetic subgroup of ALLHAT, the rates of CVD and CHF were significantly higher in participants randomized to doxazosin (relative risk = 1.24 [P<0.0001] and = 2.14 [P<0.0001], respectively). Otherwise, existing data do not clearly mandate one antihypertensive drug class for this population.

Major CVD events were reduced in the diabetic subgroups in SHEP (Curb 1996) and HDFP with therapy initiated with a diuretic. In the 758 patients in the tight control group of UKPDS, the ACE inhibitor captopril and the beta-blocker atenolol were equally effective in reducing the incidence of diabetic macrovascular and microvascular complications (UKPDS 1998b). In the Captopril Prevention Project (CAPPP), there were no significant differences in CVD mortality or MI for captopril versus conventional treatment with diuretics and/or beta-blockers in the nearly 11,000 hypertensive patients (although strokes were 25% more frequent with captopril). However, in a *post hoc* subgroup analysis in the 572 patients with diabetes, the risk reduction for the primary CVD endpoint was 41% (P=0.019) with captopril vs conventional treatment (Hansson 1999). In the second Swedish Trial in Old Patients with Hypertension (STOP-2), there was no difference for the primary outcome (cardiovascular mortality) between patients randomized to diuretics and/or beta-blockers versus ACE inhibitors versus calcium antagonists, both overall and in the 719 patients with diabetes (Hansson 1999). In a *post hoc* analysis of the diabetic subgroup (n=492) of the Syst-Eur Trial, an antihypertensive regimen initiated with the dihydropyridine calcium channel blocker nitrendipine reduced CVD mortality and events compared to placebo (Tuomilehto 1999).

Several relatively small controlled trials in diabetic hypertensive patients have reported lower cardiovascular event rates with an ACE inhibitor compared with a calcium channel blocker. The 470 diabetic hypertensive participants in the ABCD trial had a 7-fold higher incidence of fatal and nonfatal MIs with the dihydropyridine calcium channel blocker nisoldipine than with the ACE inhibitor enalapril through five years of follow-up (Estacio 1998), although microvascular outcomes were not different between the two drugs (Estacio 2000). In the Fosinopril Amlodipine Cardiovascular Events Trial (FACET), 380 diabetic hypertensive patients experienced a 51% lower incidence of the combination of acute MI, hospitalized angina, and stroke with fosinopril compared with amlodipine (P=0.03) over 2.8 years of follow-up (Tatti 1998).

Therefore, diuretics, ACE inhibitors, beta-blockers, and calcium channel blockers have been associated with reduced major macrovascular or microvascular events in diabetic hypertensive patients compared with placebo or a less intensively treated control group in randomized controlled trials. Comparisons between drugs are less clear, except for the higher risk with an alpha blocker seen in ALLHAT (ALLHAT 2000). It would also appear reasonable to avoid treating hypertension in diabetic patients with single-drug therapy with a calcium channel blocker until more data are available.

1.4 Conclusions of Recent Expert Panels Convened to Discuss Diabetes and Cardiovascular Disease

The report of the Macrovascular Disease Subcommittee of the NIH-sponsored Diabetes Conference in September 1997 "enthusiastically recommended a large scale clinical trial to determine whether the level of glucose control … will decrease the incidence of CHD in a diabetic population." The report also noted that "about 50 percent of excess heart disease in diabetic patients can be attributed to associated abnormalities in other known CVD risk factors" and that "the same risk factors that predict large vessel disease (i.e. stroke, heart attack and peripheral arterial disease) in the general population also affect the diabetic." A trial comparing the cost-effectiveness of different therapeutic approaches (such as contrasting optimal glucose control with aggressive lipid lowering) was advocated by some members of the panel. The panel also emphasized the importance of selecting diabetic patients at particularly high risk for developing CVD for inclusion in any trial.

Similar conclusions were reached by the NHLBI Special Emphasis Panel on Prevention and Treatment of Cardiovascular Disease in Diabetes Mellitus. Notably, a number of panel members recommended testing not only the relative benefit of different diabetic regimens, but also different target levels or intensities of treatment for lipids or blood pressure, using a factorial design. The rationale for a factorial design is that although a number of studies in progress are collectively addressing treatment of lipids, blood pressure or glycemic control in diabetic patients, none of them would shed light on the comparative benefit of treating hyperglycemia and aggressively treating blood pressure and lipids.

Additional support for a large clinical trial testing the benefit of tight glycemic, lipid, and blood pressure control was given by an *ad hoc* advisory group convened by NHLBI in May 1998.

1.5 Specific ACCORD Hypotheses

ACCORD is designed as a double 2x2 factorial design with factors consisting of: intensive versus standard glycemic control, intensive versus standard blood pressure control, and in the presence of desirable LDL-C levels, fibrate use versus placebo. As shown in Figure 1.2 below, all 10,000 participants will be randomized to the glycemic interventions; 5,800 participants meeting the lipid entry criteria will be randomized to the lipid interventions in one 2x2 trial; 4,200 participants who meet the blood pressure entry criteria will be randomized to the blood pressure interventions in the second 2x2 trial.

Figure 1.2:
Projected Allocation of Participants in ACCORD

		Lipid Trial		SBP Trial		
		Fibrate	Placebo	Intensive	Standard	
10,000 Participants in Glycemia Trial →	Intensive	1450	1450	1050	1050	5000
→	Standard	1450	1450	1050	1050	5000
		2900	2900	2100	2100	

Participants not recruited for the lipid trial will be referred to their usual source of care for treatment of any lipid abnormalities. Similarly, participants not recruited for the blood pressure trial will be referred for treatment of any blood pressure abnormality. Recommendations for goals of these treatments will be provided (see Section 3.5). High risk participants with and without a history or evidence of vascular disease will be recruited at approximately 60 Clinical Sites administratively located within 7 Clinical Center Networks in the United States and Canada. Recruitment will occur over two non-contiguous periods (described below and in Section 7.1) and participants followed for about 4 to 8 years (approximate mean of 5.6 years).

The three specific primary ACCORD hypotheses are:

In middle-aged or older people with type 2 diabetes who are at high risk for having a cardiovascular disease (CVD) event:

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

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

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

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

The intervention-specific secondary hypotheses are specified in Section 7.1.b. The intervention-specific subgroup hypotheses are specified in Section 7.1.c.

1.6   Timetable/The Vanguard Phase

ACCORD will be conducted over a 11.25 year period, from October 1, 1999 to December 2010. There are eight operational phases for the trial:

Phase	# of Months in Phase	Calendar Time	Trial Activities
I	10	10/1/99 to 7/30/00	Initial Protocol Development
II	2	8/1/00 to 9/30/00	Procedure Finalization /Training
III	3	10/1/00 to 12/31/00	Vanguard Startup and Screening
IV	24	1/1/01 to 12/31/02	Vanguard Recruitment/Follow-up/ Review/Protocol Revision
V	33	1/1/03 to 9/30/05	Main Recruitment and Follow-up
VI	41	10/1/05 to 2/28/09	Follow-up Only
VII	4	3/1/09 to 6/30/09	Participant Close-out
VIII	18	7/1/09 to 12/31/10	Analysis and Reporting/Non-treatment clinical event follow-up of participants by phone

As noted above, recruitment will occur in two non-contiguous periods: an initial period that began in January 2001 in the Vanguard Phase (Phase IV) of the trial (during which approximately 1200 participants were recruited), and then a subsequent period beginning in January 2003 (after review of the vanguard data) and ending in September 2005 (during which the remainder of the 10,000 participants will be recruited).

During Phase IV, the ACCORD investigators, the Data and Safety Monitoring Board, and the National Heart, Lung, and Blood Institute monitored the feasibility of the Vanguard protocol. The specific goals of the Vanguard, which were used to judge its success, are described in Section 7.5. After extensive review of the data, the ACCORD Protocol was revised to increase the likelihood of achieving all of the trial objectives.

December 12, 2008 Change to Protocol (Amendment 32): It was reported on June 12, 2008 in the *New England Journal of Medicine* (N Engl J Med 2008;358:2545-59) that the use of intensive glycemic therapy to target normal glycated hemoglobin levels during the trial increased mortality and did not significantly reduce major cardiovascular events. Because of the increase in mortality, the glycemia ACCORD trial was stopped on February 6, 2008. The blood pressure and lipid trials of this factorial study are continuing.

To determine whether differences seen during the trial in mortality and cardiovascular events persist or change over time, a post-trial, non-treatment, observation-only period is established during which participants who give consent will continue to be followed by phone by ACCORD clinic staff every six months from the anniversary of their close-out visit until December 31, 2010.

Chapter 2
Participant Selection and Follow-up

2.1   Eligibility Criteria

The objective of setting inclusion/exclusion criteria is to identify a trial population that will ensure adequate event rates for statistical power, provide maximum generalizability, and maximize safety. Inclusion/exclusion criteria were made as simple as possible.

In addition to fulfilling the overarching glycemia trial entry criteria, to be eligible for ACCORD a screenee also needs to fulfill the entry criteria for either the lipid and/or blood pressure components of the trial. To reduce the possibility of bias by having clinic staff decide whether a screenee should be in the lipid or blood pressure component, eligibility for both components needs to be assessed.

2.1.a Inclusion Criteria

1.   Type 2 diabetes mellitus defined according to the 1997 ADA criteria:
   - Fasting plasma glucose >126 mg/dl (>7.0 mmol/l), or
   - Symptoms of hyperglycemia with casual plasma glucose > 200 mg/dl (>11.1 mmol/l), or
   - 2 hour plasma glucose > 200 mg/dl (>11.1 mmol/l) after a 75 gram oral glucose load

2.   HbA1c (obtained within 3 months prior to anticipated date of randomization):
   - 7.5 to 11%
     a) if on insulin, $\leq$ 1 u/kg plus on 0 or 1 oral agent, or
     b) if not on insulin, on 0, 1, or 2 oral agents

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

     Oral agents include: a) insulin secretagogues (sulfonylurea, meglitinides), b) biguanides, c) insulin enhancers (thiazolidinediones)

   The upper limits for HbA1c were selected to increase the likelihood of reaching the study's HbA1c targets. The lower limit was selected to allow for further reduction should the participant be assigned to the intensive glycemic group.

3.   Known diabetes duration > 3 months

4.   Stable diabetes therapy for > 3 months (dose of any 1 antihyperglycemic drug has not changed by more than two-fold and new agents have not been added within the previous 3 months)

5. Age at Randomization:
    - 40 to 79 years (inclusive) for anyone with a history of clinical cardiovascular disease (defined below in Item #6A), or
    - 55 to 79 years (inclusive) for anyone without a history of clinical cardiovascular disease (defined below in Item #6A)

6. At high risk of CVD events, defined as:

    A. Presence of clinical cardiovascular disease.
        - previous myocardial infarction (MI)
        - previous stroke
        - History of coronary revascularization (e.g., coronary artery bypass graft surgery, stent placement, percutaneous transluminal coronary angioplasty, or laser atherectomy)
        - History of carotid or peripheral revascularization (e.g., carotid endarterectomy, lower extremity atherosclerotic disease atherectomy, repair of abdominal aorta aneurysm, femoral or popliteal bypass)
        - angina with ischemic changes (resting ECG), ECG changes on a graded exercise test (GXT), or positive cardiac imaging study

    or

    B. If no clinical cardiovascular disease, evidence in the last 2 years suggesting a high likelihood of cardiovascular disease. Specifically, the presence of one of the following:
        - Microalbuminuria
        - Ankle brachial index < 0.9 (by simple palpation)
        - LVH by ECG or ECHO
        - $\geq$ 50% stenosis of a coronary, carotid, or lower extremity artery

    or

    C. The presence of at least 2 of the following factors that increase CVD risk:
        - On lipid lowering medication or untreated LDL-C >130 mg/dl (3.38 mmol/l)
        - Low HDL-C (< 40 mg/dl (1.04 mmol/l) for men and < 50 mg/dl (1.29 mmol/l) for women)
        - On BP lowering medication or untreated SBP $\geq$140 mm Hg or DBP $\geq$ 95 mm Hg.
        - Current cigarette smoking
        - Body mass index > 32 kg/m^2

    Note: Category A represents secondary prevention participants. Categories B and C together represent primary prevention participants.

2.1.b Exclusion Criteria

Exclusion criteria were selected to enhance safety and adherence.

1. History of hypoglycemic coma/seizure within last 12 months

2. Hypoglycemia requiring 3rd party assistance in last 3 months with concomitant glucose < 60 mg/dl (3.3 mmol/l)

3. History consistent with type 1 diabetes

4. Unwilling to do frequent capillary blood glucose self-monitoring or unwilling to inject insulin several times a day

5. BMI $\geq$ 45 kg/m^2

6. Serum Creatinine > 1.5 mg/dl (132.6 umol/l) obtained within the previous 2 months

7. Transaminase >2 times upper limit of normal or active liver disease

8. Any ongoing medical therapy with known adverse interactions with the glycemic interventions (e.g., corticosteroids, protease inhibitors)

9. Cardiovascular event or procedure (as defined for study entry) or hospitalization for unstable angina within last 3 months

10. Current symptomatic heart failure, history of NYHA Class III or IV congestive heart failure at any time, or ejection fraction (by any method) < 25%

11. A medical condition likely to limit survival to less than 3 years or a malignancy other than non-melanoma skin cancer within the last 2 years

12. Any factors likely to limit adherence to interventions. For example,
    - dementia
    - alcohol or substance abuse
    - plans to move in the next 2 years.
    - history of unreliability in medication taking or appointment keeping
    - significant concerns about participation in the study from spouse, significant other, or family members
    - lack of support from primary health care provider

13. Failure to obtain informed consent from participant

14. Currently participating in another clinical trial. Note: Patient must wait until the completion of his/her activities or the completion of the other trial before being screened for ACCORD

15. Living in the same household as an already randomized ACCORD participant.

16. Any organ transplant

17. Weight loss > 10% in last 6 months

18. Pregnancy, currently trying to become pregnant, or of child-bearing potential and not practicing birth control

19. Participants with recurrent requirements for phlebotomy or transfusion of red blood cells.

2.1.c Additional Eligibility Criteria for Participants in the Lipid Component of ACCORD

Participants eligible for the glycemic component of the trial will also be eligible for the lipid component if the following criteria are met. Screening lipids may either be measured at a local laboratory or obtained from medical records. If obtained from medical records, use the most recent values recorded within the previous 12 months. If there are no lipid values recorded in the medical records within the previous 12 months, a blood test must be performed by the local laboratory.

- 60 mg/dl $\leq$ LDL-C $\leq$ 180 mg/dl (1.55 to 4.65 mmol/l) if not on a lipid-lowering agent during screening, or, if on a lipid-lowering agent, the LDL-C needs to be between the drug/dose-specific cut points <u>inclusive</u> found in Table 2.1.

   and

- HDL-C less than 55 mg/dl (1.42 mmol/l) for women or Blacks/African-Americans, or HDL-C less than 50 mg/dl (1.29 mmol/l) for all other gender-race groups

   and

- Triglycerides <750 mg/dl (8.47 mmol/l) on no therapy or < 400 mg/dl (4.52 mmol/l) on treatment with lipid lowering drugs

The rationale for the lower LDL-C limit is to exclude people with already low LDL-C levels because they would be exposed to a statin, which would likely reduce their LDL-C levels to very low, possibly harmful levels. The rationale for the upper LDL-C limit is that patients with higher LDL-C often would require a higher dose of a statin than ACCORD would provide, which would place them at higher risk for adverse events if randomized to a fibrate. The rationale for the HDL-C limit is that increasing HDL-C may have little effect among participants in whom HDL-C is already high. The triglyceride limits were selected for participant safety.

The additional exclusion criteria for the lipid intervention are:
- known hypersensitivity to statins or fibrates
- requirements for use of erythromycin, clarithromycin, cyclosporine, systemic azole antifungals, or nefazodone or trazodone
- refusal to stop current lipid-lowering drugs .
- history of pancreatitis
- untreated or inadequately treated thyroid disease
- women who are breast feeding
- documented previous occurrence of myositis/myopathy
- pre-existing gallbladder disease (eg., history of gallstones)

The recruitment goal for the lipid 2 X 2 trial is 5,800 participants.

Table 2.1: LDL-C Eligibility Ranges for Screenees on a Lipid-Lowering Agent (By Agent and Dose) (08/03/04 Revision)

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

2.1.d Additional Eligibility Criteria for Participants in the Blood Pressure Component of ACCORD

Participants eligible for the glycemic component of the trial will also be eligible for the blood pressure component:
- If the systolic blood pressure is between 130 and 160 mm Hg, inclusive, and the patient is on 0, 1, 2, or 3 antihypertensive medications, or
- If the systolic blood pressure is between 161 to 170 mm Hg, inclusive, and the patient is on 0, 1, or 2 antihypertensive medications, or

- If the systolic blood pressure is between 171 to 180 mm Hg, inclusive, and the patient is on 0 or 1 antihypertensive medication.

and

- If:

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

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

The recruitment goal for the blood pressure 2 X 2 trial is 4,200 participants.

2.2   Recruitment: Informed Consent, Screening, Baseline

The ACCORD recruitment goal is a minimum sample size of 10,000 participants: 50% females, 33% racial and ethnic minorities, and 50% primary prevention (no history of clinical CVD as defined in 2.1.a.6). Specific community resources will be used to target high risk and minority/under-served populations to ensure adequate representation of these groups in ACCORD. Recruitment strategies that worked well in other trials related to diabetes will be used. Centralized training for CCN and Clinical Site staffs regarding recruitment issues will be provided before recruitment begins. Several recruitment strategies were used successfully during the Vanguard Phase, including chart review and review of patients within investigator practices. During the main trial, additional strategies will be employed, including advertising.

2.2.a   Informed Consent

To participate in ACCORD, participants must provide written, informed consent using procedures reviewed and approved by each Clinical Site's local Institutional Review Board. Even though consent to participate in ACCORD must be obtained for all stages of the study, the process and timing of consent may vary by clinic. Descriptions of each Clinical Site's consent procedures are included as part of the Manual of Procedures, and copies of each Clinical Site's consent documents are kept at the Coordinating Center. The consent forms must include all procedures done as part of screening, a possible run-in, and follow-up. The elements of consent are presented in Section 4.5 and a model informed consent document is in Appendix I.

Of special concern regarding informed consent is the collection of blood samples for genetic analysis. The consent forms will clearly indicate that a sample may be drawn for this purpose, but that the participant has the right to refuse this procedure. The portion of the informed consent document describing the genetics component of ACCORD uses the multi-level approach recommended by the NHLBI Panel on "Opportunity and Obstacles to Genetics Research in NHLBI Clinical Studies." Also, the confidentiality of the data will be maintained.

2.2.b   Screening and Possible Run-In (Self-Monitoring of Blood Glucose)

Potential participants can be recruited for ACCORD through either of two sequences of screening or pre-randomization visits. One sequence would be used for those patients who are currently in the practices of the Clinical Sites within the ACCORD network. A second sequence would be used for those patients who come from outside the ACCORD Clinical Sites and are, therefore, less well known to the ACCORD clinical center staff.

Prior to randomization, potential participants will be asked to provide evidence that they can routinely monitor their capillary blood sugars. This evidence may be from a diary, self-monitoring blood glucose (SMBG) device that they bring to the clinic, or, if such retrospective data cannot be presented, then the screenee must prospectively go through a 2 to 4 week pre-randomization run-in period. If the data are obtained from a diary or from a SMBG device, then at least 2 weeks of data must be available and the screening visit cannot occur on the same day as the randomization visit.

2.2.b.1   Existing Populations in the Clinical Site Practices-Medical record searches or reviews of existing databases can be done initially by setting up the searches using the characteristics that match the inclusion/exclusion criteria. Additional "hand searches" may be necessary using the remaining inclusion/exclusion criteria not already part of the existing database but part of the patient's existing clinical record. It is likely that all or most all of the inclusion/exclusion criteria will be available in most medical records.

2.2.b.2   Individuals Recruited Outside Existing Clinical Site Practices-Individuals identified by any media strategy or who are otherwise identified outside of the practice of the ACCORD clinical center will have to be appropriately screened. While general screening of the population for abnormal fasting glucose levels is not permitted, referrals from health fairs or community screenings conducted by others may be a useful source of participants.

2.2.c   Screening Visits/Baseline Visit

The following are key elements of the screening and baseline visits.

A. Center notified of individual's interest in study (for individuals outside practice)
      1. Response to media
      2. Phone number of individual available
B. Phone Contact
      1. Age determined (if unknown)
      2. Administer phone screen to determine initial potential eligibility
C. Screening Visit 1
      1. Screening consent, if required by the sites's IRB
      2. Obtain HIPAA authorization
      3. Patient to sign a release of information to collect documentation
      4. Begin collection of baseline information, including additional eligibility
      information.

D. Screening Visit 2
1. Perform required labs
2. Continue collection of baseline/eligibility information
3. Possible run-in period begins
E. Baseline visit (Randomization Visit)
1. Criteria for self-monitoring of blood glucose is satisfied
2. Confirmation that all inclusion/exclusion criteria satisfied
3. Perform physical examination
4. Randomization Consent
5. Patient randomized
6. Trial intervention begins

2.3 Schedule of Follow-up Visits

As described in Tables 2.2A through 2.2F, post-randomization follow-up visit schedules differ by treatment group assignment. For participants in the intensive glycemia group (regardless of BP/Lipid trial assignment) and for participants in the standard glycemia group + intensive blood pressure group, post-randomization visits will occur at Months 1, 2, 3, 4, and every 2 months thereafter. For participants in the standard glycemia group + either the standard BP or lipid trial, post-randomization visits will occur at Months 1, 4, and every 4 months thereafter. Additional visits can be scheduled as needed to monitor and assure appropriate implementation of the study interventions. For the purpose of event ascertainment, all participants in all treatment groups will be queried regarding the occurrence of a possible event on the same schedule, specifically every 4 months.

2.4 Procedures by Visit

Clinical center staff will be treating and following six different types of participants in ACCORD. These are participants who are randomized to the:
- Intensive Glycemia and Intensive Blood Pressure Groups
- Intensive Glycemia and Standard Blood Pressure Groups
- Intensive Glycemia Group and in the Lipid Trial
- Standard Glycemia and Intensive Blood Pressure Groups
- Standard Glycemia and Standard Blood Pressure Groups
- Standard Glycemia Group and in the Lipid Trial.

Note that for the lipid trial, participants in the masked fibrate and placebo groups will be treated identically by clinic personnel.

Scheduled examination components are shown by treatment group assignment and by visit in Tables 2.2A through 2.2F. Because during follow-up the components of the visits differ according to the portion of the trial the participant is in, these tables are specific to the glycemia/blood pressure/lipid trial treatment group assignment.

Assessments performed at the various visits include questionnaires, physical examinations, other clinical studies, laboratory tests, and performance of study-related procedures as described below. Baseline characteristics to define the patient population include sociodemographics, anthropometrics, blood pressure, pulse, current and past medical history, basic physical examination, concomitant medications, laboratory, and quality of life measurements.

2.4.a Questionnaires

2.4.a.1 Sociodemographics

Information is collected during screening and baseline regarding age, ethnicity, gender, level of education, persons living with participants and United States ZIP code/Canadian postal code. These data will be used to identify eligible participants and to characterize the final study population. Social Security Number/Medicare Number/Canadian Social Insurance Number/Provincial Health Insurance Number will be collected for tracking purposes.

2.4.a.2 Medical History

Medical history data are collected at baseline in the form of a detailed initial medical history and collected at specified follow-up visits in the form of an abbreviated interval history. Important aspects of the medical history include eligibility criteria, allergies, cardiovascular disease, smoking status, and diabetes. The presence of CVD prior to entry into the study serves as an eligibility and stratification factor. Data regarding the duration of diabetes and the presence of complications of diabetes are important for descriptive purposes, subgroup analyses, and prognostic analyses.

2.4.a.3 Concomitant Medications

Information regarding the participants' concomitant medication therapy is collected and documented at baseline and then reviewed and revised at annual follow-up visits. Appropriate sources for obtaining this information include participant (significant other) report, current pharmacy action profiles, and verification of medications documented in the medical record. Although data are collected on all standing therapies, emphasis is placed on concurrent antihypertensive, glycemic and lipid-lowering therapy as well as background risk reduction (eg., aspirin) therapy.

2.4.a.4 Diet, Physical Activity, Health-Related Quality of Life Substudy, Cost Effectiveness Substudy, Eye Substudy, Memory in Diabetes (MIND) Substudy

Diet and physical activity data are collected from a random sample of 2000 participants at Baseline, Month 12, Month 36, and Month 48. This random sample will also participate in the Health-Related Quality of Life Substudy (see Section 6.2), which is itself a random sample nested within the 4288 participants participating in the Cost

Effectiveness Substudy (see Section 6.3). As with the diet and physical activity data, HRQL data will be collected at Baseline, Month 12, Month 36, and Month 48. Cost data will be collected at baseline and every four months for the duration of the trial.

For the ACCORD Eye Substudy, conducted in a subset of 4065 participants, a full ophthalmologic examination and fundus photography will be performed at Baseline and at Month 48.

For the Memory in Diabetes (MIND) Substudy, conducted in a subset of 2,800 participants, a battery of cognitive neuropsychological tests will be conducted at Month 1, Month 20, and Month 40. (The Month 1 Visit will serve as the Baseline Visit.) In addition to the neuropsychological tests, a subsample of 640 MIND participants will have a Baseline and Month 40 MRI examination.

2.4.b Physical Examination Measures

2.4.b.1 Anthropometric Measurements

Body fat is a significant predictor for the onset of diabetes, as well as for subclinical and clinically manifested cardiovascular disease. Excessive body and abdominal obesity also hinders diabetes control and increases the likelihood of the development of cardiovascular disease in this patient population. Successful management of type 2 diabetes includes exercise and dietary modification with the goal of reducing total body fat, particularly abdominal fat. It is the intent of this study to gather data that will elucidate the impact of body fat and body composition on the course of cardiovascular disease among patients with diabetes without extreme burden to study participants and clinical investigators.

Anthropometric measures gathered for ACCORD include (1) standing height, (2) weight, and (3) waist circumference. Body mass index (BMI, calculated as kg/m^2) is commonly used in clinical trials and population-based epidemiologic studies as an estimate of overweight/obesity. Guidelines are currently available for the assessment of overweight and obesity based on BMI values. BMI correlates well with adipose tissue composition measured by more burdensome procedures such as cardiothoracic scan, underwater weighing, and bioelectrical impedance. Similarly, abdominal obesity, as assessed by a measurement of waist circumference, is an easily measured indicator that has been shown to be predictive of both diabetes and cardiovascular disease risk.

2.4.b.2 Blood Pressure and Pulse

Using an automated device (the Omron 907), blood pressure (BP) and pulse are measured three times at each clinic visit. The seated BP and pulse readings for ACCORD are the averages of the first, second and third systolic and diastolic BP's and pulses.

2.4.b.3 Other Physical Examination Components

The physical examination includes the items noted above (anthropometric measurements, ascertainment blood pressure and heart rate) and a system-oriented approach for the remainder of the examination. Participants will undergo both full physical examinations and abbreviated aspects of the examination during the course of their participation in the trial. Elements of the examination to be completed will vary depending upon the time and type of visit (initial, interval, annual, final) and will comply with recommended standards of diabetes care.

The systems physical examination includes: general survey, skin, head, ears, eyes, nose, throat (including funduscopic) neck, chest, heart, abdomen, musculoskeletal/ extremities, pulse assessment, and neurological (including lower extremity).

Table 2.2A: Scheduled Examination Components by Visit: For Participants Randomized to the <u>Intensive Glycemia</u> + <u>Intensive Blood Pressure</u> Groups

Schedule in Months

Evaluations	Scrn[τ]	BL	0.5	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24	Q2	Q4	Q12	Q24	36	40	48	prn[1]	Exit
Clinic Visit	X	X		X	X	X	X	prn	X	prn	X	prn	X	prn	X	X	X	X	X	X	X								X	X
BP/Pulse	X	X		X	X	X	X		X		X		X		X	X	X	X	X	X	X									X
Weight	X	X		X†	X†	X†	X	X†	X	X†	X	X†	X	X†	X	X†	X	X†	X	X†	X									X
BP Mileposts[γ]							M				M				M		M		M		M					M				
HbA1c (POC)[Δ]		X		X	X	X	X	prn	X	prn	X	prn	X	prn	X	X	X	X	X	X	X									X
HbA1c		C					C				C				C		C		C		C		C							C
FPG		C					C				C				C						C			C						C
Potassium		C					C				C				C						C			C				C		C
Creatinine	L	C					C				C				C						C			C				C		C
Lipid Profile	L	C													C						C			C						C
ALT	L	C					C				C				C						C			C				C		C
CPK		C																												C
Urinalysis	L	C																			C						C	C		C
ECG	L	C																			C							C		C
Events		X					X				X				X	X		X	X	X										X
Diet,Phys Actv*		X													X											X		X		
HRQL*		X													X											X		X		
Costs*		X					X				X				X	X		X	X	X										
Eye Substudy		C[φ]																									C			
Visual Acuity		X																			X			X						X
MIND:Cognitive[ξ]				X																X								X		
MIND: MRI				C[λ]																								C[λλ]		
Serum Storage		C													C						C						C			C
EDTAPlasma Storage		C																			C									
Urine Storage		C																			C									
Phone f/u#			X					X		X		X		X	Intensive Glyc Group: Phone calls <u>must</u> be made between <u>all</u> regularly scheduled clinic visits															

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Notes for Table 2.2A:

X: This evaluation/procedure applies at this visit

τ: A second screening visit is required to document hypertension for potentially eligible screenees (see Figure 2.2):
        (a) not currently on antihypertensive therapy
        (b) but who had a SBP $\geq$ 130 mm Hg on the first clinic visit
        (c) and for whom there is no notation in the medical record of another SBP $\geq$ 130 mm Hg within 3 months prior to randomization.

1:   prn ('as needed') includes:
        (a) Monitoring K^+ and Creatinine after starting and/or significantly changing ACEI, ARB and thiazides
        (b) Patients initiated on thiazolidinediones will be monitored, as recommended by the manufacturer, with ALT levels every two months for the first 12 months after the initiation of this therapy, and annually thereafter.

γ: Milepost blood pressure visits (marked as **M**) are only for participants who are assigned to the intensive BP group. After 2 years of follow-up, these visits will occur annually.

Δ: Each participant in the Intensive Glycemic Group will have a point-of-care (POC) HbA1c measurement at each clinic visit.

*   These evaluations will be done in a subset of participants (4288 participants in the Cost Study and, within this subset, 2000 will complete HRQL, diet and physical activity assessments [i.e., all 2000 participants are in HRQL/diet/physical activity])

ϕ   For the Eye Substudy (in a subset of 4065 participants), the baseline eye exam/fundus photography can be performed up to 2 months post-randomization.

ξ   For the clinics participating in the MIND Cognitive Substudy (conducted in a subset of 2,800 participants), a battery of cognitive neuropsychological tests will be obtained at 1, 20 and 40 months post-randomization. (The 1 month visit will serve as the baseline visit.)

λ   In addition to the neuropsych tests, a subsample of 640 MIND participants will have a baseline MRI within 45 days <u>after</u> the baseline neuropsych test date.

λλ   Participants in the MRI portion of MIND will have a follow-up MRI +/- 45 days around the 40 month neuropsych test date.

**In addition to the phone contacts noted in the table, calls <u>must</u> also be made between <u>all</u> other regularly scheduled clinic visits**

†   Measurement documented in source notes only.

Scrn=Screening Visits; **BL**=Baseline Visit; **C**=Central reading center or lab; **POC**=Point of Care; **L**=Local lab; **BP**=blood pressure; **CPK**=Creatine phosphokinase; **FPG**=fasting plasma glucose

Table 2.2B: Scheduled Examination Components by Visit: For Participants Randomized to the <u>Intensive Glycemia</u> + <u>Standard Blood Pressure</u> Groups

Schedule in Months

Evaluations	Scrn[τ]	BL	0.5	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24	Q2	Q4	Q12	Q24	36	40	48	prn[1]	Exit
Clinic Visit	X	X		X	X	X	X	prn	X	prn	X	prn	X	prn	X	X	X	X	X	X	X	X							X	X
BP/Pulse	X	X		X			X				X				X		X		X		X		X							X
Weight	X	X		X[†]	X[†]	X[†]	X		X[†]		X		X[†]		X	X[†]	X	X[†]	X	X[†]	X	X[†]	X							X
BP Mileposts[γ]		(none)																												
HbA1c (POC)[Δ]		X		X	X	X	X	prn	X	prn	X	prn	X	prn	X	X	X	X	X	X	X	X								X
HbA1c		C					C				C				C	C	C		C		C		C							C
FPG		C					C				C				C						C			C						C
Potassium		C					C				C				C						C			C				C		C
Creatinine	L	C					C				C				C						C			C				C		C
Lipid Profile	L	C													C						C			C						C
ALT	L	C					C				C				C						C			C				C		C
CPK		C																												C
Urinalysis	L	C																			C						C	C		C
ECG	L	C																			C							C		C
Events		X					X				X				X		X		X		X		X							X
Diet,Phys Actv*		X													X											X	X			
HRQL*		X													X											X	X			
Costs*		X					X				X				X		X		X		X		X							
Eye Substudy		C[φ]																									C			
Visual Acuity		X																			X			X						X
MIND:Cognitive[ξ]				X															X								X			
MIND: MRI				C[λ]																						C[λλ]				
Serum Storage		C													C						C						C			C
EDTAPlasma Storage		C																			C									
Urine Storage		C																			C									
Phone f/u#			X					X		X		X		X	X	Intensive Glyc Group: Phone calls <u>must</u> be made between <u>all</u> regularly scheduled clinic visits														

Notes for Table 2.2B:

X: This evaluation/procedure applies at this visit

τ: A second screening visit is required to document hypertension for potentially eligible screenees (see Figure 2.2):
   (a) not currently on antihypertensive therapy
   (b) but who had a SBP $\geq$ 130 mm Hg on the first clinic visit
   (c) and for whom there is no notation in the medical record of another SBP $\geq$ 130 mm Hg within 3 months prior to randomization.

1:   prn ('as needed') includes:
   (a) Monitoring K^+ and Creatinine after starting and/or significantly changing ACEI, ARB and thiazides
   (b) Patients initiated on thiazolidinediones will be monitored, as recommended by the manufacturer, with ALT levels every two months for the first 12 months after the initiation of this therapy, and annually thereafter.

γ: Milepost blood pressure visits are only for participants in the Intensive BP group.

Δ: Each participant in the Intensive Glycemic Group will have a point-of-care (POC) HbA1c measurement at each clinic visit.

*   These evaluations will be done in a subset of participants (4288 participants in the Cost Study and, within this subset, 2000 will complete HRQL, diet and physical activity assessments [i.e., all 2000 participants are in HRQL/diet/physical activity])

φ   For the Eye Substudy (in a subset of 4065 participants), the baseline eye exam/fundus photography can be performed up to 2 months post-randomization.

ξ   For the clinics participating in the MIND Cognitive Substudy (conducted in a subset of 2,800 participants), a battery of cognitive neuropsychological tests will be obtained at 1, 20 and 40 months post-randomization. (The 1 month visit will serve as the baseline visit.)

λ   In addition to the neuropsych tests, a subsample of 640 MIND participants will have a baseline MRI within 45 days <u>after</u> the baseline neuropsych test date.

λλ   Participants in the MRI portion of MIND will have a follow-up MRI +/- 45 days around the 40 month neuropsych test date.

**In addition to the phone contacts noted in the table, calls <u>must</u> also be made between <u>all</u> other regularly scheduled clinic visits.**

†   Weight measurement documented in source notes only.

Scrn=Screening Visits; **BL**=Baseline Visit; **C**=Central reading center or lab; **POC**=Point of Care; **L**=Local lab; **BP**=blood pressure; **CPK**=Creatine phosphokinase; **FPG**=fasting plasma glucose

Table 2.2C: Scheduled Examination Components by Visit: For Participants Randomized to the <u>Intensive Glycemia</u> Group + <u>Lipid Trial</u>

Schedule in Months

Evaluations	Scrn[τ]	BL	0.5	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24	Q2	Q4	Q12	Q24	36	40	48	prn[1]	Exit
Clinic Visit	X	X		X	X	X	X	prn	X	prn	X	prn	X	prn	X	X	X	X	X	X	X	X								X	X
BP/Pulse	X	X					X				X				X		X		X		X		X							X
Weight	X	X		X†	X†	X†	X		X†		X		X†		X	X†	X	X†	X	X†	X	X†	X							X
BP Mileposts[γ]			(none)																											
HbA1c (POC)[Δ]		X		X	X	X	X	prn	X	prn	X	prn	X	prn	X	X	X	X	X	X	X	X								X
HbA1c		C					C				C				C		C		C		C		C							C
FPG		C					C				C				C						C			C						C
Potassium		C					C				C				C						C								C	C
Creatinine	L	C					C				C				C		C		C		C	C							C	C
Lipid Profile	L	C					C				C				C						C			C					C[σ]	C
ALT	L	C		C			C				C				C						C			C					C	C
CPK		C		C			C				C				C						C			C					C	C
Urinalysis	L	C																			C							C	C	C
ECG	L	C																			C							C		C
Events		X					X				X				X		X		X		X									X
Diet,Phys Actv*		X													X											X	X			
HRQL*		X													X											X	X			
Costs*		X					X				X				X		X		X		X									
Eye Substudy		C[φ]																										C		
Visual Acuity		X																			X			X						X
MIND:Cognitive[ξ]				X															X								X			
MIND: MRI				C[λ]																									C[λλ]	
Serum Storage		C													C						C							C		C
EDTAPlasma Storage		C																			C									
Urine Storage		C																			C									
Phone f/u#			X					X		X		X		X	Intensive Glyc Group: Phone calls <u>must</u> be made between <u>all</u> regularly scheduled clinic visits															

Notes for Table 2.2C:

X: This evaluation/procedure applies at this visit

1:    prn ('as needed') includes:
- (a) Monitoring K^+ and Creatinine after starting and/or significantly changing ACEI, ARB and thiazides
- (b) Patients initiated on thiazolidinediones will be monitored, as recommended by the manufacturer, with ALT levels every two months for the first 12 months after the initiation of this therapy, and annually thereafter.

γ: Milepost blood pressure visits are only for participants in the Intensive BP group.

Δ: Each participant in the Intensive Glycemic Group will have a point-of-care (POC) HbA1c measurement at each clinic visit.

*   These evaluations will be done in a subset of participants (4288 participants in the Cost Study and, within this subset, 2000 will complete HRQL, diet and physical activity assessments [i.e., all 2000 participants are in HRQL/diet/physical activity])

φ   For the Eye Substudy (in a subset of 4065 participants), the baseline eye exam/fundus photography can be performed up to 2 months post-randomization.

ξ   For the clinics participating in the MIND Cognitive Substudy (conducted in a subset of 2,800 participants), a battery of cognitive neuropsychological tests will be obtained at 1, 20 and 40 months post-randomization. (The 1 month visit will serve as the baseline visit.)

λ   In addition to the neuropsych tests, a subsample of 640 MIND participants will have a baseline MRI within 45 days <u>after</u> the baseline neuropsych test date.

λλ   Participants in the MRI portion of MIND will have a follow-up MRI +/- 45 days around the 40 month neuropsych test date.

**In addition to the phone contacts noted in the table, calls <u>must</u> also be made between <u>all</u> other regularly scheduled clinic visits.**

†   Measurement documented in source notes only.

σ   An additional lipid profile would be required at the next 4 month visit (after dietary/adherence counseling) if notified by the Coordinating Center that the LDL-C has exceeded 130 mg/dl (3.36 mmol/L) and/or that the triglyceride level has exceeded 750 mg/dl (8.47 mmol/l) (see Section 3.3.c for details)

Scrn=Screening Visits; **BL**=Baseline Visit; **C**=Central reading center or lab; **POC**=Point of Care; **L**=Local lab; **BP**=blood pressure; **CPK**=Creatine phosphokinase; **FPG**=fasting plasma glucose

Table 2.2D: Scheduled Examination Components by Visit : For Participants Randomized to the <u>Standard Glycemia</u> + <u>Intensive Blood Pressure</u> Groups

Evaluations	Scrn[τ]	BL	0.5	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24	Q2	Q4	Q12	Q24	36	40	48	prn[1]	Exit
Clinic Visit	X	X		X	X	X	X	prn	X		X		X		X	X	X	X	X	X	X	X							X	X
BP/Pulse	X	X		X	X	X	X		X		X		X		X	X	X	X	X	X	X	X								X
Weight	X	X		X[†]	X[†]	X[†]	X		X[†]		X		X[†]		X	X[†]	X	X[†]	X	X[†]	X	X[†]	X							X
BP Mileposts[γ]							M				M				M		M		M		M			M						
HbA1c (POC)[Δ]			(as needed)																											
HbA1c		C					C				C				C	C	C				C		C							C
FPG		C					C				C				C						C			C						C
Potassium		C					C				C				C						C			C				C		C
Creatinine	L	C					C				C				C						C			C				C		C
Lipid Profile	L	C													C						C			C						C
ALT	L	C					C				C				C						C			C				C		C
CPK		C																												C
Urinalysis	L	C																			C						C	C		C
ECG	L	C																			C							C		C
Events		X					X				X				X		X		X		X	X								X
Diet,Phys Actv*		X													X											X	X			
HRQL*		X													X											X	X			
Costs*		X					X				X				X		X		X		X	X								
Eye Substudy		C[φ]																									C			
Visual Acuity		X																			X			X						X
MIND:Cognitive[ξ]				X															X									X		
MIND: MRI				C[λ]																							C[λλ]			
Serum Storage		C																												
Serum Storage		C									X										C						C			C
EDTAPlasma Storage		C																			C									
Urine Storage		C																			C									
Phone f/u			(as needed)																											

Notes for Table 2.2D:

X: This evaluation/procedure applies at this visit

τ: A second screening visit is required to document hypertension for potentially eligible screenees (see Figure 2.2):
   (a) not currently on antihypertensive therapy
   (b) but who had a SBP $\geq$ 130 mm Hg on the first clinic visit
   (c) and for whom there is no notation in the medical record of another SBP $\geq$ 130 mm Hg within 3 months prior to randomization.

1:     prn ('as needed') includes:
   (a) Monitoring K^+ and Creatinine after starting and/or significantly changing ACEI, ARB and thiazides
   (b) Patients initiated on thiazolidinediones will be monitored, as recommended by the manufacturer, with ALT levels every two months for the first 12 months after the initiation of this therapy, and annually thereafter.

γ: Milepost blood pressure visits (marked as **M**) are only for participants who are assigned to the intensive BP group. After 2 years of follow-up, these visits will occur annually.

Δ: Only participants in the Intensive Glycemic Group need to have a point-of-care (POC) HbA1c measurement at each clinic visit.

*   These evaluations will be done in a subset of participants (4288 participants in the Cost Study and, within this subset, 2000 will complete HRQL, diet and physical activity assessments [i.e., all 2000 participants are in HRQL/diet/physical activity])

ϕ   For the Eye Substudy (in a subset of 4065 participants), the baseline eye exam/fundus photography can be performed up to 2 months post-randomization.

ξ   For the clinics participating in the MIND Cognitive Substudy (conducted in a subset of 2,800 participants), a battery of cognitive neuropsychological tests will be obtained at 1, 20 and 40 months post-randomization. (The 1 month visit will serve as the baseline visit.)

λ   In addition to the neuropsych tests, a subsample of 640 MIND participants will have a baseline MRI within 45 days <u>after</u> the baseline neuropsych test date.

λλ   Participants in the MRI portion of MIND will have a follow-up MRI +/- 45 days around the 40 month neuropsych test date.

†   Measurement documented in source notes only.

Scrn=Screening Visits; **BL**=Baseline Visit; **C**=Central reading center or lab; **POC**=Point of Care; **L**=Local lab; **BP**=blood pressure; **CPK**=Creatine phosphokinase; **FPG**=fasting plasma glucose

Table 2.2E: Scheduled Examination Components by Visit: For Participants Randomized to the <u>Standard Glycemia</u> + <u>Standard Blood Pressure</u> Groups

Evaluations	Scrn[τ]	BL	0.5	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24	Q2	Q4	Q12	Q24	36	40	48	prn[1]	Exit
Clinic Visit	X	X		X			X				X				X		X		X		X								X	X
BP/Pulse	X	X		X			X				X				X		X		X		X									X
Weight	X	X		X[†]			X				X				X		X		X		X									X
BP Mileposts[γ]			(none)																											
HbA1c (POC)[Δ]			(as needed)																											
HbA1c		C					C				C				C		C		C		C		C							C
FPG		C					C				C				C						C		C							C
Potassium		C					C				C				C						C		C					C		C
Creatinine	L	C					C				C				C						C		C					C		C
Lipid Profile	L	C													C						C		C							C
ALT	L	C					C				C				C						C		C					C		C
CPK		C																												C
Urinalysis	L	C																			C						C	C		C
ECG	L	C																			C						C			C
Events		X					X				X				X		X		X		X	X								X
Diet,Phys Actv*		X													X											X		X		
HRQL*		X													X											X		X		
Costs*		X					X				X				X		X		X		X	X								
Eye Substudy		C[φ]																									C			
Visual Acuity		X																			X			X						X
MIND:Cognitive[ξ]				X															X								X			
MIND: MRI				C[λ]																							C[λλ]			
Serum Storage		C													C						C						C			C
EDTA Plasma Storage		C																			C									
Urine Storage		C																			C									
Phone f/u			(as needed)																											

Notes for Table 2.2E:

X: This evaluation/procedure applies at this visit

τ: A second screening visit is required to document hypertension for potentially eligible screenees (see Figure 2.2):
   (a) not currently on antihypertensive therapy
   (b) but who had a SBP $\geq$ 130 mm Hg on the first clinic visit
   (c) and for whom there is no notation in the medical record of another SBP $\geq$ 130 mm Hg within 3 months prior to randomization.

1:    prn ('as needed') includes:
   (a) Monitoring K^+ and Creatinine after starting and/or significantly changing ACEI, ARB and thiazides
   (b) Patients initiated on thiazolidinediones will be monitored, as recommended by the manufacturer, with ALT levels every two months for the first 12 months after the initiation of this therapy, and annually thereafter.

γ: Milepost blood pressure visits are only for participants in the Intensive BP group.

Δ: Only participants in the Intensive Glycemic Group need to have a point-of-care (POC) HbA1c measurement at each clinic visit.

*   These evaluations will be done in a subset of participants (4288 participants in the Cost Study and, within this subset, 2000 will complete HRQL, diet and physical activity assessments [i.e., all 2000 participants are in HRQL/diet/physical activity])

ϕ   For the Eye Substudy (in a subset of 4065 participants), the baseline eye exam/fundus photography can be performed up to 2 months post-randomization.

ξ   For the clinics participating in the MIND Cognitive Substudy (conducted in a subset of 2,800 participants), a battery of cognitive neuropsychological tests will be obtained at 1, 20 and 40 months post-randomization. (The 1 month visit will serve as the baseline visit.)

λ   In addition to the neuropsych tests, a subsample of 640 MIND participants will have a baseline MRI within 45 days <u>after</u> the baseline neuropsych test date.

λλ   Participants in the MRI portion of MIND will have a follow-up MRI +/- 45 days around the 40 month neuropsych test date.

†   Measurement documented in source notes only.

Scrn=Screening Visits; **BL**=Baseline Visit; **C**=Central reading center or lab; **POC**=Point of Care; **L**=Local lab; **BP**=blood pressure; **CPK**=Creatine phosphokinase; **FPG**=fasting plasma glucose

Table 2.2F: Scheduled Examination Components by Visit: For Participants Randomized to the <u>Standard Glycemia</u> Group + <u>Lipid Trial</u>

Evaluations	Scrn†	BL	0.5	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24	Q2	Q4	Q12	Q24	36	40	48	prn[1]	Exit
Clinic Visit	X	X		X			X				X				X		X		X		X		X						X	X
BP/Pulse	X	X					X				X				X		X		X		X		X							X
Weight	X	X		X†			X				X				X		X		X		X		X							X
BP Mileposts^γ		(none)																												
HbA1c (POC)^Δ		(as needed)																												
HbA1c		C					C				C				C	C	C		C		C		C							C
FPG		C					C				C				C						C			C						C
Potassium		C					C				C				C													C	C	C
Creatinine	L	C					C				C				C	C	C		C		C		C					C	C	C
Lipid Profile	L	C					C				C				C						C			C					C^σ	C
ALT	L	C		C			C				C				C						C			C				C	C	C
CPK		C		C			C				C				C						C			C				C	C	C
Urinalysis	L	C																			C						40=C	C	C	C
ECG	L	C																			C						C			C
Events		X					X				X				X		X		X		X		X							X
Diet,Phys Actv*		X													X										X		X			
HRQL*		X													X										X		X			
Costs*		X					X				X				X		X		X		X		X							
Eye Substudy		C^φ																									C			
Visual Acuity		X																			X				X					X
MIND:Cognitive^ξ				X															X								X			
MIND: MRI				C^λ																							C^λλ			
Serum Storage		C													C						C						C			C
EDTAPlasma Storage		C																			C									
Urine Storage		C																			C									
Phone f/u		(as needed)																												

Notes for Table 2.2F:

X: This evaluation/procedure applies at this visit

1: prn ('as needed') includes:
- (a) Monitoring K^+ and Creatinine after starting and/or significantly changing ACEI, ARB and thiazides
- (b) Patients initiated on thiazolidinediones will be monitored, as recommended by the manufacturer, with ALT levels every two months for the first 12 months after the initiation of this therapy, and annually thereafter.

γ: Milepost blood pressure visits are only for participants in the Intensive BP group.

Δ: Only participants in the Intensive Glycemic Group need to have a point-of-care (POC) HbA1c measurement at each clinic visit.

∗ These evaluations will be done in a subset of participants (4288 participants in the Cost Study and, within this subset, 2000 will complete HRQL, diet and physical activity assessments [i.e., all 2000 participants are in HRQL/diet/physical activity])

ϕ For the Eye Substudy (in a subset of 4065 participants), the baseline eye exam/fundus photography can be performed up to 2 months post-randomization.

ξ For the clinics participating in the MIND Cognitive Substudy (conducted in a subset of 2,800 participants), a battery of cognitive neuropsychological tests will be obtained at 1, 20 and 40 months post-randomization. (The 1 month visit will serve as the baseline visit.)

λ In addition to the neuropsych tests, a subsample of 640 MIND participants will have a baseline MRI within 45 days <u>after</u> the baseline neuropsych test date.

λλ Participants in the MRI portion of MIND will have a follow-up MRI +/- 45 days around the 40 month neuropsych test date.

† Measurement documented in source notes only

σ An additional lipid profile would be required at the next 4 month visit (after dietary/adherence counseling) if notified by the Coordinating Center that the LDL-C has exceeded 130 mg/dl (3.36 mmol/L) and/or that the triglyceride level has exceeded 750 mg/dl (8.47 mmol/l) (see Section 3.3.c for details)

Scrn=Screening Visits; **BL**=Baseline Visit; **C**=Central reading center or lab; **POC**=Point of Care; **L**=Local lab; **BP**=blood pressure; **CPK**=Creatine phosphokinase; **FPG**=fasting plasma glucose

2.4.c Other Clinical Measures

2.4.c.1 Ankle Brachial Index

The ankle brachial index (ABI) is a hemodynamic measure that identifies and quantifies severe arterial obstructive disease in the lower extremities. The ABI is be a measure of subclinical cardiovascular disease, and persons with low ABI may at increased risk of clinical cardiovascular disease. In ACCORD, the ABI may be measured during the screening process to assist in the identification of a high risk subgroup of persons with diabetes but no clinical cardiovascular disease. Measurement of ABI is not required.

2.4.c.2 Electrocardiography

A 12-lead ECG is obtained at baseline in order to assess eligibility, and at the biennial follow-up visits (i.e., every 2 years) and close-out visit to ascertain the occurrence of silent (unrecognized) MI. The baseline ECG is used to identify previous (including silent) MIs, and to identify evidence of left ventricular hypertrophy.

2.4.d Laboratory Procedures

The schedule for laboratory procedures is shown in Tables 2.2A through 2.2F. Data regarding glycemic control (fasting plasma glucose and HbA1c) are important for determining eligibility status (see Section 2.1). During follow-up, HbA1c levels are used to enable the titration of hypoglycemic therapy to goals. Level of control also serves as an important variable in analyses exploring the mechanism of effect of hypoglycemic therapy on outcomes.

Blood and urine samples will be stored for future measurements of other less traditional risk factors. White blood cells will also be stored for future DNA extraction for genetic studies. It may prove possible to identify subgroups, defined by specific genes or genetic markers, which respond differentially to the various treatment strategies.

For safety purposes, potassium, ALT, CPK and creatinine measurements will be performed periodically (see Tables 2.2A through 2.2F).

2.4.e Drug Dispensing, Ordering, Storage, and Disposal

<u>Drug Dispensing</u>

The complexity created by the large number of medications and multiple treatment strategies requires substantial attention to the process of medication dispensing. All study medications dispensed to the participants will be labeled and identified with the study name, participant's name, medication name, strength and quantity, directions for use, and authorized prescriber's name. An emergency study-related phone number for study drug information will also appear on the label. All participants are instructed orally

on medication administration. Written instructions will also be provided. (See also Chapter 9: *Adherence*.)

Participants receive medication supplies at scheduled visits in sufficient quantity to last until the next scheduled visit. Medication dispensing may occur in the intervening periods between visits in case of emergency, loss, or schedule changes. A tracking mechanism is maintained for all dispensing actions. It is recommended that authorized dispensing personnel be limited in number to assure proper adherence with established accountability and dispensing procedures.

Drug Supply Ordering

Each Clinical Site, upon completion of procedures for study initiation, will receive a standard initial shipment (determined by the Coordinating Center and prepared by the Drug Distribution Center) of study drug supplies for each portion of the trial. It is expected that this initial shipment will suffice for a specified number of visits for a given number of randomized participants. Subsequent ordering for these and additional participants will then become the responsibility of each Clinical Site.

The Drug Distribution Center (DDC) in consultation with each Clinical Site sets inventory levels for each item. When an item reaches the reorder point, additional stock is automatically shipped from the DDC.

Drug Receipt and Storage

Drug shipments are sent to the Clinical Site in care of a designated staff member. The shipment is inspected for damage and its contents reconciled with the accompanying ACCORD Shipping Notice. The inventory is logged using the established tracking mechanism. Packing slips are filed in a secure location. Any damage or discrepancies in the shipment are to be reported promptly to the Drug Distribution Center for corrective action. Each Clinical Site is responsible for storing the study drug supplies in a locked, secure area with limited access. Manufacturer recommendations and local policies for drug storage are followed.

Drug Disposal

Clinical Sites are authorized to destroy ACCORD stock locally, complying with any local policies and procedures. Destruction will be documented on the ACCORD Local Destruction Form, with a copy sent to the DDC. All study drugs are labeled with an expiration date. Prior to expiration, the DDC will automatically ship replacement stock. Notification of these shipments will be made via the Coordinating Center. Once replacement stock is received the clinical site will destroy expired stock and document destruction as described above.

Chapter 3
Interventions

3.1 Introduction

ACCORD is designed to test the effects on CVD events of (1) intensive glycemia control compared with the current standard of care for glycemia, (2) raising HDL-cholesterol and lowering triglycerides with fibric acid therapy in the context of desirable LDL-C, and (3) intensive blood pressure control compared with standard blood pressure control.

This chapter presents descriptions of the three trial interventions. The chapter also presents the lifestyle/background recommendations provided for all ACCORD participants.

All interventions and lifestyle recommendations will begin at randomization.

3.2 Glycemic Control Intervention

3.2.a Glycemia Research Question

In middle-aged or older people with type 2 diabetes who are at high risk for having a cardiovascular disease (CVD) event, does a therapeutic strategy that targets a HbA1c of < 6.0% reduce the rate of CVD events more than a strategy that targets a HbA1c of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%) ?

3.2.b Research Design

Ten thousand (10,000) individuals with type 2 diabetes who meet the ACCORD eligibility criteria (see Section 2.1) will be randomized to one of two different glycemic targets: an HbA1c of < 6% or an HbA1c of 7.0% to 7.9%. Several approaches will be used to achieve and maintain near normal glycemia in the intensive group, including a minimum of bimonthly visits, telephone contacts, point-of-care HbA1c testing, targeting postprandial and preprandial glucose levels, aggressive early use and titration of several different oral agents, self-titration strategies, early use of insulin, and emphasis on combinations of agents.

3.2.c Glycemic Targets

In this trial, participants will be randomized to one of two treatment groups based on the targeted level of glycemic control. Both the intensive and standard therapy groups will utilize all currently available glucose-lowering therapies. The two treatment groups will have different glycemic targets and will have different thresholds of glycemic control at which therapeutic changes will be considered (Table 3.1).

Table 3.1: Glycemic Targets and Thresholds for Action for ACCORD			
		"Action Required" Threshold	
Group	**HbA1c Targets**	**HbA1c**	**> 50% of SMBG Results/4 days**
Standard Therapy	7 – 7.9%	> 7.9%* or $\leq$ 6.5%[#] (anytime) or 6.6%-6.9% [#] (twice consecutively)	fasting/ac < 90 mg/dl (5.0 mmol/l)[#]
Intensive Therapy	< 6.0%	$\geq$ 6.0%*	fasting/ac > 100 mg/dl (5.6 mmol/l) or 2 hrs pc > 140 mg/dl (7.8 mmol/l)*

pc: postcibal; ac: antecibal; SMBG: self monitoring of blood glucose; *antihyperglycemic therapy will be advanced if either the HbA1c or the SMBG "action required" criteria are met at any participant encounter
[#] therapy with drugs that increase the risk of hypoglycemia (e.g. insulin, sulfonylureas, meglitinides) will be reduced to avoid hypoglycemia if these criteria are met

To achieve these glycemic targets, participants will require self-management education and dietary and lifestyle interventions, as well as pharmacologic therapy. They will also require different drug choices and treatment intensities. For example, within 6 months of randomization, most intensive group participants will likely be on 3 or more injections of insulin per day in addition to 2 or 3 oral agents. Conversely, standard therapy participants are less likely to be on insulin, will be on $\leq$ 2 injections per day if insulin is used, and will be taking fewer oral agents. Moreover, the frequency with which self-management behavior is applied and participants are contacted will vary between the two levels of glycemic control.

3.2.d Self-Management Education

The goal of self-management education is to empower the participant to take responsibility for making the day-to-day changes in therapy required to maintain the targeted level of glycemic control. Proficiency in self-monitoring of blood glucose (SMBG) is a key component of self-management, as is knowledge of how to use SMBG data to alter therapy to achieve target glycemia. The importance of self-management and SMBG will be stressed. Indeed, SMBG will be expected of all ACCORD participants, and unwillingness or inability to do SMBG is an exclusion criterion (Chapter 2). Instructions and information on SMBG will be made available to all participants.

3.2.e Dietary and Lifestyle Interventions

All participants will be provided with the same dietary and lifestyle recommendations to optimize their glucose control. These will include: a) advice that blood glucose control may be more critical than weight control in reducing the risk of complications of diabetes; b) teaching dietary principles including carbohydrate counting; c) advice to engage in regular aerobic exercise (if medically fit to do so according to the physician who provides their medical care); d) teaching the technical and interpretative skills of blood glucose monitoring; and e) education of participants' families regarding the management of hypoglycemia.

Specific dietary and exercise recommendations will be tailored to each participant. Because group consultation is as effective as individual consultation for achieving glycemic improvement, sites may utilize either approach.

3.2.f Approach to Targeting and Achieving Different Levels of Glycemic Control

Targeting and achieving two different levels of glycemic control (Table 3.1) without causing clinically significant hypoglycemia is critically important to the success of the trial. Differences in visit frequency, the intensity and frequency of inter-visit contacts, the prompt response to HbA1c results, the frequency of SMBG, and different approaches to self-adjustment of glycemic therapy based on SMBG results and carbohydrate intake (if on insulin) will be used to achieve these two levels of glycemic control. Table 3.2 summarizes the different approaches that will be implemented in the standard and intensive groups to target the levels described in Table 3.1. As noted above, self management and SMBG are part of every participant's care in ACCORD. The standard and intensive groups will differ in the intensity of these activities as noted in Table 3.2.

Table 3.2 Achieving Glycemic Goals		
	Standard Group	**Intensive Group**
Visits (1st 4 months)	Monthly – Q 4 mo*	Monthly
Visits (> 4 months)	Q 2 – 4 mo*	Q 2 mo
Phone contact	Participant initiated (prn)	Research staff initiated (≥1 inter-visit)
Supplemental contact	Severe hypoglycemia/hyperglycemia HbA1c in action required range Frequent (>50%/4 days) premeal SMBG levels <90 mg/dl (5.0 mmol/l)	Severe hypoglycemia OR HbA1c in action required range OR SMBG in action required range (based on review of logbooks)
Point of Care HbA1c	Optional	Mandatory
Routine use of postprandial SMBG values to guide therapy	No	Yes
SMBG freq.[a] (not on insulin)	≤7/wk (daily at different times or >1/day on certain days)	≥ 2/day and 4/day if glucose is > target (2 ac/day and 2 pc/day)
SMBG freq.[a] (on insulin)	≤3/day	4-8/d (at least 2 ac/day and 2 pc/day; occasional 3 am test prn)
Self titration principles	Avoid severe hypoglycemia and premeal SMBG levels < 90 mg/dl (5.0 mmol/l)	Avoid severe hypoglycemia[b] AND Adjust Rx q4d AND Use CHO/patterns (if on insulin Rx)
Initial Minimum Rx	Diet/lifestyle	Diet/lifestyle AND 2 oral agents
Insulin Use (when needed)	Generally ≤ 2 injections/day	Flexible

* depending on the blood pressure group to which the person has been assigned; [a]less frequent if goals are achieved; [b] including avoiding SMBG levels < 70 mg/dl (3.9 mmol/l) on > 1/4 of the readings.

3.2.g Visit Frequency and Inter-Visit Contacts

Tables 2.2A through 2.2F describe the activities to be performed at each ACCORD follow-up visit. Participants will have different scheduled visit frequencies based on their allocated glycemic therapy group, their most recent HbA1c (if a central measurement and a point-of-care measurement differ, the higher of the two will be used), and other clinically important considerations, such as hypoglycemic episodes. The importance of contacting the research staff if any of the following occurs will be reinforced: any major illness or

hospitalization, any new diagnosis or drug prescription, any episode of hypoglycemia requiring assistance, or any other concerns regarding their therapy. Supplemental visits will be arranged whenever required.

Both the standard and intensive therapy groups will have a visit 1 month after randomization. Subsequently, individuals in the standard therapy group who are also allocated to intensive blood pressure therapy will have monthly visits until month 4, and then bimonthly visits for the rest of the trial; the remaining standard therapy participants will have a visit at 4 months and then every 4 months thereafter. Conversely, all intensive group participants will have monthly visits for the first 4 months and bimonthly visits thereafter. In addition, the research staff will contact all intensive group participants on at least one occasion between these visits (by telephone, FAX or email) to reinforce adherence, answer any questions, check for serious adverse events (including severe hypoglycemic episodes requiring third party assistance), review self-monitoring of blood glucose (SMBG) records, and determine whether a supplemental visit is required. Supplemental contacts will occur for any participant who has experienced an episode of severe hypoglycemia or whose last HbA1c is in the "action required" range, and for any intensive therapy participant whose SMBG values are above the targets noted in Table 3.1. Finally, all intensive therapy participants will be asked to mail, email, FAX or telephone biweekly logs of their capillary glucose values so that the research assistant can respond to them in a proactive fashion.

3.2.h   Response to HbA1c Results

Local immediate measurement of HbA1c (using a point-of-care testing system at each Clinical Site) will be used to guide prompt changes in therapy at each visit. Such an approach provides immediate feedback regarding glycemic control to both patients and clinical staff, and has been shown to lead to better glycemic control than more conventional laboratory-based approaches. Every participant in the Intensive Group will have a point-of-care HbA1c measurement at each clinic visit; this measurement may also be made in the standard group at the discretion of the research staff. The results will be recorded, along with the action taken in response to the result. Such action must be taken and documented whenever a participant's HbA1c is within the "action required" ranges specified in Table 3.1. The central lab and point-of-care HbA1c results will be compared regularly to ensure that they are similar. If there is a systematic difference between these results, the "action required" HbA1c thresholds in Table 3.1 (that were chosen based on "gold standard" HbA1c results measured in a central lab) may be translated into "point-of-care" HbA1c thresholds for action to ensure that these systematic differences are taken into account. For example, if the point-of-care HbA1c result consistently reads 0.2% lower than the central lab result, the "action required" threshold for a point-of-care measurement in the intensive group would be 5.8%.

HbA1c will also be measured centrally every 4 months. This measure will be used as the HbA1c value for reporting the study results, and provides a quality control check for the individual point-of-care samples. Sites will be notified by the Coordinating Center (CC) whenever a participant's centrally measured HbA1c is in the "action required" range; such notification will be linked to a note reminding the Clinical Site of the participant's treatment group assignment and the glycemic goals for that group. A response from the Clinical Site

regarding the changes in therapy made to achieve or maintain target levels will be required on case report forms after any such notification.

3.2.i   Frequency of Self-Monitoring of Blood Glucose (SMBG)

All participants will also be asked to do self-monitoring of blood glucose (SMBG) according to the frequency noted in Table 3.3. Less frequent testing may be acceptable if participants have safely achieved the glycemic targets specific for their group. The SMBG results will be used to ensure that individuals in both groups are not having frequent hypoglycemic episodes (defined in Table 3.2) and to guide adjustments in therapy to prevent hypoglycemia.

In addition, these levels will be used for the intensive therapy participants to intensify therapy. The next dose or drug will be introduced for individuals in whom >50% of the fasting SMBG values exceed 100 mg/dl (5.6 mmol/l) and in whom > 50% of the 2 hour postprandial values exceed 140 mg/dl (7.8 mmol/l). Thus, therapy in the intensive group will be intensified on the basis of either these SMBG values, or any HbA1c >6% (provided that intensification is not contraindicated in the judgment of the investigator because of frequent severe hypoglycemic episodes or other serious adverse effects)**.**

Table 3.3: Self-Monitoring Blood Glucose (SMBG) Targets and Frequency		
SMBG	Standard Group	Intensive Group
Frequency (diet/oral tx only)	≤7 tests/week (daily at varying times or more frequently on selected days)	≥ 2/day; QID if > target (2 ac/day and 2 pc/day)
Frequency (if on insulin)	≤3 tests/day	4-8 tests/day (at least 2 ac/day and 2 pc/day; and the occasional 3 am test prn)

*the target is for at least 50% of the SMBG values to be in this range

3.2.j   Self-titration of Anti-hyperglycemic Therapy

Standard therapy participants will be provided with simple algorithms to allow them to self-titrate their oral therapy or insulin to avoid hypoglycemia. They will also be instructed to call the clinic if they are recording frequent low SMBG values (see Table 3.2); if they have any episode of severe hypoglycemia; if they are experiencing frequent episodes of symptomatic hypoglycemia (>1/week); or if they have any symptoms of hyperglycemia. In these instances, therapy can be adjusted.

Intensive therapy participants will be provided with algorithms to allow them to self-titrate their oral therapy or insulin (i.e., make changes every 4 days) according to the pattern of their SMBG results and to avoid hypoglycemia or hyperglycemia. Moreover, participants requiring insulin will also be taught how to vary their dose according to the carbohydrate content of meals, with supplemental adjustments for ambient glucose levels and variations in exercise.

3.2.k Adjustment of Glycemic Therapy

The target and "Action Required" HbA1c and SMBG values for both groups are noted in Table 3.1. These targets will be achieved by using the same combination of dietary, lifestyle and pharmacologic approaches in both groups. As outlined above, however, the groups will differ in the intensity of follow-up, frequency of changes to glycemic therapy, and self-titration interventions. Whenever antihyperglycemic therapy needs to be increased (to reduce the HbA1c), participants will either move to a higher dose of their current therapy or, if already on the highest dose, will move to the next agent. For example, if action is required for a participant on maximum dose of metformin, sulfonylurea and a thiazolidinedione, evening insulin will be added.

The suggested algorithm for pharmacologic interventions is shown in Figures 3.1 and 3.2. For participants on intensive therapy whose HbA1c values are in the "Action Required" range (i.e., $\geq 6\%$), it calls for immediate institution of combination therapy with 2 classes of oral agents. It also calls for self-titration of therapy between visits for the intensive group as described in Section 3.2.j and in Table 3.2, and for titration of therapy at the visits based on the HbA1c or the SMBG results.

The exact time at which insulin will be started in individuals not taking insulin at the time of randomization is not explicitly defined. Nevertheless, evening basal insulin will be added for intensive group participants on maximal oral therapy whenever their glucose values are in the "Action Required" range as noted in Table 3.1. Moreover, sites will be prompted to add rapid acting insulin to intensive group individuals whose HbA1c is in the "action required" range with postprandial SMBG levels > 140 mg/dl (7.8 mmol/l). Figure 3.3 describes the algorithm for the use of insulin.

Antihyperglycemic therapy will not be reduced for participants in either group whose HbA1c is within or above the target range (noted in Table 3.1) unless required because of severe hypoglycemia or adverse effects.

Antihyperglycemic therapy will be reduced for participants in the standard group for the following reasons (Figure 3.2):
1. any severe hypoglycemia
2. more than 1 episode of symptomatic hypoglycemia per week
3. $\geq 50\%$ of SMBG levels < 90 mg/dl (5 mmol/l)
4. adverse effects of antihyperglycemic drugs
5. HbA1c $< 6.5\%$ on one occasion or 6.6-6.99% on 2 consecutive occasions and either on insulin or a secretagogue, a history of 1 or more episodes of symptomatic hypoglycemia since the previous visit, or 1 or more SMBG levels below 90 mg/dl (5 mmol/l) since the previous visit.

3.2.l   Glycemia Medications Available Within ACCORD

The following classes of antihyperglycemic drugs are available within ACCORD:
    a) biguanides (e.g., metformin)
    b) secretagogues (e.g., sulfonylureas such as glimepiride and meglitinides such as repaglinide)
    c) thiazolidinediones (e.g., rosiglitazone)
    d) alpha-glucosidase inhibitors (e.g., acarbose)
    e) insulins (e.g., NPH, ultralente, glargine, aspart, regular).

3.2.m   Alternatives and Contraindications for Glucose-Lowering Drugs

Acarbose may be used at the investigator's discretion to deal with postprandial spikes that may be difficult to control with other medications. Whether or not acarbose is used does not influence the algorithm in Figure 3.1.

Repaglinide, an insulin secretagogue in the meglitinide (benzoic acid derivative) class, may be substituted for sulfonylurea therapy in those individuals with erratic meal schedules or with hypoglycemia or sustained postprandial hyperglycemia. Repaglinide and sulfonylureas should not be combined because they are both insulin secretagogues.

Metformin may have gastrointestinal side effects especially if high initial doses are used. Therapy will therefore be initiated at a dose of 500 mg with dinner, increasing the dose by 500 mg every week until the patient meets target goals or reaches the clinically effective maximum dose of 1000 mg twice/day or is unable to tolerate higher doses. Contraindications to the use of metformin include a) serum creatinine $\geq$1.4 mg/dl for women or $\geq$ 1.5 mg/dl for men, b) drug-treated congestive heart failure, c) severe obstructive pulmonary disease, d) evidence of significant impairment of hepatic function (AST or ALT > 2.5 times the upper limit of normal), e) ongoing metabolic or respiratory acidosis, or f) other high risk condition for the development of acidosis or cardiovascular collapse.

Thiazolidinediones may cause fluid retention (including edema, anemia and CHF), liver toxicity, ovulation, and weight gain. Contraindications to their use include: a) ALT >2.5X upper limit of normal at start of therapy, or b) NYHA Class III or IV CHF. They should be used with caution in patients with prior edema. Rosiglitazone will be the thiazolidinedione provided by the study. Patients with mildly elevated liver enzymes (ALT levels $\leq$2.5X upper limit of normal) at baseline or during therapy with rosiglitazone should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with rosiglitazone in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X the upper limit of normal in patients on therapy with rosiglitazone, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with rosiglitazone should be discontinued.

Sulfonylurea contraindications include a) the use of repaglinide, b) severe allergic reaction to sulfa containing compound (anaphylaxis, Stevens-Johnson).

Figure 3.1
Treatment Algorithm for Intensive Glycemic Therapy Group (Goal: HbA1c<6%)
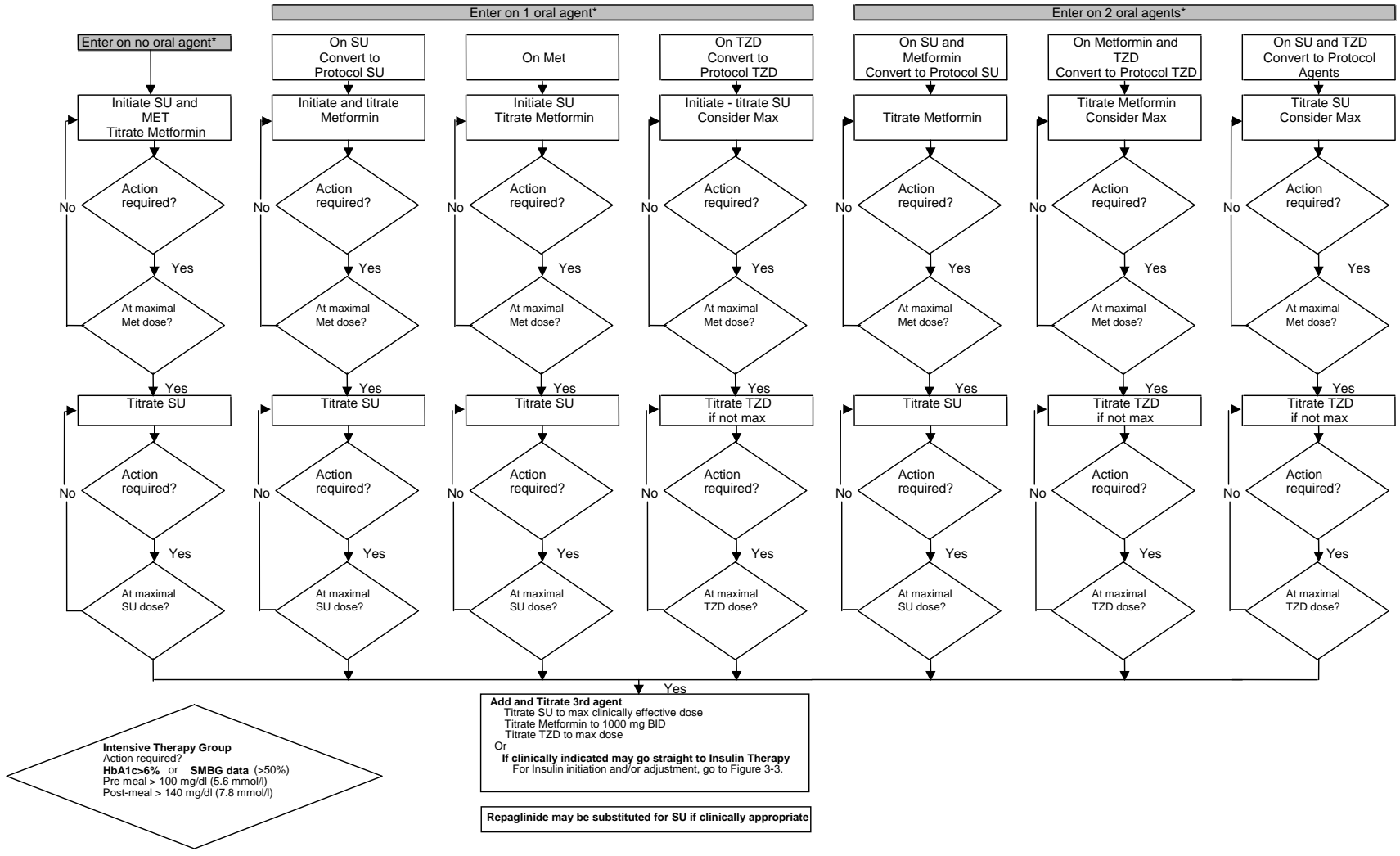
Figure 3.2:
Treatment Group Algorithm for Standard Glycemia Therapy Group (Goal: HbA1c 7% to 7.9%)
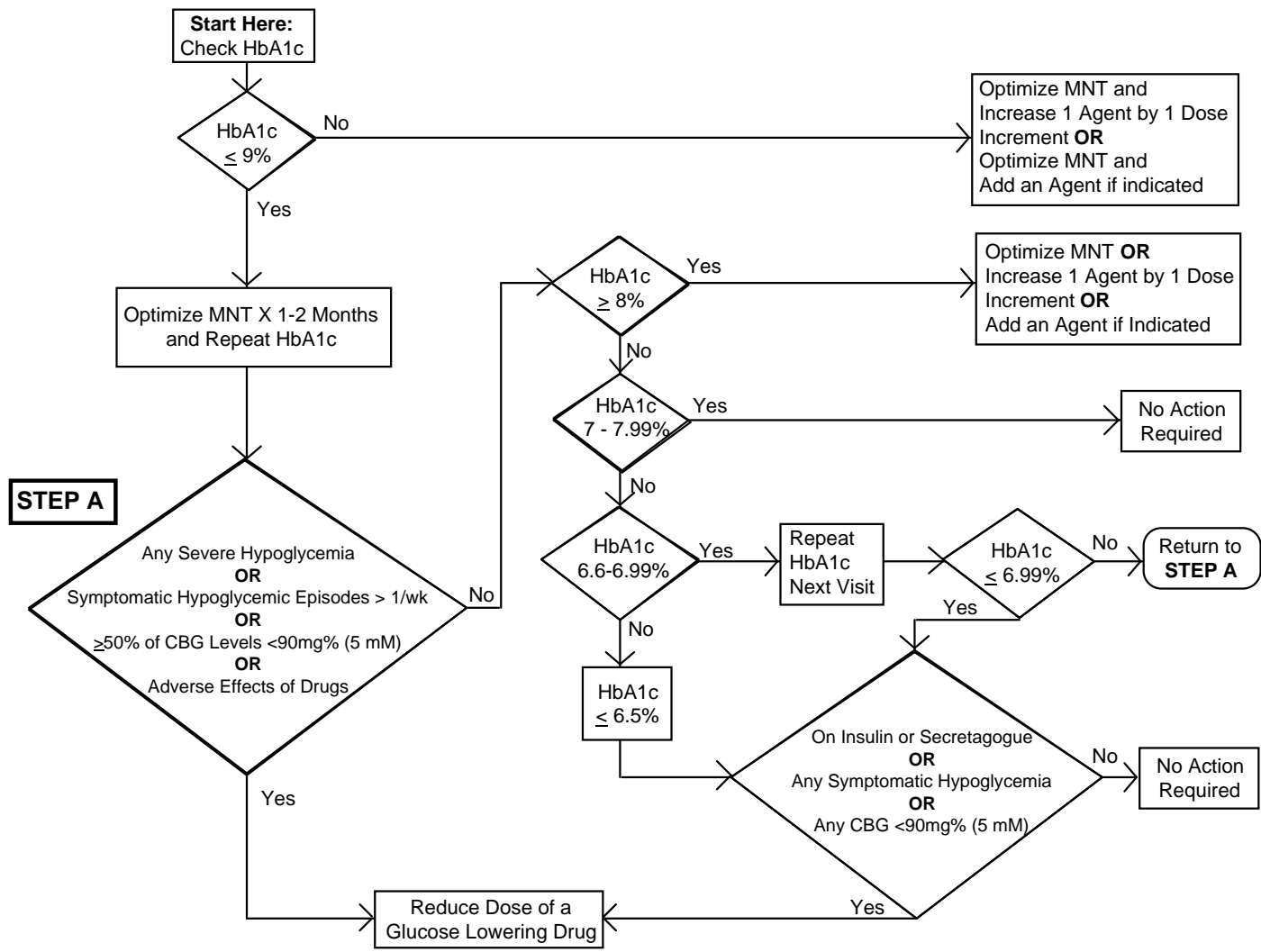
Figure 3.3:
Use of Insulin for Participants On Maximal Oral Therapy
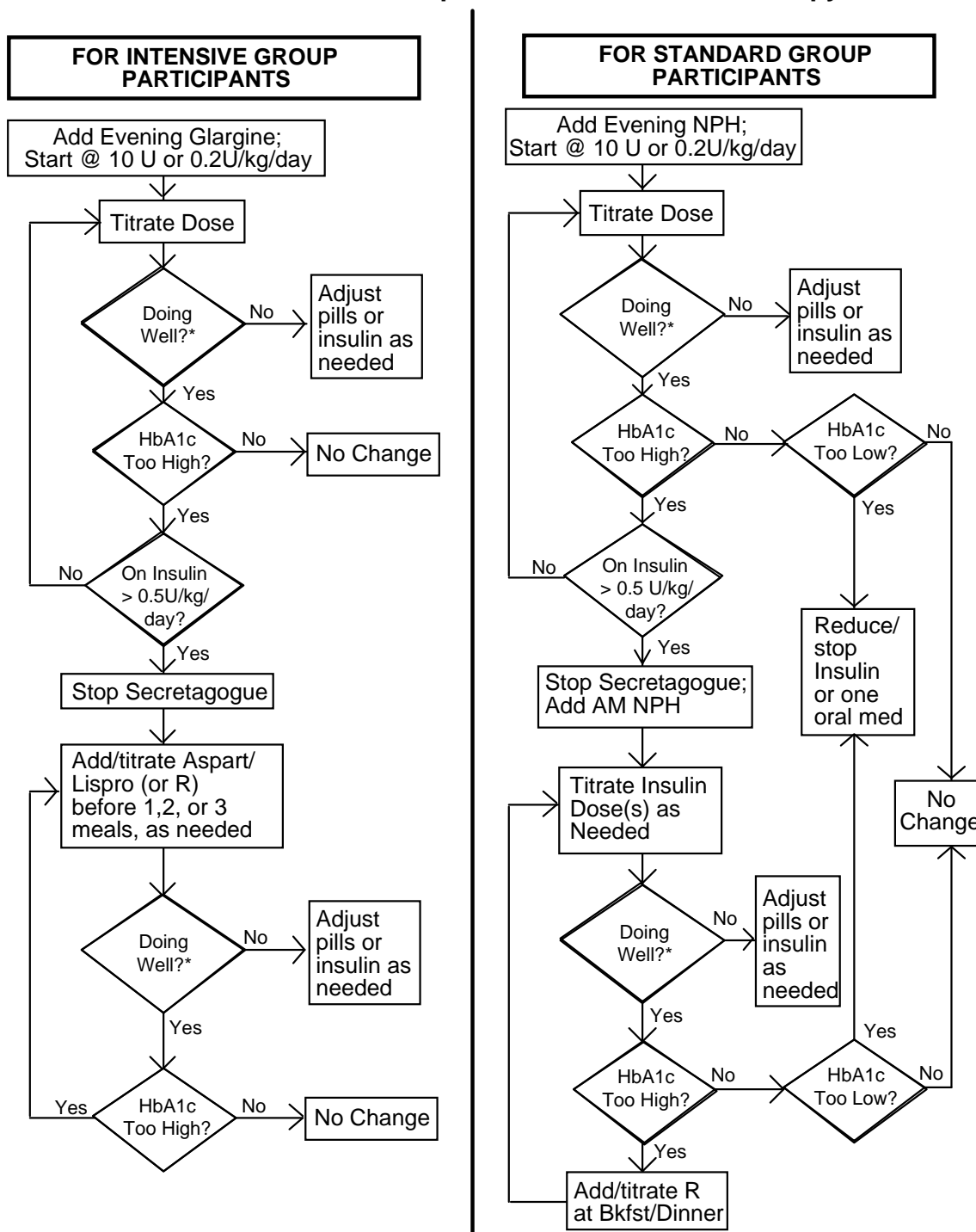
*Doing well: no severe hypoglycemic or adverse event <u>or</u> no reason to reduce therapy (as described in Figure 3.2)

3.3   Lipid Intervention

3.3.a   Lipid Research Question

In middle-aged or older people with type 2 diabetes who are at high risk of having a CVD event and in the context of good glycemic control, does a therapeutic strategy that uses a fibrate to raise HDL-C/lower triglyceride levels and uses a statin for treatment of LDL-C reduce the rate of CVD events compared to a strategy that only uses a statin for treatment of LDL-C? The specific fibrate to be used in ACCORD is fenofibrate and the specific statin is simvastatin.

3.3.b   Research Design

The lipid component of ACCORD is a fully masked, randomized trial of 5,800 participants. Eligible participants will be randomized to fenofibrate or placebo; all participants will be treated with simvastatin. To be eligible for the lipid trial, the observed or estimated LDL-C at screening (in the absence of treatment) must be between 60 and 180 mg/dl (1.55 and 4.65 mmol/l), inclusive. HDL-C must be less than 55 mg/dl (1.42 mmol/l) for women or Blacks/African-Americans, or less than 50 mg/dl (1.29 mmol/l) for all other gender-race groups. Other eligibility criteria are noted in Section 2.1.

The upper limit for triglyceride (TG) eligibility for screenees not on a lipid lowering agent is 750 mg/dl (8.47 mmol/l) and 400 mg/dl (4.52 mmol/l) for screenees on a lipid-lowering agent. It is expected that initial diet and glucose control will rapidly reduce TG levels in the very few participants near these limits. If an untreated participant has a TG level between 400 (4.52 mmol/l) and 750 mg/dl (8.47 mmol/l), he/she will have a beta-quantification performed by ultracentrifugation by the Central Chemistry Laboratory to allow direct determination of LDL-cholesterol level. Ten percent of participants are expected to be in this range.

The 4,200 participants who are not enrolled in the lipid portion of ACCORD (i.e., the 4,200 participants in the blood pressure portion of the trial) will be treated by their usual physicians (who may also be study investigators). The recommended LDL-C goals for these 4,200 participants will be based on the National Cholesterol Education Program (NCEP) guidelines (National Cholesterol Education Program 2001). Based on published data on the percent of participants reaching goals, it is expected that this group will have a mean LDL-cholesterol of about 110 mg/dl (2.84 mmol/l). As noted in Section 1.2.f, the 2001 NCEP guidelines define diabetes as a CHD-equivalent.

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

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

identical placebo tablet. Those with a calculated GFR between 30 and <50 will start at the reduced dose of 54 mg/day fenofibrate or placebo (or will be placed on 160 mg tablet every other day if the 54 mg dose is unavailable). The masked medication should be administered with the morning meal.

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

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

The starting dose of open-labeled simvastatin will be determined by presence of cardiovascular disease at randomization. Primary prevention participants (those participants without clinical cardiovascular disease) will start at a simvastatin dose of 20 mg/day, administered once daily after the evening meal or at bedtime. Secondary prevention participants (those with a history of clinical cardiovascular disease as defined in Chapter 2, Section 2.1.a.6.A.) will start at a simvastatin dose of 40 mg/day.

For participants starting at 20 mg/day of simvastatin, if the LDL-C is greater than 100 mg/dl (2.59 mmol/l) on two consecutive follow-up visits, the daily dose of simvastatin will be increased to 40 mg. Additionally, if a cardiovascular event occurs (as defined in Chapter 2, Section 2.1.a.6.A) during follow-up, the participant's simvastatin dose will be increased to 40 mg/day. If, during follow-up, the LDL-C is > 120 mg/dl (> 3.10 mmol/l) on two consecutive measurements following titration of simvastatin to 40 mg/day, the participant will be referred to their own physician for individualized treatment. This is described below in Section 3.3.c.

The order of therapy will be simvastatin first (at randomization), with the fenofibrate/placebo started at the next monthly visit. Participants and physicians will be masked to fibrate/placebo assignment, and to LDL-cholesterol, triglyceride, and HDL-cholesterol levels throughout the trial. This will be the only fully masked part of the ACCORD study.

During the trial, a fasting plasma lipid profile is scheduled to be obtained and centrally analyzed at four months, eight months, twelve months and yearly thereafter (see Tables 2.2C and 2.2F). Participants who have triglyceride levels greater than 400 mg/dl (4.4 mmol/l) at any time will have a beta-quantification performed to allow for determination of LDL-cholesterol levels at all time points. Safety profiles, including liver function tests and CPK levels, will be determined at one month, four months, eight

months, and twelve months for the first year and annually thereafter. To monitor renal function during follow-up, all lipid participants will be required to have an additional tube of blood drawn for creatinine at the routine blood draw every 4 months, which will be analyzed centrally (as noted in Tables 2.2C and 2.2F). If at any time the participant has relevant symptoms or signs suggestive of drug-induced toxicity, liver function tests and/or CPK levels will be obtained through the Central Laboratory.

3.3.c. Lipid Goals/Safety Issues

The goal of statin therapy is to achieve LDL-C values consistent with current NCEP and ADA guidelines. Under this lipid trial protocol, primary prevention participants will be on 20 mg simvastatin (which could conservatively lower LDL-C by 30%) and secondary prevention participants will be on 40 mg simvastatin (which could lower LDL-C by 40%). In addition, any participant on 20 mg simvastatin whose follow-up LDL-C values are greater than 100 mg/dl (2.59 mmol/l) on two consecutive occasions and any primary prevention participant who experiences a cardiovascular event (Section 2.1.a.6.A) will be placed on 40 mg/day simvastatin Using these assumptions/expectations as guides, the following conservative estimates are made:

Baseline LDL-C*	Estimated Mean LDL-C in Strata	Expected Mean On-treatment LDL-C in Strata
> 60 to < 80 mg/dl (> 1.55 to < 2.07 mmol/L)	70 mg/dl (1.81 mmol/L)	46 mg/dl (1.19 mmol/L)
> 80 to < 100 mg/dl (> 2.07 to < 2.59 mmol/L)	90 mg/dl (2.33 mmol/L)	59 mg/dl (1.53 mmol/L)
> 100 to < 120 mg/dl (> 2.59 to < 3.10 mmol/L)	110 mg/dl (2.84 mmol/L)	73 mg/dl (1.89 mmol/L)
> 120 to < 140 mg/dl (> 3.10 to < 3.62 mmol/L)	130 mg/dl (3.36 mmol/L)	86 mg/dl (2.22 mmol/L)
> 140 to < 160 mg/dl (> 3.62 to < 4.14 mmol/L)	150 mg/dl (3.88 mmol/L)	90 mg/dl (2.33 mmol/L)
> 160 to < 180 mg/dl (> 4.14 to < 4.65 mmol/L)	170 mg/dl (4.40 mmol/L)	102 mg/dl (2.64 mmol/L)

*This would be the observed LDL for participants not on a lipid-lowering agent at baseline,
but an estimated LDL for participants on a lipid-lowering agent.
Estimation based on the expected LDL effects of the drug/dose participant is taking.

It is further estimated that 5% of the participants would be in the first stratum at baseline, 15% in the second, 20% in the third, 25% in the fourth, 20% in the fifth, and 15% in the sixth. Thus, the expected overall mean on-treatment LDL-C would be approximately 82 mg/dl mg/dl (2.12 mmol/L).

Also, because the upper limit for entry LDL-C is 180 mg/dl, and because 40 mg simvastatin should provide about an average 40% percent reduction in LDL-cholesterol, it is expected that few participants will have an on-treatment LDL-C of more than 120 mg/dl. However, if a participant has an LDL-cholesterol level that is persistently greater than 120 mg/dl (3.10 mmol/l) even with treatment of 40 mg/day simvastatin, ACCORD will, consistent with NCEP guidelines, take the participant off the masked study medication and continue treatment with simvastatin until placed on a non-study statin by his/her primary caregiver.

Specifically, if the measured LDL-C goes above 120 mg/dl (3.10 mmol/l) the Coordinating Center will notify the clinic staff who ought to confirm compliance with the study statin, refer the participant to a nutritionist for dietary instruction/reinforcement (if appropriate), and schedule a blood draw for the visit four months from the visit at which the LDL-C was above 120 (3.10). This blood specimen needs to be sent to the ACCORD Central Chemistry Laboratory for lipid analysis.

If the participant has an LDL-C above 120 mg/dl (3.10 mmol/l) on two consecutive visits after titrating simvastatin to 40 mg/day (even after compliance review and dietary counseling), the following will occur:

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

If the centrally measured LDL-C is ever less than 40 mg/dl (1.03 mmol/l) during follow-up, the Coordinating Center will advise the clinic site. Clinic personnel should then determine compliance with study statin and fibrate/placebo (to make sure that the participant is not taking more than the prescribed number of pills daily), refer participant to nutritionist for dietary counseling to ensure that the participant is eating a balanced, adequate diet, and schedule a blood draw for the visit four months from the visit at which

the LDL-C was less than 40 (1.03). If the centrally measured LDL-C is ever less than 40 mg/dl (1.03 mmol/l) on two consecutive measurements, the following will occur:

- The investigator will be notified by the Coordinating Center to take the participant off simvastatin.
- The participant will remain on the masked study medication.

As a minimal goal, all participants will have LDL-C lower than 120 mg/dl (3.10 mmol/l) and triglycerides less than 750 mg/dl (8.47 mmol/l) during the study. Triglyceride values will be maintained at a level that does not pose a risk of pancreatitis.

If the centrally measured triglyceride ever exceeds 750 mg/dl (8.47 mmol/l) during follow-up, the Coordinating Center will advise the clinic site. Clinic personnel should then determine compliance with study statin and fibrate/placebo, refer participant to nutritionist for dietary instruction/reinforcement (if deemed appropriate) and determine and modify potential exacerbating disorders i.e. alcohol or simple sugar intake, hypothyroidism, hyperglycemia. Also, the clinic needs to schedule a blood draw for the visit four months from the visit at which the triglyceride exceeded 750 (8.47).

If the triglyceride exceeds 750 mg/dl (8.47 mmol/l) on two consecutive measurements, even after the above measures have been conducted, the following will occur:

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

If the estimated GFR falls below 30 mL/min/1.73m^2 at any time, a confirmatory blood draw will be required within 2 weeks. If the estimated GFR remains below 30 mL/min/1.73m^2, the masked study medication will be permanently discontinued, regardless of fenofibrate or placebo assignment.

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

3.4   Blood Pressure Control Intervention

3.4.a   Blood Pressure Research Question

In middle aged or older people with type 2 diabetes who are at high risk of having a CVD event and in the context of good glycemic control, does a therapeutic strategy that targets a systolic blood pressure (SBP) of < 120 mm Hg reduce the rate of CVD events compared to a strategy that targets a SBP of < 140 mm Hg?

3.4.b   Research Design

The blood pressure component of ACCORD is an unmasked, open labeled, randomized trial of 4,200 participants. Eligibility criteria are described in Sections 2.1.a, 2.1.b, and 2.1.d.

If the investigator believes the participant is likely to be eligible for the BP intervention, medications may be adjusted prior to the randomization visit to determine whether the participant's SBP will rise or fall to the BP criteria. No more than 2 visits after any adjustment of any antihypertensive therapy will be permitted for a participant to meet the BP eligibility criteria before entry into ACCORD.

If previously untreated for hypertension, a participant should have documentation of SBP $\geq$130 mm Hg on 2 visits within 3 months prior to the randomization visit in order to be included in the BP intervention.

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

3.4.c   Blood Pressure Goals

Participants eligible for the BP component will be randomized to one of two goals: SBP <120 mm Hg for the more intense goal and SBP <140 mm Hg for the less intense goal. Figures 3.4 and 3.5 describe the treatment algorithms for the two blood pressure treatment groups.

For ACCORD participants not participating in the blood pressure portion of ACCORD (i.e., the 5,800 participants in the lipid portion of the trial), recommendations for BP treatment will be made to their usual source of care. (See Section 3.5.e).

3.4.d   Antihypertensive Classes (Agents)

Use of once daily preparations of the study antihypertensive agents will be encouraged unless alternate dosing frequency (e.g., BID) is indicated.

The following classes of agents may be used and are provided by the study.

Angiotensin converting enzyme (ACE)-inhibitors
Diuretics
Beta-blockers
Dihydropyridine and Non-dihydropyridine CCBs
Alpha-blockers
Angiotensis II receptor blockers (ARBs)
Sympatholytics
Alpha-beta blockers

Combinations:
    Thiazide diuretic/potassium sparing diuretic
    Beta-blocker/diuretic
    ACE-inhibitor/diuretic
    ARB/diuretic
    Dihydropyridine CCB/ACE-inhibitor
    Non-dihydropyridine CCB/ACE-inhibitor

The investigator may select among the available ACCORD antihypertensive medications for initiation of therapy. Other drugs not supplied by the trial may be used as the investigator determines appropriate. However, all antihypertensive regimens should include a drug class associated with reduced cardiovascular events in diabetic participants: diuretic, beta-blocker, calcium channel blocker, or ACE inhibitor. Based on currently completed trials, some experts believe that monotherapy with a calcium channel blocker may be less desirable in a diabetic patient. If an alpha blocker is used, it should be used in combination with at least one agent proven to reduce cardiovascular events in diabetic hypertensive patients. For participants in the intensive BP group (Figure 3.4), a combination of a diuretic and either an ACE inhibitor or a beta-blocker should be initiated at randomization.   Drug doses should be increased and/or additional antihypertensive medications should be added at each visit in the intensive group until the participant's goal has been reached.

For participants in the intensive blood pressure group, "Milepost Visits" will occur at 4 month intervals for the first 2 years of follow-up and annually thereafter. If at a Milepost Visit the SBP is not less than 120 mm Hg, then an antihypertensive drug from a different class than what is being taken must be added, unless there are compelling reasons to wait. Milepost Visits do not apply to the standard blood pressure group.

Medication doses may be decreased or medications changed whenever the ACCORD therapist considers it clinically appropriate, such as when adverse effects occur that are believed to be secondary to an antihypertensive medication. Rechallenge is encouraged if a trial off the medication is not associated with resolution of the adverse effect, or if the adverse experience was not serious and the agent is strongly indicated for another condition (e.g., an ACE inhibitor in heart failure).

Most multi-drug regimens are more effective if a diuretic is included as one of the agents. Regimens are more effective if the drugs combined have very different mechanisms of action. For example, an ACE inhibitor or ARB will usually be more effective when combined with a diuretic or calcium antagonist than with a beta-blocker. Only a few specific combinations are to be avoided, such as a beta-blocker with the calcium antagonists verapamil or diltiazem. However, a beta-blocker combines very effectively and safely with a dihydropyridine calcium antagonist. It is expected that most ACCORD participants in the intensive BP intervention group will require at least 2 and up to 5 antihypertensive medications to achieve their BP goals. If a participant is not at goal on 4 drugs, consultation with the Clinical Center Network is recommended.

3.4.e Initiation of Blood Pressure Therapy

It is recommended that the BP intervention begin at the first visit at the same time glycemia treatment is initiated. Intensive group participants should be seen at least monthly until at BP goal (< 120 mm Hg). Once a participant's BP goal has been achieved, the antihypertensive medication regimen may still be altered subsequently to maintain BP near goal, to avoid excessive hypotension, or to alleviate or minimize adverse effects.

3.4.f Achieving and Monitoring Blood Pressure Control

Figures 3.4 and 3.5 describe the treatment algorithms for the two blood pressure treatment groups. The BP treatment protocol of ACCORD is designed to be flexible in terms of choice and dose of drugs. For the intensive BP group, the algorithm is structured for adding additional medications for those participants who are above their BP goals at the Milepost Visits.

At the point of randomization, all participants in the intensive group of the hypertension study will automatically be assigned a series of milepost dates. Milepost dates will be assigned for the entire duration of the study. Between these designated visits, the ACCORD therapist may adjust dose of medications within the recommended dose range or add medications. However once a milepost date has been reached and the participant remains above goal BP the therapist is required to add an additional class of drug to the existing regimen.

Each clinic and individual participant will have their BP and drug status monitored closely by the Coordinating Center and CCN. The clinical center will be notified before the Milepost Visit that adding drug is required if BP is above goal at that visit. In situations where adding a drug could in the opinion of the therapist be potentially harmful to the participant then adding a drug at this visit can be waived, however the therapist must justify this decision on a "Milepost Exception Form." The number of Milepost exception forms will be closely monitored in each ACCORD clinic and regular feedback provided to the clinic for the degree of adherence to the drug protocol.

For intensive group participants, once the ACCORD participant has been prescribed 5 drugs, if the BP remains above goal at subsequent milepost visits it will be permitted to substitute a different class into the regimen instead of adding another drug, or increasing the dose of drug.

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

Also, if the SBP is > 120 mm Hg at any regular clinic visit for a participant in the intensive BP group, blood pressure medications must be added or titrated and the participant seen monthly until the SBP goes below 120 mm Hg or until a clinical decision is made that therapy should not be increased further. (See Figure 3.4). Again: if the visit is a Milepost Visit, BP the therapist must add an additional class of drug to the existing regimen.

For standard BP group participants, medication dose titration or addition of another drug is indicated if SBP >160 mm Hg at a single visit or >140 mm Hg at two successive visits. Down-titration ('step-down') of therapy in the standard group is allowed at the discretion of the ACCORD therapist, after consultation with the participant, if the SBP < 130 mm Hg at a single visit or < 135 mm Hg at two consecutive visits. (See Figure 3.5).

The blood pressure treatment protocol in ACCORD is designed to treat SBP intensively to a goal less than 120 mm Hg in the intensive arm and to <140 mm Hg in the standard arm of the blood pressure study. Evidence from clinical trials, such as UKPDS and HOT, supports a SBP goal of 140 mm Hg in persons with hypertension and diabetes. It is not known if lowering SBP to the more intensive ACCORD goal of 120 mm Hg is beneficial or even harmful in patients like those entered into the ACCORD trial compared with the standard goal of 140 mm Hg. ACCORD is designed to provide definitive evidence for the intensive control of SBP in Type 2 Diabetics. Based on this rationale, step-down (a reduction of dose or number of antihypertensive drugs) can be done with participants in the standard goal group. Step-down is allowed at the discretion of the ACCORD therapist, after consultation with the participant, when the SBP has been <135 mm Hg on two successive clinic visits or is < 130 mmHg at any single visit.

3.4.g   Monitoring Potassium and Creatinine

If an ACE-inhibitor, AII receptor blocker (ARB), or a thiazide is started or if the dose is significantly increased, the potassium and creatinine levels should be monitored.

**Figure 3.4: Treatment Algorithm for Intensive Blood Pressure Group
(Goal: SBP < 120 mm Hg)**
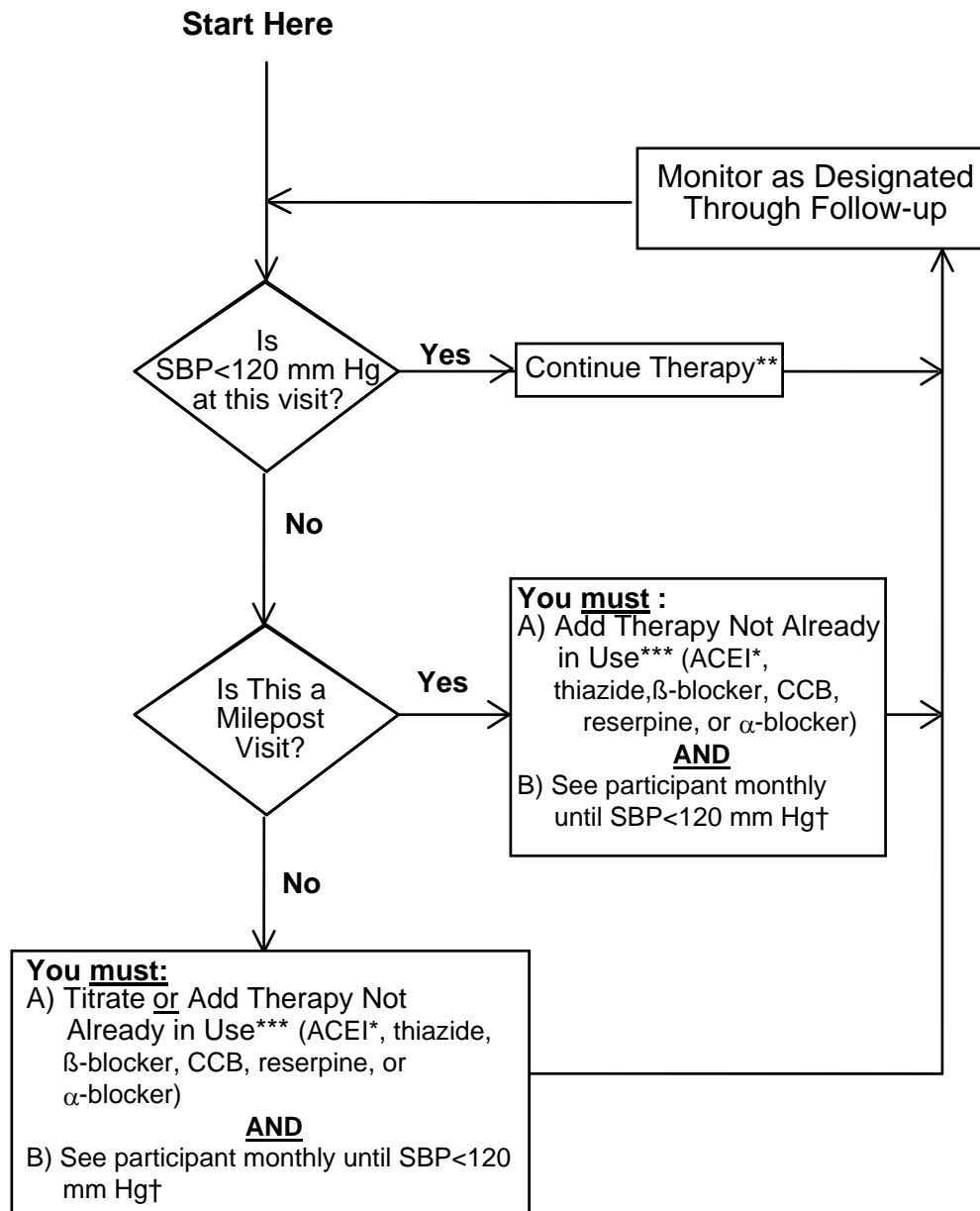
Start Here

Monitor as Designated Through Follow-up

Is SBP<120 mm Hg at this visit? **Yes** → Continue Therapy**

No

Is This a Milepost Visit? **Yes** →

You must :
A) Add Therapy Not Already in Use*** (ACEI*, thiazide,ß-blocker, CCB, reserpine, or α-blocker)
AND
B) See participant monthly until SBP<120 mm Hg†

No

You must:
A) Titrate or Add Therapy Not Already in Use*** (ACEI*, thiazide, ß-blocker, CCB, reserpine, or α-blocker)
AND
B) See participant monthly until SBP<120 mm Hg†

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

**Figure 3.5: Treatment Algorithm for Standard Blood Pressure Group
(Goal: SBP < 140 mm Hg)**
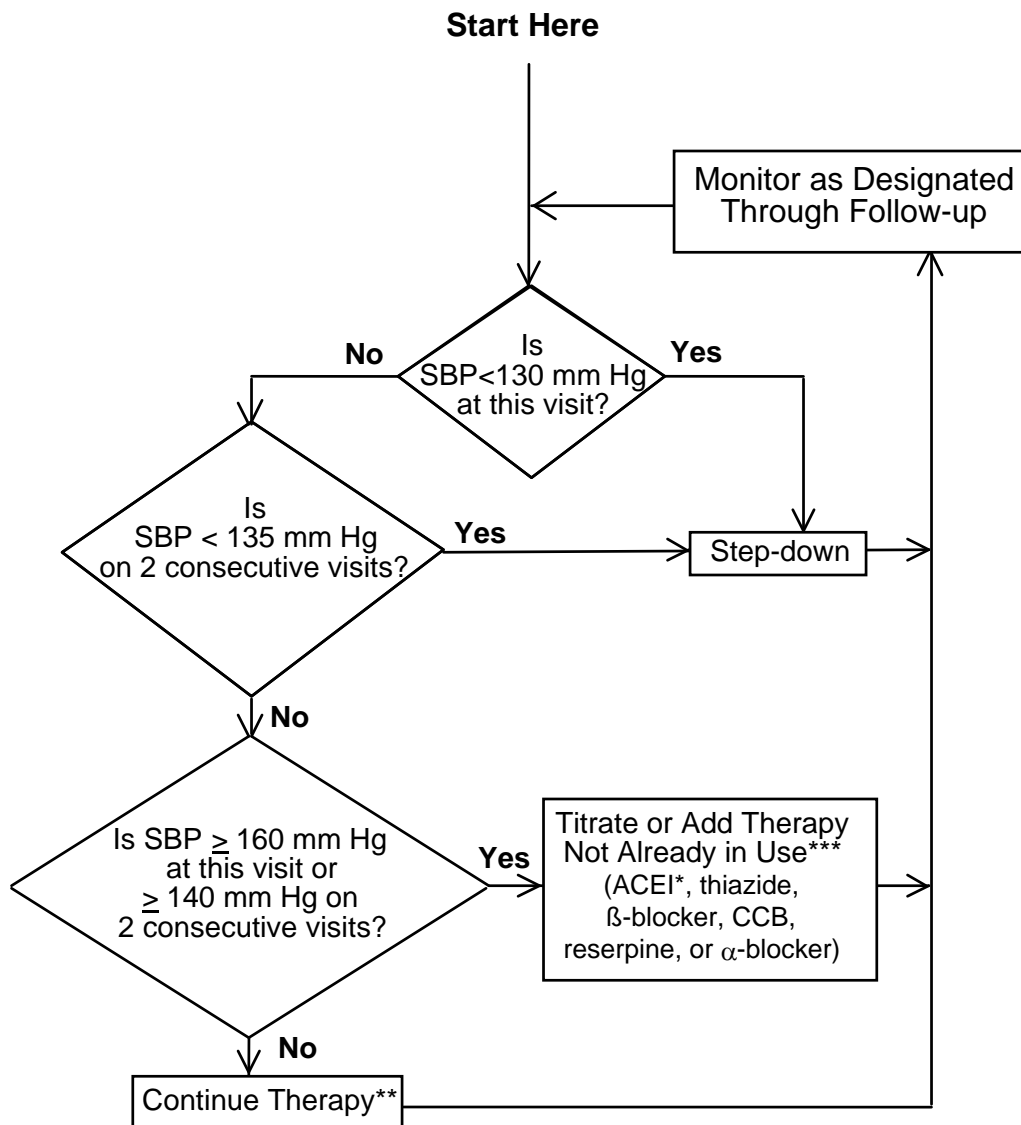
Start Here

```
                                    ┌──────────────────────┐
                                    │ Monitor as Designated │
                                    │  Through Follow-up     │
                                    └──────────────────────┘
```

No ← ◇ Is SBP<130 mm Hg at this visit? ◇ → **Yes**

◇ Is SBP < 135 mm Hg on 2 consecutive visits? ◇ → **Yes** → Step-down

No

◇ Is SBP ≥ 160 mm Hg at this visit or ≥ 140 mm Hg on 2 consecutive visits? ◇ → **Yes** → Titrate or Add Therapy Not Already in Use*** (ACEI*, thiazide, ß-blocker, CCB, reserpine, or α-blocker)

No

Continue Therapy**

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

3.5 Lifestyle Recommendations and Background Therapy

The purpose of including lifestyle recommendations and background therapy in ACCORD is two fold. First, it fosters high quality general diabetes care in all ACCORD participants in accordance with current practice guidelines. Second, it minimizes bias by increasing the likelihood that background therapies that alter the risk of cardiovascular events and that are not being studied in ACCORD are utilized equally across all study arms. The background therapy recommendations will be provided to the participants and their physicians. Background therapy is considered part of usual recommended care for diabetes and, as such, is not covered by research study costs. The delivery of these background therapies will be left up to the participants' own clinicians.

Lifestyle therapy, which includes medical nutrition therapy (MNT) and physical activity, is somewhat different. The primary glycemia research question is not a question exclusively of drug effects, but of the effects of the higher degree of glycemic control. To achieve a difference in HbA1c between the intensive and standard arms requires both lifestyle and medication interventions. Counseling in both MNT and physical activity is expected to be delivered by ACCORD clinicians. Participants randomized to the intensive glycemic control arm of the study will receive more intensive reinforcement of lifestyle therapy by way of more frequent assessments and instruction in order to achieve their treatment goals.

The Lifestyle and Background Therapy Working Group will coordinate the provision of relevant participant educational materials to be made available for study-wide use. These will include the topics of general diabetes care, medical nutrition therapy, physical activity, smoking cessation, and anti-thrombotic therapy and will complement educational materials related to the glycemia, blood pressure, and lipid interventions that are part of the trial. Unlike most educational materials for diabetes, the ACCORD materials will not include specific goals for glucose, HbA1c, blood pressure, and lipids, as these will depend on randomized treatment assignment.

General diabetes education should be carried out by the ACCORD clinics in accordance with national standards for diabetes self-management education programs (ADA 1999). Achieving the lifestyle and background therapy goals will require a coordinated team effort along with education and/or supplemental materials.

Periodic reviews for updating recommendations will be conducted.

3.5.a Medical Nutrition Therapy

Medical Nutrition Therapy (MNT) consists of weight control and dietary modification. The American Diabetes Association (ADA) position statement on "Nutrition Recommendations and Principles for People with Diabetes Mellitus" reports that "medical nutrition therapy is integral to total diabetes care and an essential component of successful diabetes management" (ADA 2000a). Physical activity is a

closely related component of diabetes care. MNT is considered integral to the current study for achieving optimal diabetes management.

The overall goal of MNT is to assist individuals with diabetes in making changes in nutrition habits and body weight leading to improved metabolic control**.** There is no one proven strategy or method that can be universally implemented, but recommendations regarding weight control and nutritionally adequate meal plans can be made to foster progress toward the goal.

The following recommendations and general principles will apply to all participants in ACCORD, regardless of randomized group assignment. However, as noted above, participants randomized to the intensive glycemic control arm of the study will receive more intensive reinforcement of MNT.

3.5.a.1 Weight Control

Participants who are considered overweight (BMI $\geq$ 25 kg/m^2 according to the NHLBI Obesity Education Initiative) are advised and encouraged to lose 10% of their current weight, or 5-9 kg, whichever is less, over a 6-month period. A moderate caloric restriction (250-500 calories less than the average daily intake calculated from a food history) and a nutritionally adequate meal plan should be encouraged. Non-overweight participants are encouraged to maintain weight. These guidelines are based on the NHLBI Obesity Education Initiative (Obesity Education Initiative Expert Panel 1998).

3.5.a.2 Dietary Modification

Dietary modifications are recommended based both on glycemic control and also on control and prevention of CVD risk factors common in people with diabetes. For individuals using insulin therapy, it is recommended that meals be eaten at consistent times synchronized with the time-action of the insulin preparation used (ADA 2000a).

The National Cholesterol Education Program (NCEP) Step I diet is recommended (National Cholesterol Education Program 1993). This includes limiting fat intake to <30% of total calories with saturated fat restricted to <10% of total calories. Polyunsaturated fat intake should be < 10% of calories with monounsaturated fat consumption 10-15% of calories. Cholesterol intake should be limited to < 300 mg/day. If LDL-cholesterol is persistently elevated after a sufficient trial and compliance with the Step I diet, the Step II diet should be prescribed. This diet calls for further reduction in saturated fat and cholesterol (NCEP 1993). Some authorities recommend minimizing transfatty acid intake as well because they increase LDL-cholesterol, decrease HDL-cholesterol and are associated in cohort studies with increased CVD incidence (Ascherio 1997; Ascherio 1999; Mann 1997).

The percent of calories from carbohydrate intake will vary and is individualized based on the participants' eating habits, glucose, and lipid goals. First priority should be

given to the total amount of carbohydrate consumed rather than the source of the carbohydrate (ADA 2000).

A reduced sodium intake (2.4-3.0 g/day) is recommended for all people with diabetes (ADA 2000a). For people with hypertension and nephropathy, less than 2 gms/day is recommended by the ADA (ADA 2000a). The National High Blood Pressure Education Program recommends less than 2.4 g/day of sodium for those with mild to moderate hypertension (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 1997) and to prevent hypertension (National High Blood Pressure Education Program 1993). Therefore, ACCORD will recommend that dietary sodium intake be reduced to less than 2.4 gms/day for the ACCORD study population and less than 2 g/day for those with nephropathy.

It is recommended that trial participants limit daily alcohol intake to no more than 1 ounce (30ml) of ethanol for men and 0.5 ounces (15 ml) for women (ADA 2000a). One ounce of ethanol is equivalent to 24 ounces (720 ml) of beer, 10 ounces (300 ml) of wine or 2 ounces (60ml) of 100-proof whiskey. These recommendations are consistent with JNC VI (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 1997) and the U.S. Dietary Guidelines (USDA & USDHHS 1995).

3.5.b   Physical Activity

Physical activity recommendations for ACCORD participants are made in accordance with current national recommendations for physical activity in the general population (Pate 1995; USDHHS 1996) and for physical activity in diabetic patients (ACSM 1994; ACSM & ADA 1997; ADA 2000). Regular moderate-to-vigorous aerobic physical activity can improve metabolic control in people with diabetes and help with weight loss and weight control.

Participants will be encouraged to accumulate 30 minutes or more of moderate-intensity aerobic physical activity on 5 or more days of the week. Moderate-intensity aerobic activity is defined as repetitive motion using large muscle groups that increases the heart rate to 50-70% of maximal, is perceived as fairly light to somewhat hard, or is equivalent in perceived intensity to brisk walking (3-4 miles per hour for most people, or walking as if you are in a hurry). Maximal heart rate can be estimated by subtracting age from 220. Persons on beta-blockers cannot use the heart rate criterion, as beta-blockers attenuate the increase in heart rate, so perceived exertion or comparable intensity to brisk walking should be recommended. Thirty minutes of physical activity may be accumulated in bouts of 8-10 minutes. Warm-up and cool-down activities will be encouraged, as will foot protection and inspection and maintenance of hydration (ADA, 2000b).

Sedentary ACCORD participants will be encouraged to increase their physical activity levels gradually, starting with lower-intensity, shorter-duration, and less frequent activities (eg., moderately paced walking for 5 minutes twice a week) and increasing

gradually over weeks or months to moderate-intensity and longer-duration activities (eg., brisk walking for 20-30 minutes, 5 days a week). The CCNs and Clinical Sites are encouraged to develop and maintain lists of low cost or free local resources for safe physical activity to provide to patients.

To prevent adverse events, patients with proliferative retinopathy, nephropathy, or peripheral neuropathy with loss of protective sensation should be advised to avoid vigorous or strenuous exercise, high-impact exercise (eg., jogging, high-impact aerobics, racquet sports, competitive sports), weight training, and for those with peripheral neuropathy, prolonged walking (ACSM & ADA 1997). Recommended exercises include brisk walking (3-4 miles per hour), swimming, stationary cycling, and rowing.

In accordance with national recommendations for people with diabetes and at high risk for underlying cardiovascular disease (ACSM 1994; Mahler 1995; Pate 1995; ACSM & ADA 1997; ADA 2000b), screening should be considered for ACCORD participants beginning an unsupervised exercise program or increasing their intensity of physical activity. The recommended screening is an exercise stress test, or documentation of an exercise stress test within the previous 3 months, that is negative for ischemia and significant arrhythmias at a workload of 4-5 METS (i.e., moderate intensity, equivalent to brisk walking). Persons continuing their current regular physical activity or increasing duration of activity at the same intensity do not need this screening. Persons experiencing symptoms of ischemia during physical activity should undergo diagnostic evaluation.

3.5.c   Smoking Cessation

There are consistent results from both cross-sectional and prospective studies showing enhanced risk for micro- and macrovascular disease, as well as premature mortality, from the combination of smoking and diabetes. The smoking cessation literature is extensive, generally well-designed, and encouraging regarding the impact of cost-effective practical office-based interventions. System-based approaches that make smoking cessation intervention a routine part of office contacts and provide multiple prompts, advice, assistance, and follow-up support are particularly effective. Although there is minimal information on the effectiveness of cessation interventions specifically for people with diabetes, there is no reason to assume that cessation intervention would be less effective in this population. The following recommendations are based on guidelines of the American Diabetes Association (ADA 2000c; Haire-Joshu 1999) and Agency for Health Care Policy and Research (Fiore 1996).

All participants who are tobacco users will be strongly encouraged to stop. The widely accepted AHCPR guidelines and model include the following steps:

1. ASK – each participant about tobacco use
2. ADVISE – current smokers to quit using a brief, unambiguous, strong and personalized message
3. ASSESS – current smokers' willingness to quit

4. <u>ASSIST</u> – current smokers who express willingness to make a quit attempt by developing a quit plan, encouraging adjunctive pharmacotherapy, and providing supplementary materials
5. <u>ARRANGE</u> follow-up, either by a health care provider or in a specialized smoking cessation program

3.5.d   Antithrombotic Therapy

Large-scale collaborative trials and meta-analyses of trials support the view that low-dose aspirin lowers the rate of recurrent cardiovascular events in men and women with diabetes and cardiovascular disease (Antiplatelet Trialists' Collaboration 1994; ETDRS Investigators 1992; Johnson 1999). Substantial evidence suggests that low-dose aspirin therapy should also be used as a primary prevention strategy in men and women with diabetes who are at high risk for cardiovascular events (Steering Committee of the Physicians' Health Study Research Group 1989; ETDRS Investigators 1992). Based on these studies, the American Diabetes Association also recommends low-dose aspirin as secondary prevention, and as primary prevention in high-risk men and women over the age of 30 with diabetes (ADA 2000d; Colwell 1997). All of the ACCORD participants will fall into one of these two categories. Aspirin is safe and effective across a dosage range from 75-325 mg daily (Antiplatelet Trialists' Collaboration 1994; Johnson 1999). Therefore, aspirin 75-325 mg daily is recommended for all ACCORD participants unless contraindicated by allergy, bleeding disorder, recent gastrointestinal bleeding or need for anticoagulant therapy.

3.5.e   Treatment of Hypertension and Dyslipidemia

Because ACCORD includes a full factorial trial for both the blood pressure and lipid components, there will be participants enrolled in the lipid component who may have hypertension and participants in the blood pressure component who have dyslipidemia. These participants will receive care for their conditions, if present, from their usual source of medical care.

Blood pressure and lipid goals for treatment are recommended in these patients based on the investigators' synthesis of clinical trial evidence. In some cases, these may differ from national recommendations from consensus panels. It is suggested that the patient's physician take all these guidelines under consideration when individualizing treatment for each patient.

A blood pressure goal of <140/85 mm Hg is recommended for participants not in the BP intervention. This goal is supported by evidence for cardiovascular disease prevention. National guidelines that recommend a lower goal in people with diabetes of <130/85 mm Hg, including JNC VI (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 1997) and the American Diabetes Association (ADA 2000j) will also be provided.

For participants not in the lipid intervention, an LDL-cholesterol goal of <100 mg/dl is recommended. Information on national guidelines will also be provided that recommend behavioral and/or pharmacologic treatment for LDL-cholesterol levels >100 mg/dl in people with diabetes whether or not CHD is present (ADA 2000e, National Cholesterol Education Program 2002).

As current guidelines are revised, the most current recommendations will be conveyed to the participants' physicians.

3.5.f   Angiotensin-Converting-Enzyme Inhibitors (ACE-Inhibitors)

Evidence for the effectiveness of angiotensin-converting-enzyme (ACE) inhibition in reducing adverse outcomes in patients with type 2 diabetes has been increasing. Meta-analyses and randomized clinical trials have shown that ACE inhibitors reduce mortality in acute MI, with greater effect sizes in diabetic patients (ACE Inhibitor Myocardial Infarction Collaborative Group 1998); (Zuanetti 1997), and reduce sudden cardiac death following acute MI (Domanski, et al., 1999). Meta-analysis has shown that mortality and subsequent hospitalizations for CHF are reduced in patients with congestive heart failure treated with ACE-inhibitors, including patients in all four NYHA CHF classes if their ejection fractions is < 35% (Garg 1995).

Some randomized controlled trials have suggested that ACE-inhibitors are superior to other treatments for hypertension in hypertensive type 2 diabetic patients (Estacio 1998; Tatti 1998; Hansson 1999a) Other studies have found ACE-inhibitors to be equivalent to other treatments (Hansson 1999b; UKPDS 1998). Given these inconsistent results, there is no clear consensus at the present time to use ACE-inhibitors over other antihypertensive treatments. However, the Heart Outcomes Prevention Evaluation Study (HOPE) compared ACE-inhibitors with placebo in participants at high risk for cardiovascular disease and found a 25% reduction in the combined outcome of MI, stroke, and cardiovascular death, which did not appear to be explained by the degree of blood pressure reduction (Yusuf 2000). The effect was significant in participants with and without diabetes, participants with and without a past history of coronary artery disease, and participants with and without microalbuminuria (Yusuf 2000). In the subgroup of patients with diabetes, there was a reduction in relative risk in patients with and without microalbuminuria and in patients with and without hypertension, although effects in some of the subgroups did not reach significance (HOPE 2000).

There is strong evidence that ACE-inhibitors improve renal outcomes (nephropathy and albumin excretion) in type 2 diabetes when compared with placebo in hypertensive participants as well as non-hypertensive participants with and without microalbuminuria (Ravid 1996; Ravid 1998; Yusuf 2000).

Based on this evidence, the ACCORD study will recommend the use of ACE-inhibitors for reducing cardiovascular morbidity and mortality in patients who have experienced acute MI, congestive heart failure, nephropathy, and in patients with type 2 diabetes with at least one additional risk factor for cardiovascular disease.

3.5.g   Diabetes Related General Medical Care

ACCORD participants will also receive diabetes related general medical care. The following recommendations are based on guidelines of the American Diabetes Association (ADA 2000f).

1. All participants should receive an annual dilated eye and visual exam by an ophthalmologist or optometrist (ADA 2000g).
2. All participants should receive a foot examination at least annually to assess skin integrity, foot structure and biomechanics, vascular status, and protective sensation (ADA 2000h, Mayfield 1998). A standardized examination will be described in the Manual of Procedures.
3. Patients with diabetes (in particular those with end organ complications of cardiac and renal disease) are at high risk for cardiopulmonary complications, hospitalization, and death from influenza and pneumococcal disease. Although there are few clinical trials of influenza and pneumococcal vaccine efficacy specifically in patients with diabetes, subgroup analyses of patients with diabetes reported in clinical narrative and case-control studies support the fact that vaccination against influenza has been effective in reducing hospital admissions during influenza epidemics (Smith 2000; Nichol 1994). Therefore, all participants should receive annual influenza vaccine and, if previously unvaccinated, one dose of pneumococcal vaccine (ADA 2000i).

3.5.h   Monitoring Lifestyle Recommendations and Background Therapy

Use of aspirin therapy, ACE-inhibitors, and smoking status will be documented on regular visit forms with the same frequency for all study participants. Weight will be measured at all clinic visits. A foot examination will be conducted as part of the baseline and annual study physical examinations. Visual acuity will be measured at baseline, every other year thereafter, and at the end of the study. Diet and physical activity will be measured at baseline, and at years 1, 3, and 4.

Chapter 4
Participant Safety and Confidentiality

4.1   Introduction

Assuring participant safety and the confidentiality of participant data are essential components of ACCORD. Each participating investigator has primary responsibility for the safety of the individual participants under his/her care, while the Data and Safety Monitoring Board will have primary responsibility for monitoring the accumulating study data for signs of adverse trends in morbidity/mortality and drug toxicity.

4.2   Exclusions

Persons with contraindications to the study statin or fibrate therapy drug will not be eligible to be enrolled in the lipid component. Exclusions are detailed in Sections 2.1.b (*General Exclusions*), 2.1.c (*Lipid Component Exclusions*), and 2.1.d (*Blood Pressure Component Exclusions*).

4.3   Adverse Reactions and Discontinuation of Study Drug

Given the number of drugs employed in ACCORD, adverse reactions could be caused by single drugs or by drug-drug interactions.   Recently, among the thiazolidinedione class of drugs for type 2 diabetes mellitus, troglitazone was removed from the U.S. market based upon FDA's review of liver toxicity data, which suggested that it is more toxic than two newer agents from the same class, rosiglitazone (Avandia) and pioglitazone (Actos) (FDA 2000). Myopathy and rhabdomyolysis have been reported after combination therapy with statins and fibrates (Ellen 1998, Pierce 1990).

Possible adverse effects of the study drugs will be assessed at each follow-up visit by patient history, including hypoglycemia episodes and, in the lipid component, muscle pain. Chemistry tests will be performed periodically to monitor safety issues, as indicated in Tables 2.2A through 2.2F. Patients initiated on thiazolidinediones will be monitored, as recommended by the manufacturer, with ALT levels every two months for the first 12 months, and annually thereafter. Patients treated with ACE inhibitors, AII receptor blockers, or diuretics will be monitored for hypo- or hyperkalemia and for renal dysfunction. Patients in the lipid portion of the trial will be monitored periodically with CPK enzymes and creatinine levels. Serious and unexpected reactions to study drugs will be reported to the FDA. Hypoglycemia episodes requiring assistance by medical/paramedical personnel will be reported to the Coordinating Center as Serious Adverse Experiences (SAEs) using study-specific forms.

ACCORD will monitor the frequency and severity of muscle symptoms at every clinic visit. For participants in the lipid trial, CPK concentrations will be measured at baseline, 1 month, 4 months, 8 months and 12 months and as needed for moderate to severe unexplained

muscle symptoms. In addition to the FDA definition of myopathy, we will monitor by treatment group the frequency and severity of reported muscle symptoms and the frequency of CPK elevations with and without symptoms. These procedures will provide valid and important data regarding the occurrence and severity of myopathy. To insure participant safety, patients will be withdrawn from lipid-lowering therapy for CPK in excess of 10 times the upper limit of normal in the absence of symptoms or for CPK in excess of 5 times the upper limit of normal in the presence of symptoms. In addition, reductase inhibitor therapy will be avoided in participants who developed myositis while taking the fibrate placebo. This procedure should ensure that no one who was assigned to the fibrate placebo is rechallenged with a reductase inhibitor (the only active agent for the participant).

As described in Section 3.3.b, participants in the lipid trial will have serum creatinine measured at baseline and at least every four months thereafter. The starting dose of masked fenofibrate/placebo medication will be determined by the calculated glomerular filtration rate (GFR) using the baseline serum creatinine level and the abbreviated MDRD equation (Levey 2003). Those participants with a baseline GFR $\geq$50 ml/min/1.73m^2 will begin at a starting dose of 160 mg of fenofibrate or identical placebo tablet. Those with a calculated GFR between 30 and <50 will start at the reduced dose of 54mg/day fenofibrate or placebo. If the participant had started on the 160 mg dose of the masked medication, this dose will be down-titrated if the participant's estimated follow-up GFR falls between 30 and <50 mL/min/1.73m^2 on two consecutive measurements taken four months apart. Participants with GFRs in this range will receive either 54 mg/day of fenofibrate or matching placebo. If the estimated GFR falls below 30 mL/min/1.73m^2 at any time, the Coordinating Center will notify the clinic site that a confirmatory blood draw for repeat estimated GFR will be required within 2 weeks. If the confirmatory estimated GFR is below 30 mL/min/1.73m^2, the masked study medication will be permanently discontinued, regardless of fenofibrate or placebo assignment.

If necessary, the study physician may at his/her discretion reduce or stop administration of any study drug. Depending on the situation, the change may be temporary or permanent. Situations that may require temporary reduction or elimination of a study medication include: worsening congestive heart failure, acute myocardial infarction, severe hypoglycemia episodes, and other illnesses. Events that may require permanent cessation of a study drug include: jaundice, myopathy, other adverse drug reaction, need for active therapy with closely related compounds, cardiac transplantation, repeated severe hypoglycemia episodes, other conditions, and participant request.

4.4   Unmasking Procedure for the Fibrate/Placebo Intervention

In some special circumstances (e.g., a medical emergency), a patient's assigned fibrate/placebo treatment group may need to be revealed. If the request to unmask comes from a physician unfamiliar with the patient (e.g., emergency medicine department), the caller will be referred to that participant's ACCORD physician or site coordinator to discuss the relevant medical issues. If appropriate, an effort will be made to maintain the blinding of the patient and the ACCORD staff.

The ACCORD Drug Distribution Center (DDC) will be contacted for the purpose of unmasking a participant's therapy. The telephone number is (505) 248-3203 and it is available 24 hours a day (answering service after hours). The caller should state that he/she is calling in reference to the ACCORD trial. The appropriate DDC personnel will be contacted to respond to the call. They will record the participant's ACCORD I.D. number, name of physician requesting code break and reason the unmasking is necessary.

The DDC must have either the participant's I.D. number or fibrate/placebo bottle number in order to access the patient's therapy (active drug or placebo). Any unmasking done by the DDC will be reported immediately to the Clinical Site investigator or coordinator for inclusion in the patient's ACCORD medical record. The CCN PI, Project Office and Coordinating Center will also be notified of any unmasking that occurred, although the clinic staff should remain masked if possible.

4.5   The Elements of Informed Consent

Consent to participate in a research study includes the elements listed below. The ACCORD consent process will include all elements. (A model informed consent document is in Appendix I).

- Participants must be advised that the study involves research. Staff must explain the purposes of the research, the expected duration of participation, and a description of the procedures to be followed, including identification of experimental procedures.

- Anticipated benefits of the trial must be explained to the participant.

- Attendant discomforts and risks "reasonably to be expected" must be described.

- Appropriate alternative procedures that might be advantageous for the participant must be disclosed.

- The extent, if any, to which confidentiality of records identifying the participant will be maintained must be described.

- Prospective participants must be advised of the availability or non-availability of medical treatment or compensation for physical injuries incurred as a result of participation in the study, and if available, what they consist of, or where further information can be obtained.

- Persons responsible for the study must explain whom a participant can contact for answers to pertinent questions about the research and his or her rights, and whom to contact in the event of a research-related injury.

- Participants must be told that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled,

and the participant may discontinue participation at any time without penalty or loss of benefits to which he or she is otherwise entitled.

4.6   Confidentiality

The confidentiality of all participant information (including but not limited to any genetic analysis) must be protected at the Clinical Sites, the Clinical Center Networks, and the Coordinating Center. Paper records and computer files must be appropriately safeguarded from unauthorized access.

Paper records for study participants will be stored at the Clinical Sites. Copies of signed informed consents and records pertaining to SAEs and study-defined clinical events, including necessary medical records, will be stored at the Coordinating Center. These records will receive the same care as would ordinary medical records. They will be stored in locked filing cabinets and/or filing rooms within secure office space. Only study personnel who have completed ACCORD training in data handling will have access to study forms.

Similar care will be used in the handling of the computer records of study data stored at each Clinical Site. Access to the data in the local ACCORD database will be controlled by a system of user identification names and passwords. Each Clinical Site staff member must complete the ACCORD data handling training program before being given an ID and password to use the data system. The privileges allowed to each ID can be individually specified by the local Clinic Coordinator. All passwords stored within the system will be encrypted using Secure Socket Layer (SSL) encryption.

Confidentiality of information within the Coordinating Center will be protected through a variety of procedures and facilities:

1. The confidential nature of the data collected, processed, and stored at the Coordinating Center is explained to all new personnel, who must sign a confidentiality certification after discussion with their supervisor.

2. All access to Coordinating Center office space containing data is controlled through a single door, which is locked with a keypunch lock. This door remains locked at all times.

3. All participant data sent to the Coordinating Center is encrypted as described above.

4. All participant data stored on the Wake Forest University's mainframe computers are likewise encrypted. In addition, all such databases are protected by passwords that must be supplied before the data can be accessed. Passwords are released only to Coordinating Center staff with a need to use the particular file, and are changed on a regular schedule.

5. All printouts, plots, and reports containing individually identifiable data are produced on printers and plotters within the Coordinating Center's secure office space. All such reports are kept in locked storage cabinets within the Coordinating Center.

6. No participant identifiers will be present on any data for files transmitted to the Data and Safety Monitoring Board or the sponsor.

4.7   Vanguard Participants

The Vanguard Phase participants will be asked to provide consent to be treated and followed according to this revised main trial protocol.

Chapter 5
Clinical Outcome Measures

5.0 Outcomes

This chapter describes the components of the ACCORD primary and secondary clinical outcomes. The cardiovascular disease (CVD) events occurring during follow-up will be classified by a Working Group of the Morbidity and Mortality subcommittee.

5.1 Primary (Macrovascular) Outcome

The primary endpoint for ACCORD is the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Cardiovascular deaths are defined in Section 5.1.a, myocardial infarctions are defined in Section 5.1.b, and strokes are defined in Section 5.1.c

5.1.a Cardiovascular Death

5.1.a.1 <u>Unexpected death:</u> Unexpected death presumed to be due to ischemic cardiovascular disease, occurring within 24 hours of the onset of symptoms without confirmation of cardiovascular disease, and without clinical or post mortem evidence of other etiology.

5.1.a.2 <u>Fatal Myocardial infarction (MI):</u> death within 7 days of the onset of documented MI (see 5.1.b).

5.1.a.3 <u>Congestive heart failure (CHF):</u> death due to clinical, radiological or postmortem evidence of CHF without clinical or postmortem evidence of an acute ischemic event (cardiogenic shock to be included).

5.1.a.4 <u>Death after invasive cardiovascular interventions:</u> death associated with the intervention, i.e., within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterization, arrhythmia ablation, angioplasty, atherectomy, stent deployment, or other invasive coronary or peripheral vascular intervention.

5.1.a.5 <u>Documented arrhythmia:</u> death due to bradyarrhythmias or tachyarrhythmias not associated with an acute cardiac ischemic event.

5.1.a.6 <u>Death following non-cardiovascular surgery:</u> death due to cardiovascular causes as defined in 5.1.a.1-5.1.a.5, 5.1.a.7-5.1.a.8 within 30 days of surgery.

5.1.a.7 <u>Stroke:</u> death due to stroke occurring within 7 days of the signs and symptoms of a stroke (see 5.1.c).

5.1.a.8 <u>Other cardiovascular diseases:</u> death due to other vascular diseases including pulmonary emboli and abdominal aortic aneurysm rupture.

5.1.a.9 <u>Presumed cardiovascular death:</u> Suspicion of cardiovascular death with supporting clinical evidence that may not fulfill criteria otherwise stated. Example: Patient admitted with typical chest pain of 3 hours duration and treated as an MI, but without ECG and enzymatic documentation to meet usual criteria.

5.1.b Myocardial Infarction

The definitions for MI are presented below. If necessary for a definition, prolonged ischemic symptoms must last 20 minutes, and the cardiac enzymes of interest are Troponin T or I and/or serum CK-MB mass. Silent MIs will be identified by the ACCORD ECG Reading Center.

5.1.b.1 <u>Q-wave MI:</u> Diagnosis based on the occurrence of a compatible clinical syndrome with prolonged ischemic symptoms, associated with the development of new significant Q waves (defined in the ECG Reading Center Manual of Procedures). Diagnostic elevation of cardiac enzymes will include: increase in CK-MB mass to a level > twice the upper limit of normal, and/or and increase in Troponin T or I to a level that indicates myonecrosis in the laboratory performing the study.

5.1.b.2 <u>Non Q-wave MI:</u> Diagnosis based on the occurrence of a compatible clinical syndrome with prolonged ischemic symptoms, associated with elevation of serum enzymes, as for Q-wave MI. Only in the case that both Troponin and CK-MB mass measurements are not available, would the elevation of total CK to $\geq$ twice the upper limit of normal qualify for diagnosis.

5.1.b.3 <u>Silent (unrecognized) MI:</u> development of new significant Q waves without other evidence of myocardial infarction (the date of event will be assigned halfway between the date of discovery and last normal ECG).

5.1.b.4 <u>Probable non Q-wave MI:</u> Diagnosis based on the occurrence of a compatible clinical syndrome with prolonged ischemic symptoms, without documentation of cardiac enzyme elevation, but associated with the development of new and persistent significant ST-T changes (>24 hr in duration). (Changes are defined in the ECG Reading Center Manual of Procedures).

5.1.b.5 <u>MI after cardiovascular invasive interventions</u> Diagnosis based upon the occurrence of CK-MB (or Troponin) elevations to a level increased 3-5 times normal for the laboratory performing the studies, occurring within 7 days of cardiac catheterization, arrhythmia ablation, angioplasty, atherectomy, stent deployment or other invasive coronary, carotid or peripheral vascular intervention.

5.1.b.6 <u>MI after coronary bypass graft surgery</u>: Diagnosis based upon the occurrence of CK-MB (or Troponin) elevations to a level increased $\geq$ 5-10 times normal for the laboratory performing the studies, occurring within 30 days of cardiac surgery.

5.1.b.7 <u>MI after non-cardiovascular surgery:</u> MI (as defined above, occurring within 30 days of non-cardiovascular surgery.

5.1.c Stroke

5.1.c.1 <u>Definite ischemic stroke:</u> CT or MRI scan within 14 days of onset of a focal neurological deficit lasting more than 24 hours with evidence of brain infarction (mottled cerebral pattern or decreased density in a compatible location), no intraparenchymal hemorrhage by CT/MRI, no significant blood in the subarachnoid space by CT/MRI or by lumbar puncture, or autopsy confirmation. A nonvascular etiology must be absent.

5.1.c.2 <u>Definite primary intracerebral hemorrhage:</u> Focal neurological deficit lasting more than 24 hours. Confirmation of intraparenchymal hemorrhage in a compatible location with CT/MRI scan within 14 days of the deficit onset, or at autopsy, or by lumbar puncture.

5.1.c.3 <u>Subarachnoid hemorrhage:</u> Sudden onset of a headache, neck stiffness, loss of consciousness. There may be a focal neurological deficit, but neck stiffness is more prominent. Blood in the subarachnoid space by CT/MRI or lumbar puncture or intraventricular by CT/MRI.

5.1.c.4 <u>Stroke of unknown type etiology:</u> Definite stroke of unknown etiology when CT, MRI, or autopsy are not done. Information is inadequate to diagnose ischemic (infarction), intracerebral hemorrhage, or subarachnoid hemorrhage.

5.1.c.5 <u>Non-fatal stroke after cardiovascular invasive interventions:</u> stroke (as defined in 5.1.c.1-5.1.c.4) associated to the intervention within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterization, arrhythmia ablation, angioplasty, atherectomy, stent deployment or other invasive coronary or peripheral vascular interventions.

5.1.c.6 <u>Non-fatal stroke post non-cardiovascular surgery:</u> stroke (as defined in 5.1.c.1-5.1.c.4) occurring within 30 days of non-cardiovascular surgery.

5.2 Secondary Outcomes

The secondary endpoints for ACCORD are as follows. (See Section 7.1.b for the intervention-specific secondary hypotheses.)

- An expanded macrovascular outcome, specifically the combination of the primary endpoint plus any revascularization (defined in Section 5.3.a) plus hospitalization for congestive heart failure (defined in Section 5.3.b)
- Total mortality

- Cardiovascular mortality
- Major coronary heart disease event, specifically fatal events (defined in Section 5.1.a.1 through 5.1.a.6 and 5.1.a.8 through 5.1.a.9), nonfatal myocardial infarction (defined in Section 5.1.b), and unstable angina (defined in Section 5.3.c).
- Total stroke, specifically fatal strokes (defined in Section 5.1.a.7) and nonfatal strokes (defined in Section 5.1.c).
- Congestive Heart Failure Death (defined in Section 5.1.a.3) or Hospitalization for Congestive Heart Failure (with documented clinical and radiological evidence)
- Health-related quality of life (see Chapter 6)
- Cost-effectiveness (see Chapter 6)
- The main microvascular outcome of the ACCORD study is the primary outcome of the ACCORD Eye Substudy, namely: "the combined outcome of progression of diabetic retinopathy of at least 3 stages on the ETDRS scale, photocoagulation, or vitrectomy for diabetic retinopathy". This substudy will only take place in approximately half of the ACCORD study population.
- A second composite microvascular endpoint will be examined in the entire ACCORD population: fatal or non-fatal renal failure (as defined in 5.4.a.3) or retinal photocoagulation or vitrectomy for diabetic retinopathy. This endpoint essentially replicates the composite microvascular endpoint in the UKPDS.

5.3   Other ACCORD Outcomes

5.3.a   All cardiovascular revascularization procedures, including:
- PTCA (balloon)
- PTCA with stent
- CABG
- Carotid angioplasty with stent
- Carotid endarterectomy
- Peripheral angioplasty with or without stent
- Peripheral vascular surgery (including aortic aneurysm repair)
- Limb amputation: including partial or digit amputation due to vascular disease.

5.3.b   Unstable angina: new onset exertional angina, accelerated or rest angina, or both, and at least 1 of the following (Downs 1998):
   a) at least 1-mm ST segment deviation and reversible defect on stress perfusion study, or
   b) angiographic findings of at least 90% epicardial coronary artery or at least 50% stenosis in the left main coronary artery, or
   c) at least 1-mm ST segment deviation with pain on ECG stress testing and/or rest ECG and evidence of at least 50% stenosis in a major epicardial coronary artery.

5.3.c   Total cancer mortality, including:
- Primary site of cancer is gastrointestinal
- Primary site of cancer is lung.
- Primary site of cancer is breast
- Primary site of cancer is prostate.

- Primary site of cancer is brain.
- Primary site of cancer is 'other'
- Primary site of cancer is multi site.
- Primary site of cancer is genito-urinary.

5.4 Microvascular Outcomes

5.4.a   Development of nephropathy
  5.4.a.1 Doubling of serum creatinine or a 20 ml/min/1.73m^2 decrease in estimated glomerular filtration (GFR) as estimated by the MDRD equation (GFR = 186 x (serum creatinine in mg/dl)$^{-1.154}$ x (age in years)$^{-0.203}$ x 0.742 in females x 1.210 in African-Americans
  5.4.a.2 Development of macroalbuminuria (albumin/creatinine ratio $\geq$ 300 mg albumin per gram creatinine in random urine sample)
  5.4.a.3 Development of renal failure as defined by renal transplantation or initiation of dialysis or a rise in serum creatinine > 3.3 mg/dl in the absence of an acute reversible cause
  5.4.a.4 Composite nephropathy outcome (any of the three above-named outcomes)
  5.4.a.5 Development of microalbuminuria (albumin/creatinine ratio $\geq$ 30 mg albumin per gram creatinine in a random urine sample)

5.4.b   Development of diabetic eye complication
  5.4.b.1 Use of retinal photocoagulation or vitrectomy for diabetic retinopathy
  5.4.b.2 Cataract extraction
  5.4.b.3 Three-line change in visual acuity using Log MAR visual acuity chart
  5.4.b.4 Severe vision loss due to diabetes (<5/200)

5.4.c   Development of diabetic neuropathy
  5.4.c.1 Scoring > 2.5 on the Michigan Neuropathy Screening Instrument (this is a composite neuropathy endpoint employed in the DCCT study)
  5.4.c.2 Loss of vibratory sensation (128 Hz tuning fork)
  5.4.c.3 Loss of ankle jerk during Jendrassic maneuver
  5.4.c.4 Loss of pressure sensation (monofilament with 10 gram force)

Chapter 6
Health-Related Quality of Life/
Cost-Effectiveness Outcome Measures

6.1   Hypotheses

6.1.a. Health-Related Quality of Life (HRQL) Hypotheses

6.1.a.1 Primary HRQL Hypotheses (Main Effects Comparisons)

(1) Intensive control of blood glucose compared with less intensive control in patients with diabetes will:

   a) decrease symptoms and side effects as assessed by the *Symptoms Distress In Diabetes Questionnaire*.
   b) decrease symptoms and disability associated with cardiovascular events as assessed by the *SF-36v2* and the *Health Utilities Index III*.
   c) improve self-reported treatment satisfaction (and consequently treatment adherence and drop-outs) as assessed by the *Diabetes Treatment Satisfaction Questionnaire* (DTSQ).

(2) Treatment of lipids with statins and fibrates (to lower LDL-C and triglycerides and raise HDL-C) compared with treatment of lipids with statins alone (to lower LDL-C) will:

   a) decrease symptoms and side effects as assessed by the *Symptoms Distress In Diabetes Questionnaire*.
   b) decrease symptoms and disability associated with cardiovascular events as assessed by the *SF-36v2* and the *Health Utilities Index III*.
   c) improve self-reported treatment satisfaction (and consequently treatment adherence and drop-outs) as assessed by the *Diabetes Treatment Satisfaction Questionnaire* (DTSQ).

(3) Intensive control of blood pressure compared with less intensive control in patients with diabetes will:

   a) decrease symptoms and side effects as assessed by the *Symptoms Distress In Diabetes Questionnaire*.
   b) decrease symptoms and disability associated with cardiovascular events as assessed by the *SF-36v2* and the *Health Utilities Index III*.
   c) improve self-reported treatment satisfaction (and consequently treatment adherence and drop-outs) as assessed by the *Diabetes Treatment Satisfaction Questionnaire* (DTSQ).

6.1.a.2 Secondary HRQL Hypotheses (Pair-wise "Reference Case" Comparisons)

(1) Intensive control of glucose and blood pressure, when compared to standard treatment for glucose and blood pressure, will:

a) decrease symptoms and side effects as assessed by the *Symptoms Distress In Diabetes Questionnaire*.
b) decrease symptoms and disability associated with cardiovascular events as assessed by the *SF-36v2* and the *Health Utilities Index III*.
c) improve self-reported treatment satisfaction (and consequently treatment adherence and drop-outs) as assessed by the *Diabetes Treatment Satisfaction Questionnaire* (DTSQ).

(2)   Intensive control of glucose and lipids (with fibrate) when compared to standard treatment for glucose and placebo will
a) decrease symptoms and side effects as assessed by the *Symptoms Distress In Diabetes Questionnaire*.
b) decrease symptoms and disability associated with cardiovascular events as assessed by the *SF-36v2 and the Health Utilities Index III*.
c) improve self-reported treatment satisfaction (and consequently treatment adherence and drop-outs) as assessed by the Diabetes Treatment Satisfaction Questionnaire (DTSQ).

6.1.a.3 Event-Related HRQL [Feeling Thermometer (FT)] Hypotheses

(1)   Participants experiencing cardiovascular events in the preceding 4 months will show greater declines in feeling thermometer (pre-post) ratings than those who do not experience events.

(2)   Participants experiencing ≥3 hypoglycemic episodes in the preceding 4 months will show greater declines in feeling thermometer ratings than those without hypoglycemic episodes

(3)   Participants in the intensive glucose control group will show more rapid recovery of feeling thermometer ratings after cardiovascular events than those participants in the standard glucose control group

6.1.b. Cost-Effectiveness Hypotheses

6.1.b.1 Primary Cost-Effectiveness Hypotheses (Main Effects Comparisons)

(1)   The incremental cost effectiveness ratio of intensive control of blood glucose, in the presence of lipid therapy or blood pressure control, will not be larger than the maximum acceptable "ceiling" level of the cost per cardiovascular disease free year gained and cost per quality adjusted life-year (QALY) gained when compared to less intensive control.

(2)   The incremental cost effectiveness ratio of intensive lipid treatment (adding a fibrate to a statin), in the presence of control of glucose, will not be larger than the maximum acceptable "ceiling" level of the cost per cardiovascular disease free year gained and cost per quality adjusted life-year (QALY) gained when compared to less intensive control.

(3)   The incremental cost effectiveness ratio of intensive blood pressure control, in the presence of control of glucose, will not be larger than the maximum acceptable "ceiling" level of the cost per cardiovascular disease free year gained and cost per quality adjusted life-year (QALY) gained when compared to less intensive control.

6.1.b.2 Secondary Cost-Effectiveness Hypotheses (Pair-wise "Reference Case" Comparisons)

(1)   The incremental cost effectiveness ratio of intensive control of blood glucose and blood pressure will not be larger than the maximum acceptable "ceiling" level of the cost per cardiovascular disease free year gained and cost per quality adjusted life-year (QALY) gained when compared to standard treatment for glucose and blood pressure.

(2)   The incremental cost effectiveness ratio of intensive control of blood glucose and lipids (with fibrate) will not be larger than the maximum acceptable "ceiling" level of the cost per cardiovascular disease free year gained and cost per quality adjusted life-year (QALY) gained when compared to standard treatment for glucose and placebo.

6.2 Health-Related Quality of Life (HRQL)

6.2.a Rationale

HRQL measurement is a key means of determining the value of ACCORD interventions and outcomes from the patient's point of view. While mortality reduction is a secondary outcome in ACCORD, all other outcome measures concern nonfatal health outcomes. HRQL assessment enables an assessment of the relative importance of these various outcomes (from amputation to cognitive impairment) to the patients themselves. HRQL assessment provides an understanding of the balance between the burdens and benefits of intensive glucose and lipid control, and intensive glucose and blood pressure control from the patient's point of view. HRQL information should also provide valuable insight into adherence results and into the practicality of clinically implementing these interventions after the trial is over. Assessment of HRQL in ACCORD is designed to study treatment effects from the patient's point of view concerning: 1) short term symptoms and 2) longer-term rates of macrovascular and microvascular events.

The ACCORD HRQL instruments were selected based upon the following criteria: 1) brevity, 2) inclusion of the major dimensions shown in the literature to be affected by diabetes and its treatment, 3) proven responsiveness to treatment-related changes, and 4) appropriateness for the age range in ACCORD and ethnic diversity of type 2 diabetic patients. For these purposes, specific symptoms distress measures, generic health status, and depression measures were chosen.

6.2.b   Health Related Quality of Life (HRQL)

The HRQL measures will be administered to a random sample of 250 participants in each cell of the 8 ACCORD treatment groups (2000 participants in total) at 0, 12, 36 and 48 months. This sample of 2000 participants will be nested within the larger random sample of 4288

participants participating within the cost effectiveness assessment substudy (described in Section 6.3).

General health status will be measured by the self-administered SF-36v2. This is the most widely used general health status measure with extensive validation and population norms available. It allows comparison of the ACCORD population with those of other studies and other chronic diseases. Eight scale scores will be generated in the following domains: general health, physical function, role-physical, role-emotional, vitality, social function, mental health, and pain. It can also be scored in terms of physical health and mental health component scores. The SF-36v2 offers expanded response options on the role function items, offering greater sensitivity in this area.

The Symptom Distress In Diabetes Questionnaire developed by Testa and colleagues (1993,1994 Phase V Technologies) will be used. This self-administered instrument has been shown to be responsive to improved glycemic control in a randomized, double-masked placebo-controlled clinical trial of diet and either 5 or 20 mg of glipizide (Testa 1998). Based upon existing data and item pools, a 60-item version of this instrument has been developed for ACCORD by eliminating questions while maintaining internal consistency. Furthermore, a 7-item diabetes-specific treatment satisfaction measure (validated in previous trials) will be used to assess the impact of intensive treatment.

Due to its documented relation with cardiovascular events and glycemic control, clinical depression will also be measured. The 9-item depression measure from the Patient Health Questionnaire (PHQ) will be used. The PHQ is the self-report version of the PRIME-MD, a well-validated psychiatric diagnostic interview for use in primary care settings. The PHQ depression measure offers the briefest measure that provides diagnostic information, severity information, and responsiveness to depression treatment.

Effect sizes on the Symptom Distress Measure ranged from 0.6 to 0.2 SD units in the glipizide trial. There is evidence from previous treatment trials that hypoglycemic, lipid-lowering, and anti-hypertensive drug effects and their reflection in patient-rated HRQL will show non-additive properties. Therefore, it is of interest to compare individual cells receiving different combinations of interventions, rather than just marginal effects of each intervention. To allow us to address possible non-additive treatment effects, a sample of participants randomized to each 2x2 trial will be assessed for HRQL. Sample size calculations used an ANOVA model and assumed similar treatment effects within each trial (glycemic plus lipid or glycemic plus blood pressure). To detect a 0.3 SD difference between the group that receives intensive therapies and the group that receives no intensive therapies, an estimated 250 participants per group would provide approximately 90% power. The total sample size would thus be 2000 of the 10,000 randomized participants (=250 X 8 treatment groups).

6.2.c Health State Utility Measure

If cost-effectiveness analyses are going to include the patient's perspective they must assess the value or utility of the patient's health state. Interviews such as the standard gamble or time trade-off generate utilities from the study patients themselves. The use of either approach

will be burdensome in ACCORD. Therefore the most valid alternative is to use a measure with previously derived population-based utility values.

The Health Utilities Index (HUI), is one such measure, and will be used to assess health state utility. The HUI is a general HRQL measure which includes a health-status classification system and a preference-based scoring formula. The HUI Mark 3 (HUI3) has eight attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain) with five to six levels per attribute. With the recent release of a multiplicative multi-attribute utility function for the HUI3 system, users are now able to generate utility scores for HUI3 health states. The HUI3 scoring function is based on preference measurements obtained from a random sample of the general population (>16 years of age) in Hamilton, Ontario, Canada. There is a high level of agreement between directly measured utility scores for HUI3 health states and scores obtained using the multiplicative function.

The HUI is a self-administered 15-item instrument that takes approximately 8 minutes to complete. It will be administered to the full ACCORD sample at the same intervals as the HRQL instrument is administered to the sub-sample. The measurement intervals are at 0, 12, 36, 48 months and study exit. This is important for the following reasons. First, it allows the sub-samples assessed for HRQL and the sub-samples assessed for cost effectiveness to be linked in analysis. Second, it allows for detection of the HRQL effects of diabetes complications occurring in a minority of ACCORD participants, which requires a large sample size. Third, it allows the calculation of valid incremental cost-utility scores for the various intensities of treatments to be tested in ACCORD.

6.2.d Event-Related HRQL

Patients eventually accommodate to most decrements in health status. In the HRQL literature, this has been referred to as "response shift." In order to capture the effect of events (such as MI, hospitalization or side-effects prompting medication discontinuation or drop-out) close to the time when they occur, the single-item "feeling thermometer" from the EUROQOL instrument will be used as part of the Interval History Form (every four months) for the full sample. This asks patients to rate their health state from 0 (worst imaginable health state) to 100 (best imaginable health state). Through selection of various events already recorded in the ACCORD database and an appropriate control group, the HRQL change related to many different kinds of events can be assessed using this single item.

6.3 Cost Effectiveness Assessment

6.3.a Rationale

For this trial, the economic research questions are: 1) is the intensive glycemic therapy more cost-effective than the standard glycemic therapy? 2) is the intensive lipid-lowering therapy more cost-effective than standard lipid-lowering therapy? 3) is the intensive hypertension therapy more cost-effective than standard hypertension therapy? and 4) is the intensive glycemic therapy in combination with intensive blood pressure therapy or intensive glycemic therapy in

combination with intensive lipid therapy more cost-effective than the standard therapy? These questions will be addressed by conducting incremental cost-effective analyses in which the net costs and net effectiveness of intensive therapy defined by the main trial to standard therapy will be calculated and expressed as a series of ratios. The perspective of this economic evaluation will be a single payer of national health care system.

6.3.b Effectiveness

The primary endpoints defined by the main trial are considered as primary outcome measures for this economic evaluation. Three primary effectiveness measures are identified and include: 1) CVD free-year gained, 2) life-year gained and 3) quality-adjusted life-year (QALY) gained. CVD free-year is defined as time until first occurrence of CVD endpoints. The measure of life-year gained is determined by the difference in number of life–years between intensive therapy and standard therapy. QALY's will be calculated using utility values derived from the HUI-3.

The cost effectiveness sample will comprise a total of 4,288 randomly selected participants from the ACCORD study population.

6.3.c Resources

Therapies are conceptualized as having three stages: 1) initiation of the therapy, 2) monitoring and maintenance of the ongoing therapy, and 3) treatment of side effects and complications.

Resources consumed will be classified into the following categories: 1) initiation of the therapy; 2) maintenance of the ongoing therapy, ambulatory services, and diabetes supplies; 3) inpatient services.

6.3.d Costs

Under the perspective of a national health care system, all direct medical costs associated with treatment of Type 2 diabetes and its complications and costs for treating adverse effects of the therapy will be considered. These costs will include costs of inpatient care, outpatient care, medications, medical equipment, supplies, laboratory tests, overhead, labor, and fringe benefits. The participant's costs such as waiting time, transportation, lodging, and informal care arising from the disease will not be included. Likewise, opportunity costs of premature death, productivity loss, and long-term disability will not be considered in this study.

6.3.d.1 Cost Data Collection

To reduce the burden on data collection for economic analysis, data being collected from the main trial will be used to the extent possible. Much of the data such as primary endpoints and resources for the initial and the ongoing therapy will be routinely collected according to the design of the main trial. The following sections describe methods for use in the collection of medical resource consumption data, which are not collected by the main trial. In general, two

approaches will be used to collect these data: the case report form and use of administrative data systems, including HCFA, VA, HealthPartners, and the Canadian Health System.

6.3.d.2 Intensive and standard therapy

Labor and fringe benefits of providers, overhead and resource used for patient management, including telephone calls, letters, team meetings, and adherence activities, will be collected at clinic site level. The estimated allocation of these resources to each therapy per patient will be recorded on the Clinic Resource and Cost Questionnaire. Data on medications, tests, and medical supplies for the therapies will be derived from the main trial.

6.3.d.3 Inpatient Care

Data on hospitalization will be collected at the patient-level. Cost for hospital care represents a disproportionate share of direct medical costs (~70 to ~80%) and shows extreme variability. Therefore, it is important to collect hospitalization data from all CEA study patients in order to derive cost estimates with reasonably narrow confidence intervals. We will collect hospital admission data primarily using the hospitalization form and through available administrative data systems. Research staff at each clinic site will obtain a copy of the discharge summary for each hospital admission in patients who participate in the CEA and then send a copy of the discharge summary to the coordinating center. All study patients will be requested to consent to the release of their medical records when they participate in the study. The administrative claims data will be used to examine data quality since we are not able to obtain hospitalization data for all study patients through the administrative data systems. The time period for collection of hospitalization data by the hospitalization form is at each follow-up visit and by the administrative data system is every two years. A specially trained medical coder at the coordinating center will map diagnoses and procedures into DRGs.

6.3.d.4 Ambulatory Care

Use of ambulatory care services will be collected for all patients through self-reporting at each follow-up visit and recorded into the clinic follow-up questionnaire. The data include the number of clinic and/or physician office visits, the number of emergency room visits, and number and type of outpatient diagnostic tests and procedures. Data on medication use will be collected from the main trial.

6.3.d.5 Unit Cost

Primary and secondary data sources will be used to calculate unit costs of resources used to reflect the cost for consuming an itemized service. Unit cost of hospital stay will be based on Diagnosis-Related Group (DRG) of the Medicare. Unit costs for outpatient services, outpatient procedures, laboratory tests, and consultations will be estimated using HCFA Medicare data. The unit cost for physician services will be calculated using the Medicare Fee Schedule. The unit cost of labor and fringe benefits and equipment and supplies consumed in case management services will be assessed from secondary sources. The unit cost of medications will derive from average wholesale prices using the Medical Economics Data Red Book. The total cost of each

treatment is calculated by multiplying the quantity consumed of each type of resource by the unit cost. A discount rate of 5% will be used to adjust inflation over the study years.

6.3.e. Sample Size for Cost-Effectiveness

The sample size estimates are based on the following assumptions:

- Patients are randomized in a double 2 X 2 layout and each cell has the same expected sample size.
- The decision rule in any health care system is that the intensive treatment should be implemented instead of the standard treatment if the incremental cost-effectiveness ratio (ICER) of the intensive treatment is less than maximal willingness to pay for additional health effect (*Rc*).
- There is no correlation between cost and health effect.
- The test of interest is that the observed ICER derived from the trial is significantly less than the ceiling cost-effectiveness ratio, *Rc*.

We defined the observed ICER as a ratio of extra cost to additional CVD free-year gained comparing intensive treatment and standard treatment within the trial period. The following table contains sample size estimates for the main effect of each of the intervention using Briggs's method [Brigg and Gray, 1998; Brigg and Tambour, 1998]. These estimates are based on the results of UKPDS [UKPDS, 1998]. In the UKPDS study, the median duration of follow up was 8.4 years. The mean difference in time free from diabetes related end points including coronary heart disease, cerebrovascular disease, amputations, laser treatment for retinopathy, cataract extraction, renal failure and death, was 0.55 years. The median patient follow-up year in ACCORD is expected to be 5.6 years, which is 33% shorter than UKPDS. We assume mean difference in years free from CVDs would be 20% longer, that is, 0.66 (0.55+0.11) years in ACCORD because of more intensive therapy in at least two major CVD risk factors. In addition, we assume cost of treatment for type 2 diabetes in ACCORD is similar to UKPDS. The range of *Rc* values is chosen based on O'Brien's study [O'Brien, 1998]. The $30,000 represents the upper limit of ceiling cost-effectiveness ratio (*Rc*). The total sample size for the CEA component is 4288, that is, 536 in each cell. It has 80% power to test the null hypothesis: the observed ICER > *Rc* (=$15,000) at $\alpha=0.05$ level. All eligible patients will be randomly allocated to each cell through a multi-stage randomization process.

Table 6.1 Sample Size and Power of ACCORD CEA

Maximal willingness to pay for additional health effect (*Rc*).	**Power**		
	70%	**80%**	**90%**
$5,000	607	772	1033
$10,000	459	583	781
$15,000	422	**536**	718
$20,000	405	515	689
$25,000	396	503	673
$30,000	389	495	663

6.3.f   Data Analysis for Cost-Effectiveness

Two methods of cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) will be used in the economic evaluation. The ratios of cost to outcome derived from CEA/CUA are used to compare cost-effectiveness among treatment strategies.   An incremental cost-effectiveness ratio (ICER) will be calculated, which provides a summary of the cost-effectiveness of one intervention relative to the other.

The basic formula to calculate incremental CEA ratio and CUA ratio of a specific treatment A relative to the reference treatment B is presented as following:

$$ICER_{CEA} = \frac{(Mean\ Cost_{treatment\ A} - Mean\ Cost_{treatment\ B})}{(Mean\ Effect_{treatment\ A} - Mean\ Effect_{treatment\ B})}$$

$$ICER_{CUA} = \frac{(Mean\ Cost_{treatment\ A} - Mean\ Cost_{treatment\ B})}{(Mean\ QALY_{treatment\ A} - Mean\ QALY_{treatment\ B})}$$

The ratio of incremental cost to increment effectiveness represents cost-effectiveness of the specific treatment. This ratio is a point estimate. Bootstrap methods will be used to calculate confidence intervals for cost-effectiveness ratios.   In addition, sensitivity analyses will be performed in order to examine effects of key parameters on cost-effectiveness ratios.

Chapter 7
Statistical Considerations

7.1.   Design

ACCORD is designed with factors consisting of: intensive versus standard glycemic control, intensive versus standard blood pressure control, and in the presence of LDL-C lowering, fibrate versus placebo. All 10,000 participants will be randomized to the glycemic groups, and to either the blood pressure or lipid groups in two non-overlapping 2 X 2 layouts (Figure 1.2): 5800 participants will be randomized to the lipid groups and 4200 to the blood pressure groups. Throughout this chapter, a "+" will refer to the more intensive level of an intervention whereas a "-" will refer to the less intensive level.

The first year of recruitment, treatment, and follow-up was designated the Vanguard Phase of the trial. The specific goals of the Vanguard, which were used to judge its success, are described in Section 7.5. In this phase, 1184 participants were randomized over a 5-month period and then recruitment was suspended. Vanguard participants will have approximately 18 months of follow-up, on average, when randomization for the main trial begins. Approximately 8800 participants will be randomized during the main component of ACCORD study. Randomization for this phase will take place from January 2003 through June 2005. All participants (including the 1184 recruited in the Vanguard Period) will be treated and followed through June 2009. Thus, the length of follow-up in ACCORD will range from 4.0 to 8.4 years (approximate mean of 5.6 years).

Participants eligible for the lipid intervention but not the blood pressure intervention will be randomized to one of the four cells in the lipid and glycemic control 2 X 2 layout, and similarly for those eligible for the blood pressure intervention but not the lipid intervention. Participants eligible for both the lipid and the blood pressure interventions will be randomly assigned to one or the other trial. This random assignment will be weighted to ensure that the 4200 BP/5800 Lipid split is efficiently achieved. Data from the Vanguard portion of ACCORD indicates that 30% of participants will be eligible for both blood pressure and lipid interventions, 30% will be eligible for the lipid but not the blood pressure intervention, and 40% will be eligible for the blood pressure, but not the lipid intervention.

During the Vanguard period, all randomizations were stratified by clinical center network and baseline CVD status (either primary or secondary prevention) using permuted blocks. All randomizations for the main trial will be stratified by clinical site. The reason for the change to use clinical site rather than clinical center network and CVD status as stratification factors is to provide more balance in the types of participants seen within clinical sites. Improved balance should result in clinic personnel having more experience in following the protocol for ACCORD participants randomized to each of the eight possible conditions. With randomization of 10,000 participants, it is anticipated that there will be good balance related to CVD status without including this as a randomization factor.

7.1.a Primary Hypotheses

In middle-aged or older people with type 2 diabetes who are at high risk for having a cardiovascular disease (CVD) event:

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

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

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

Analyses of each of the primary hypotheses will be conducted within separate models as comparisons of the marginal effects and not as comparisons among the individual cells. All participants will be included in the analysis for the glycemia hypothesis. Each hypothesis will be tested using a 2-sided probability of Type 1 error = 0.05.

7.1.b   Secondary Hypotheses

Several secondary hypotheses will be tested for each of the glycemia, lipid and blood pressure hypotheses. The hypotheses are to determine whether more intensive treatment compared to standard treatment reduces the occurrence of:

1) an expanded macrovascular disease outcome, consisting of the primary outcome plus revascularization plus hospitalization for heart failure (defined in Section 5.2)
2)   total mortality
3) each of the separate components of the primary outcome
4) a composite microvascular disease outcome, including kidney and eye disease (defined in Section 5.2) (with neuropathy added for the glycemia trial)

These outcomes will be analyzed as comparisons of marginal effects. HRQL and cost-effectiveness are also examined as secondary outcomes and are described in Chapter 6.

7.1.c   Subgroup Hypotheses

The two subgroup hypotheses for the glycemia intervention are to determine if:

(1) Effects of glycemic control on the primary outcome are the same across baseline levels of HbA1c, and
(2) Effects of glycemic control on the primary outcome are independent of effects due to the blood pressure and lipid interventions.

The three subgroup hypotheses for the lipid intervention are to determine if the benefits of fibrate (in the context of desirable levels of LDL- C and good glycemic control) are:

(1) Equal across levels of LDL-C measured prior to initiation of fibrate therapy,
(2) Equal across HDL-C levels measured prior to initiation of fibrate therapy, and
(3) Equal across triglyceride levels measured prior to initiation of fibrate therapy.

Consistency of the effects for the glycemia, lipids, and blood pressure interventions will also be examined in subgroups defined by gender, age, race/ethnicity, and presence of clinical CVD at baseline (i.e., primary and secondary prevention participants), and the presence/absence of the other interventions.

7.2 Analysis Plan

7.2.a Plan for Primary Hypotheses

Intention to Treat -- Primary comparisons of intervention groups will be performed according to the intention-to-treat principle. All randomized participants in these analyses will be grouped according to their intervention assignment at randomization, regardless of adherence.

Analytical Techniques -- Separate models will be used to test the primary hypothesis associated with each intervention. The main comparisons of the intervention groups with respect to the distribution of time until first identification of a CVD endpoint (described in detail in Chapter 5) will be based on survival analysis methods. Failure time will be measured from the time of randomization.

To test each primary hypothesis, a proportional hazards model will be used (Cox 1972) incorporating adjustment for important factors specified below. This will be the primary analysis.

Glycemic Hypothesis: The glycemic hypothesis will be tested in all 10,000 randomized participants. The model to be fit will contain separate indicator variables that identify participants: (a) in the BP trial, (b) in the BP trial AND randomized to the BP(+) intervention, (c) in the lipid trial, (d) in the lipid trial AND randomized to fibrate(+), and (e) randomized to intense glycemic control. In addition to these variables, indicator variables will be included that identify: (f) secondary prevention participants, and (g) Clinical Center Networks. Our reasoning

for including term (f) is that secondary prevention participants should have higher event rates than primary prevention participants. Likewise, term (g) will be included because the clinical networks contain very different types of participants that may have different event rates. For example, the VA clinics will primarily consist of men. The main comparison in this model will be based on the chi-square statistic from a likelihood ratio test obtained from proportional hazards models with/without term (e).

Lipid Hypothesis: The lipid hypothesis will be tested in approximately 5800 participants. The model to be fit will contain terms (d), (e), (f) and (g). This hypothesis will be tested using a likelihood ratio test for models with/without term (d).

Blood Pressure Hypothesis: The blood pressure hypothesis will be tested in approximately 4200 participants. The model to be fit will contain terms (b), (e), (f) and (g). This hypothesis will be tested using a likelihood ratio test for models with/without term (b).

Kaplan-Meier (Kaplan & Meier 1958) estimates of survival will be obtained for the intervention and control groups for each hypothesis. Estimates for the proportion of participants who remain event free at pre-specified time points, and the associated confidence intervals, will be constructed (Peto 1977). The hazard functions will be assessed for proportionality using log/log plots of survival and Schoenfeld residuals. An unadjusted analysis (i.e., a log-rank test) will also be performed.

7.2.b Secondary Hypotheses

Testing each of the secondary hypotheses for glycemic, blood pressure and lipid control involves analysis of the time until the occurrence of a secondary outcome. The planned analyses for each of these outcomes will parallel the analyses performed for the primary outcome. Proportional hazards models containing the terms specified in the models presented in Section 7.2.a will be specified to test each of the secondary hypotheses. The one exception to this analysis plan will be exclusion of the term controlling for Clinical Center Networks.

7.2.c Subgroup Hypotheses

Testing each of the subgroup hypotheses will be carried out using survival analysis methods, as all subgroup hypotheses involve time until the occurrence of the primary outcome. For each subgroup hypothesis, the proportional hazards model used to address the primary hypotheses will serve as the base model to which additional terms will be added to test each subgroup hypothesis.

To address the glycemia subgroup hypothesis to determine if relative risks for the primary outcome are the same across levels of HbA1c, a term representing HbA1c levels will be entered into the proportional hazards model. A test of the interaction between this term and the term representing the glycemic intervention effect will address this initial subgroup hypothesis. To address the second glycemia subgroup hypothesis, whether the effects of glycemic control on the primary outcome are independent of effects due to the blood pressure and lipid interventions,

the significance of interactions between the terms representing each of the interventions will be investigated.

Each of the three subgroup hypotheses for the lipid intervention will also be investigated through the use of interaction terms in the proportional hazards model. In particular, these hypotheses will be investigated in three separate models by testing the significance of the interactions between the variable representing the fibrate intervention and variables characterizing: (1) baseline LDL-C levels, (2) baseline HDL-C levels, and (3) baseline triglyceride levels.

Finally, consistency of effect in demographic and primary/secondary prevention participants, and in the separate 2 X 2 trials, will be tested by stratified analyses and by investigating the significance of the interaction between the variable representing the intervention and variables characterizing subgroup membership.

7.3 Power Considerations

7.3.a Summary

Given the assumptions presented below, the ACCORD study is designed to have:

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

7.3.b Computational Details and Sensitivity Analyses

As described below in Section 7.3.c, population event rates have been estimated from two major observational cohort studies conducted in the United States, (ARIC and CHS). The strategy for power calculations is to estimate cumulative event rates for each of the 8 cells of the design and then average the event rates for the "+" and "-" intervention cells appropriate for comparing the more and less intensive levels of the intervention (i.e., 4 cells with "+" versus 4 cells with"-" for glycemia, 2 cells with "+" versus 2 cells with "-" for fibrate, and 2 cells with "+" versus 2 cells with "-" for blood pressure control). Finally, a simple binomial power calculation was performed based on the two averaged event rates.

The difficult aspect of this calculation is estimation of the event rates in the two "control" cells where only less intensive interventions "-" are applied (e.g., the less intense BP and less intense glycemic interventions for participants in the BP and glycemic interventions). The strategy for estimating these control event rates is to use the ARIC and CHS data to select patients similar to those who meet the various eligibility criteria, calculate an event rate for the

selected patients, and then adjust this event rate to reflect differences between ARIC/CHS and ACCORD.

Assuming that 40% of participants will be secondary prevention and 60% will be primary prevention, then using the ARIC and CHS data, the annual population event rates are taken to be 6.56% among those who satisfy both the BP and lipid criteria and 5.60% among those eligible for the lipid intervention. Details of these calculations are deferred to the next section. As an approximation, we use the rate 6.56% for those randomized to the BP and glycemia 2 X 2, and the rate 5.60% for those randomized to the lipid and glycemia 2 X 2.

For the power computations, these rates are further adjusted by applying:

- 25% reduction in event rate due to healthy volunteer/background therapy effect in ACCORD,
- 18% reduction in event rate due to lowering HbA1c from the mean of 9.3% observed in ARIC/CHS to 7.5% in ACCORD (assuming a 1.5% reduction in HbA1c is associated with a 15% effect),
- 5% increase in event rate when silent MI is added because silent MI was not included in the ARIC and CHS rates,
- 1% reduction in event rate per 1 mg/dl drop in LDL-C from the mean of 120 mg/dl observed in ARIC and CHS.

As a result of placing all participants in the lipid and glycemia 2x2 on 20 mg of a statin, the mean LDL-C is assumed to be approximately 95 mg/dl for these ACCORD participants, and 125 mg/dl for participants enrolled in the BP and glycemia 2x2.

Based on these assumptions, event rates for the two cells involving less intensive interventions were calculated.

- Participants in the lipid trial and randomized to fibrate (-) and glycemia (-) have an estimated event rate of

$$5.6\% \times (1-0.25) \times (1-0.18) \times (1.05) \times (1-0.25) = 2.71\%.$$

- Participants in the blood pressure trial and randomized to blood pressure (-) and glycemia (-) have an estimated event rate of

$$6.56\% \times (1-0.25) \times (1-0.18) \times (1.05) \times (1+0.05) = 4.45\%.$$

For each of these rates, the rate expected after K years of follow-up was calculated using the formula $(1-(1-rate)^K)$. Vanguard participants will have a mean follow-up of approximately 8.2 years, whereas participants randomized in the main trial will have a mean follow-up of approximately 5.2 years. For each of the 8 cells in the design (Figure 1.2), the expected intervention effect was then applied to the above K-year rates to obtain the expected rate within the cell separately for Vanguard and main trial participants. Event rates contained in cells used to address each hypothesis were averaged by applying appropriate weights reflecting the number of participants randomized to each cell.

Power computations are based on having 10,000 participants in the glycemia intervention, 5800 in the lipid intervention, and 4200 participants in the blood pressure intervention, and assume that the main trial will enroll 40% secondary prevention participants. The Vanguard period had approximately 35% secondary prevention participants. The power is computed based on effect sizes of 14.7% (12% for Vanguard participants and 15% for main trial participants) for the glycemia intervention and 20% for the lipid and BP interventions, with adjustments of the main effects for attenuation attributable to the factorial design (i.e., assume that each intervention has the anticipated treatment effect). Type I error is set at 0.05 for each of the three primary hypothesis.

Power for each intervention in ACCORD is presented in Table 7.1.

Table 7.1 Power for ACCORD Trial

	Glycemia	Lipid	Blood Pressure
Power	89	87	94

Sensitivity analyses were also performed to determine how the mixture of primary/secondary prevention participants recruited during the ACCORD main trial would affect the power for each intervention. In Table 7.2, underlying assumed annual event rates and associated power are provided for assumptions of 65%, 60%, 55%, or 50% main trial primary prevention participants. Note that the 60% primary prevention assumption corresponds to the power calculations presented in Table 7.1.

Table 7.2. Sensitivity of Power to Percentage Mix of Secondary Prevention Participants

(Assuming mean LDL-C=95 mg/dl in participants in lipid intervention
and 125 mg/dl in participants not in lipid intervention)

% Primary in Main Trial	Annual Event Rates in Cells Defined By Glycemia (-)*		Power		
	BP (-)	Fibrate (-)	Glycemia	Lipid	BP
0.65	0.0428	0.0259	0.88	0.85	0.93
0.60	0.0443	0.0270	0.89	0.87	0.94
0.55	0.0458	0.0281	0.90	0.88	0.94
0.50	0.0472	0.0291	0.91	0.89	0.95

Two additional sensitivity analyses were undertaken. The first investigated the power for the glycemia intervention if the lipid and BP interventions did not work. In this situation, ACCORD has greater than 92% power for the glycemia hypothesis under each of the primary/secondary mixtures presented in Table 7.2. In addition, the power was estimated if the use of 20 mg of a statin resulted in a 20% reduction in the ARIC/CHS rates rather than the 25% assumed in Table 7.2. The effect of this changed assumption was to increase the glycemia power by 1% and the lipid power by 2% in each row of Table 7.2.

7.3.c Details of Estimation of Event Rates In ARIC and CHS

The Atherosclerosis Risk in Communities (ARIC) study is a population-based study of cardiovascular disease and atherosclerosis in 15,792 middle-aged men and women from 4 U.S. communities. Participants were 45-65 years old at the time of the baseline examination, which was conducted between 1987 and 1989. Participants have been contacted annually by phone since their baseline exam to obtain information regarding hospitalizations and cardiovascular events, which were subsequently validated by medical record review. Three follow-up examinations were conducted at 3-yr intervals between 1990 and 1998.

The Cardiovascular Health Study (CHS) is also a population based study of risk factors for cardiovascular and cerebrovascular disease in elderly men and women from four U.S. communities. The cohort consisted of 5,201 community-dwelling adults aged 65 years or older who had a baseline clinic visit in 1989-1990 (original cohort) and an additional 687 African-American adults aged 65 years or older who had a baseline clinic visit in 1992-1993 (new cohort). Incident CVD events, including myocardial infarction (MI), stroke, transient ischemic attack (TIA), and death, were identified by 6-month telephone calls and annual clinic visits. Further verification was done by the CHS Events Subcommittee, using Medicare Part A hospital discharge lists, hospital records, outpatient records, and physician reports.

ARIC and CHS data were used to determine the event rates that would be found among age-eligible diabetic participants. Secondary prevention participants were defined as those who had a history of MI, stroke or revascularization. Primary + RF participants were defined as non-secondary participants who were either current smokers, or met the ACCORD definitions for HDL-C and ABI risk factor criteria. Further exclusion criteria that were applied to define the sample were: age=>55 years, 7.5%<=HbA1c<=11%, LDL-C<=170 mg/dl, Trig<150mg/dl. For these computations, the ACCORD lipid and blood pressure selection criteria were applied to the primary and secondary prevention participants. HbA1c data were not available. For the HbA1c criterion, Fasting plasma glucose (FPG) was required to be < 216 and > 140 mg/dl. The upper limit was obtained through use of the regression equation from Avignon (1997). That paper gave a formula correlating HbA1c and FPG from linear regression: $y = 17.0x + 29.1$, $r = 0.62$ where y=FPG and x=HbA1c, so HbA1c = (FPG - 29.1)/17. Table 7.3 contains a summary of yearly event rates estimated from CHS and ARIC after applying the exclusion criteria. An event was defined as the occurrence of fatal CHD or fatal/non-fatal stroke or myocardial infarction. Averaging results from the two studies with equal weight, the event rate is estimated to be approximately 3.6% per year in primary + RF participants and 8.6% per year in secondary prevention participants.

Table 7.4 presents similar statistics to Table 7.3, except in this table systolic blood pressure was restricted to be between 130 and 170. Overall, the event rate is estimated to be approximately 4.6% per year in primary + RF participants and 9.5% per year in secondary prevention participants.

Table 7.3 Event Rates From CHS and ARIC
After Application of Lipid and HbA1c Selection Criteria

	Rate per year	Mean Age (years)	Mean LDL-C (mg/dl)	Mean SBP (mm Hg)	Mean HbAlc Based on FPG (%)
CHS					
Secondary	12.1%	73	113	137	8.3
Primary + RF	5.0%	72	116	139	9.1
ARIC					
Secondary	5.0%	61	129	130	9.8
Primary + RF	2.1%	60	127	129	9.7
Total					
Secondary	8.6%*	67	121	134	9.1
Primary + RF	3.6%*	66	121	134	9.4

* 0.4 x 8.6% + 0.6 x 3.6% = 5.6% (see Section 7.3.b)

Table 7.4 Event Rates From CHS and ARIC
After Application of Lipid, BP and HbA1c Selection Criteria

	Rate per year	Mean Age (years)	Mean LDL-C (mg/dl)	Mean SBP (mm Hg)	Mean HbAlc Based on FPG (%)
CHS					
Secondary	13.6%	73	115	146	8.4
Primary + RF	6.3%	74	118	146	9.7
ARIC					
Secondary	5.4%	61	135	144	9.2
Primary + RF	2.8%	61	126	143	10.1
Total					
Secondary	9.5%**	67	125	145	8.8
Primary + RF	4.6%**	68	122	145	9.9

** 0.4 x 9.5% + 0.4 x 4.6% = 6.56% (see Section 7.3.b)

7.4   Statistical Reports

7.4.a   Steering Committee Reports

Periodic reports will be generated for the Steering Committee, Clinical Center Networks, and Clinical Sites. These reports will include information on recruitment, loss to follow-up, adherence, baseline covariate information on the comparability of treatment groups, and adverse events. Information will be stratified by Clinical Center Networks and Clinical Sites. Other reports will include information on quality control for central facilities and data entry.

7.4.b   Data and Safety Monitoring Board (DSMB) Reports

The role and composition of the Data and Safety Monitoring Board are described in Section 13.8. Meetings of the DSMB will be held at least annually. Material for these meetings will be distributed two weeks in advance of the meetings. Up-to-date statistical analyses will be provided to the DSMB in preparation for their meetings. The analyses will include data on recruitment, outcome measures, any side- or safety effects, adherence, and quality control, and will be designed in cooperation with the DSMB. Interim analyses of the intervention effectiveness will be performed at times coinciding with the meetings of the DSMB, and will be controlled to protect the overall Type I error of the trial. These results will be for the use of the DSMB and will not be revealed to the investigators. The purpose of these analyses will be for the DSMB to assess the trial progress with respect to intervention efficacy and safety, for possible recommendations regarding early termination of the entire trial or any individual intervention.

Interim analyses will be performed periodically for the Data and Safety Monitoring Board (DSMB). Monitored parameters will include the following:
1. HbA1c separation between groups
2. HbA1c distribution within groups
3. Primary outcome results
4. Conditional power
5. Adverse events
6. Recruitment progress
7. Other Event Rates

7.5   Vanguard Phase Criteria

Recruitment and a minimum of one-year treatment/follow-up of 1184 participants was designated the Vanguard phase of the trial. The purpose of the Vanguard phase was to determine the feasibility and success of implementing the protocol treatments and of achieving the treatment goals throughout the ACCORD clinical sites. The following were the specific goals of the Vanguard phase, which were used to judge its success:

Recruitment. The goal was to randomize 1,000 Vanguard participants within four months after the first randomization.

Glycemia control. There were two glycemia control goals, which were analyzed in participants with at least 8 and 12 months of post-randomization follow-up:

a) the median achieved HbA1c in the intensive group would be less than 6.5%, and

b) the difference in median HbA1c between the standard and intensive groups would be at least 1.3%.

Blood Pressure. The study target is 20 mm Hg difference between the two BP arms. Evidence suggests that a 10-12 mm Hg difference may produce a 20% effect on CVD events. The target for the end of the Vanguard period was 10 mm Hg, which allowed time to titrate medications. An achieved mean SBP < 130 mm Hg in the intensive BP group was considered adequate for the Vanguard phase, if it also was 10 mm Hg lower than the less intensive group.

Lipid. Targets for assessment of the fibrate intervention were based on adherence. The target adherence rate to fibrate and to statin was at least 80% as measured by simple self-report.

The Vanguard Phase was successful in achieving almost all of these goals, and the trial protocol was modified to increase the likelihood of achieving all of the goals. These modifications are incorporated into this main trial protocol.

Chapter 8
Data Management and Training

8.1   Overview: Use of the World Wide Web

All Clinical Center Networks and Clinical Sites will use the World Wide Web (WWW) to enter ACCORD data collected on forms from participants seen within the Clinical Sites. In situations where an internet connection is not available at a Clinical Site, the Clinical Center Network will be responsible for entering data from participants' forms. Each Clinical Site will have a password protected area on the ACCORD home page through which data will be entered. Documentation of the data entry system will be maintained at the Coordinating Center (CC). In addition, training materials for measurement and data entry personnel will be available in downloadable format on the ACCORD web site. Site-specific reports relating to patient demographics, recruitment goals, etc., among other reports, will be available on the web site.

Data security in the web-based data system uses 128-bit encryption and Secure Socket Layer (SSL). Recovery from disasters such as natural phenomenon (water, fire, or electrical) is possible through the ability to reconstruct both the database management system and the data up to the last back-up through the use of nightly backups. This will ensure optimal recovery of data systems in the event of a disaster. Back-up tapes are kept in a locked, fire and waterproof storage cabinet away from the computer room. Additional back-up tapes will be stored at another location on the Wake Forest University School of Medicine campus.

8.2   Flow of Data from Trial Units to Analytical Databases

8.2.a   Data from Clinical Sites and Clinical Center Networks

Patient Randomization: An internet-based, web browser randomization procedure will be employed in ACCORD. Clinical Sites access the study web site and initiate the interactive randomization page. Entry into this area is password protected and encrypted. Once security requirements are satisfied, a series of questions follows, interrogating the user for identifying and eligibility information. If these questions have been appropriately answered, a patient identification number is issued. When the session is complete, an e-mail process is spawned and a record of the transaction is sent to the Clinic Coordinator, the Regional Coordinator at the appropriate Clinical Network Center, and the Project Manager at the CC indicating that the patient has been properly randomized and appended to the database.

Patient Tracking: The Patient Tracking System (PTS) is a fully integrated tracking and notification system that advises clinic staff about patient follow-up windows, as well as projected clinic and laboratory workload for a week at a time (longer if necessary). Tracking a patient begins at screening and continues automatically throughout the project by integrating patient follow-up data with predetermined follow-up "windows". When a participant is enrolled into the study, a schedule of target dates for each of the visits is automatically generated by the CC. The report details the recommended "windows" that each visit should fall into and a case file is created for the participant. In addition, the clinic will generate personalized form letters to be sent at the prescribed intervals reminding patients (and clinic staff) of an impending visit. At the end of each week, a

listing of patients that are due for follow-up detailing each patient's required tests is transmitted to the clinic to assist in staff and laboratory resource allocation for that week. Reports detailing deviations from the protocol are automatically generated and transmitted to the clinic via e-mail attachments. These data will also be available in the study web site.

Data Entry: Data entry screens are developed in HTML, with a Cold Fusion to Oracle (a relational database management system) backend. The images on the screens mirror the data collection forms for ease and accuracy of entry.

As patient visits are completed, and hard copy forms are filled out, the clinic coordinator reviews each form for accuracy and completeness, including laboratory reports and any supporting documentation (pertinent hospital records, etc.). Once any data problems have been resolved, data are entered by clinic staff into the computer via the web-based browser application. During data entry, key variables are checked for accuracy with the assignment of ranges. Where data are entered outside of preset ranges, entry is denied pending the review for accuracy. Override capabilities exist; however, these responses are flagged for review upon receipt by the CC. The Project Manager will reconcile any responses that continue to be questionable. Also, a sample of key forms is required to be double-keyed for entry verification and identification of problem fields/forms.

8.2.b   Data from Central Chemistry Laboratory and ECG Reading Center

Laboratory specimens and electrocardiographic data are sent to the Central Chemistry Laboratory and ECG Reading Center from the Clinical Sites on a fixed schedule. The Clinical Sites log each shipment specifying patient identification and visit sequence in a computerized format. This information includes dates for specimen/test acquisition as well as shipping. The Central Chemistry Laboratory and ECG Reading Center provide results to the CC on live internet feed, which will include all log information as well as the date of analysis. Depending on clinic needs, reports will be sent to assist in the clinical functions (eg., providing timely feedback to the clinic on any measurement that exceeds a predefined alert level).

8.2.c   Analytical Database Closure

At regular intervals, data queries will be carried out using SAS/Connect to perform consistency checks on key variables and forms. Although much of this will be done at the data entry level in the clinic, this additional pass through the data will serve as a quality control check before the data files are merged with the permanent SAS datasets on the CC Sun computer.

Upon study completion, after all clinic and laboratory data have been collected and filtered through the quality control routines, the Oracle database will be converted to SAS datasets and certified. The database will be taken off-line and archived on magnetic tape and/or CD-ROM. The final SAS datasets will be certified and issued version numbers to synchronize analytic efforts and distributed in accordance with ACCORD Steering Committee and NHLBI policy. The choice of media on which to copy and distribute copies of the database to the investigators will depend upon the systems and media available at that point in time. Final data tapes and documentation will be sent to NHLBI.

8.3   Feedback to Clinical Sites and Clinical Center Networks

As described in Chapter 12, a routine system of data edit reports will be generated to help ensure that all data are entered in timely and complete manner. These reports will include both the assessment for each Clinical Site of the time between data collection and entry, and the generation of reports by the CC of missing items. These reports will be provided to the Clinical Center Networks, Clinical Sites, and Measurement Procedure/Quality Control (MP/QC) Subcommittee on a regular basis so that data collection items that are troublesome can be identified and Clinical Sites not meeting the standards set by the MP/QC Subcommittee can be notified. Network Coordinators will be copied on all data reports for Clinical Sites within their network and asked to follow-up on any action that needs to be taken.

8.4 Training

Each Clinical Center Network will appoint a Training and Quality Control Liaison. This person will be responsible for the maintenance of measurement and training standards at the Clinical Sites including training of new personnel and re-certification for existing staff. The Training and Quality Control Liaison will be familiar with all measurement requirements for ACCORD and provide input into the scheduling of clinic activities so that there is adequate time for clinic staff to carry out their responsibilities while meeting quality standards.

Key clinic staff from each Clinical Center Network and Clinical Site will be trained at an initial central training session. These key staff will be responsible for training and re-training other staff members at the Clinical Site. Specific procedures for training clinic staff to obtain ACCORD data is provided in the Manual of Procedures (MOP). A copy of the MOP is on the ACCORD web site. This searchable electronic copy allows clinic personnel to quickly find an answer to any question about procedures.

Chapter 9
Adherence

9.1.   Background and Rationale

The overall adherence approach for this large and lengthy trial should be based on two essential principals (Probstfield 1986, Probstfield 1990). First, keys to good adherence in a clinical trial are anticipation and a prevention oriented approach. Second, effective adherence plans for a clinical trial are implemented during the protocol development and recruitment periods, and revised during follow-up as needed.

As part of the central pretrial training sessions, all investigators and clinical coordinators will receive instruction on adherence issues. Additionally, they will periodically have refresher instruction in the overall adherence program throughout the follow-up period. The key components of an overall adherence program are described in section 9.5.

9.2   Determining Adherence Potential

A run-in period, during which potential participants will be asked to monitor capillary blood sugars, is employed to screen out individuals who may have difficulty adhering to the requirements of the overarching glycemia component of the trial.

9.3   Monitoring Adherence

Adherence will be monitored by self-report of each of the prescribed medications for glycemic control and for the lipid lowering and blood pressure control at each visit. This approach has been used in many other trials. Also, pill counts of selected medications will be conducted during the Vanguard Phase. Details for this monitoring are provided in the Manual of Procedures (MOP).

9.4   Procedures for Maintaining/Improving Adherence

The details for an overall adherence program are provided in the MOP. Briefly, an overall program for adherence must be implemented at the time that recruitment is started. This will include a centralized training and regular refresher courses on adherence issues for the Clinical Center Network (CCN) and Clinical Site staffs throughout the trial.

The Recruitment and Retention Subcommittee will meet by conference call on a monthly basis during the follow-up portion of the trial for the purpose of monitoring adherence performance. They will review data provided by the Coordinating Center that will be directed primarily at assessing adherence at the CCN level. The variables reviewed will include the level of adherence for each of the three interventions. Also, the number of participants off an assigned intervention, the number of dropouts, and the number of participants lost-to-follow-up will also be reviewed. Adherence at the individual Clinical Site level will be reviewed by the respective CCNs. Guidance to the individual CCNs will be provided as needed.

9.5 Components of an Overall Adherence Program

The key components of an overall adherence program include the following.

- *Develop a bottom line for adherence that cannot be transgressed by any trial participant.* Although quite simple in statement, the key issue in a trial with the intent to alter the natural history of a disease is the status of every participant with respect to the primary outcome measure at termination of follow-up. This allows an intention-to-treat analysis to be performed without reservation.

- *Set goals for adherence before the trial starts. Implement strategies that make those goals possible. Evaluate them periodically.* Power calculations are routinely made taking into account numbers of participants who will go off medication and those who may crossover treatment assignment during the trial. These estimates should be used regularly as minimum goals for adherence in the study.

- *Do not randomize all "number eligible" screenees.* The eligibility criteria in this trial are very wide to allow maximum numbers to be eligible for enrollment. While the ability to discern objectively those who will not perform well in the study is limited, any exhibition of hesitancy or inability to proceed through the pre-randomization period should be regarded as a caution against randomization of that screenee.

- *Pay attention to signs and symptoms of potential poor adherence.* Codification of red flags for potential poor adherence has been used previously in trials. These may help Clinical Site staff identify potential non-adherers at any time during trial conduct.

- *Use an adherence team approach, if possible.* More than one individual sees screenees and participants in a clinic. All interactive information can be useful in the maintenance of good adherence.

- *Use a constant caretaker model, if possible.* Participant interaction with the same staff person consistently is thought to be useful. Use when possible. Transitions to other staff may be necessary. Make them as smooth as possible.

- *If necessary, modify dosing regimen.* The protocol-prescribed dose of the medications may be altered in order to accommodate the participant. Every attempt should be made to keep these intervals short, but long-term accommodations may be necessary.

- *Use adherence techniques.* There are a host of adherence techniques that have been used previously in trials, eg., occasion cards, appointment reminders, intervening phone calls, etc. These will be systematically reviewed for staff use.

- *Use the behavioral counseling approach.* Interviewing and counseling techniques have been shown to aid staff in sustaining long term adherence performance. These include identification of barriers to adherence and individualized problem solving.

- *Have an intervention program for poor adherers.* Poor adherers and drop-outs are recoverable to productive trial participation, as shown in other studies. Instruction to staff will be provided for the approach to these challenging participants.

- *Have a maintenance plan for all participants.* Sustaining long-term adherence in trials is a challenging task to begin with, and will be a key issue in this trial with its lengthy intervention and follow-up.

- *Adherence Techniques.* The specific techniques will be included in an Adherence Binder that each site will have at their clinics, along with samples of letters and ongoing additional tools for the clinical sites and CCN's to use. Centralized training of techniques will occur for ACCORD clinic staff.

Chapter 10
Ancillary Studies

10.1   Introduction

In addition to the main ACCORD protocol, investigators may wish to perform ancillary studies using the ACCORD population, blood or urine samples, or collected data.

An ancillary study is an investigation with objectives that are not related to the ACCORD protocol but uses ACCORD participants, samples, or data collected by ACCORD. In most cases, an ancillary study will involve acquisition of additional data that are not compiled as part of the standard ACCORD data set. An ancillary study may or may not use all randomized participants.

Investigators are encouraged to propose and conduct ancillary studies. Such studies enhance the value and productivity of ACCORD, and help ensure the continued interest of the diverse group of investigators who are critical to the success of the trial as a whole. These studies provide an exceptional opportunity for investigators, either within or outside of ACCORD, to conduct additional projects at minimal cost. In general, ancillary studies will require additional funding from the NIH or other sources.

10.2   Application Review Process

To protect the integrity of ACCORD, all ancillary studies must be reviewed and approved before access to ACCORD data, samples, or participants is permitted. Investigators will not be allowed access to the ACCORD participants, samples, or database without approval. New ancillary study proposals should be sent to the ACCORD Laboratory & Ancillary Studies (LAS) Subcommittee. Ancillary study forms can be obtained by calling the Coordinating Center or accessing the LAS Subcommittee website. When the application is complete, the study proposal will be sent to the LAS Subcommittee for review. The LAS Subcommittee will have two weeks to review the proposal and make a recommendation to the Steering Committee. Preliminary approval/disapproval will be made by the Steering Committee, with a final recommendation for approval/disapproval made by the Data and Safety Monitoring Board to the NHLBI Director.

An ACCORD principal investigator or co-investigator must be included as the principal investigator and/or co-investigator in every ancillary study proposal. If Coordinating Center resources are to be used, arrangements must be made with the Coordinating Center Principal Investigator. In general, costs associated with ancillary study data management at the Coordinating Center must be budgeted into each ancillary study.

All proposed ancillary studies must be submitted to the LAS Subcommittee in time for review, circulation to appropriate committees, and to obtain clearance prior to submission to a funding agency. As a beneficiary of a collaborative study, each investigator must realize that other investigators must be given an opportunity to participate in proposed studies and to offer a critique of the proposal. Such collaboration will often strengthen the ancillary study. Studies

submitted for approval less than 60 days prior to a funding application deadline may not receive timely approval.

During the review process, highest priority will be given to studies which:
- do not interfere with the main ACCORD objectives,
- have the highest scientific merit,
- produce the least burden on ACCORD participants,
- have objectives closest to those of ACCORD,
- require the unique characteristics of the ACCORD cohort, and
- provide opportunities for more junior investigators to serve as the PI of a project.

Investigators with approved ancillary studies will report to the Chair of the LAS Subcommittee every year regarding the status of study funding, initiation and terminations dates, success of data collection, and any presentations and publications derived from the ancillary study. A written progress report on ancillary studies will be made once a year to the LAS Subcommittee and to the Steering Committee.

Chapter 11
Publication Policy

11.1   Data Analysis and Release of Results

The Coordinating Center will be responsible for the collection, storage, analysis, and release of all ACCORD collaborative study data. Analyses from the main database will be performed by the Coordinating Center. In the case of ancillary studies, the Coordinating Center will review the data analyses of manuscripts using the ACCORD database. Distributed data analysis may be necessary if proposed analyses require special expertise that does not exist at the Coordinating Center, or if a particular analysis cannot be completed by the Coordinating Center within a reasonable time period. In both of these situations, verification of final distributed analyses will be performed at the Coordinating Center.

11.2   Manuscript Proposal Process

The review process of an ACCORD manuscript begins with the submission of a manuscript proposal. Instructions on the format of publications can be obtained by accessing the ACCORD website. The completed manuscript proposal will be submitted to the ACCORD Publications and Presentations (P&P) Subcommittee for review and will be forwarded to the Steering Committee for approval and Writing Group nominations. Nomination of additional Writing Group members to the list of submitted names present on a proposal is the responsibility of the Steering Committee. Each center that collects or processes the data used in a paper, and each unit represented on the Steering Committee, may nominate a Writing Group representative. Based on the nominations received from the centers, the P&P Subcommittee will select Writing Group members and a Chairperson for each manuscript. Generally, a Writing Group will consist of approximately five members with investigators from every CCN having the opportunity to participate on papers. The P&P Subcommittee may change the composition of a Writing Group that has failed to produce the required manuscript according to the schedule originally agreed upon by the Group and the P&P Subcommittee.

A limited number of ACCORD manuscripts, such as the major design paper and the main papers describing treatment effects on the major endpoints, will be authored by the ACCORD Study Group with reference to all investigators in an appendix. For some major papers, named authors may be suggested by the P&P Subcommittee with final determination by voting members of the Steering Committee. Named authorship for other papers can be suggested by the proposal's originator and will include a limited number of named authors who comprise the Writing Group. As allowed by the editorial policy of individual journals, an appendix describing the structure of the ACCORD organization and containing the names of all the ACCORD investigators will be included with publications.

The ACCORD Steering Committee will determine priorities for scheduling a start date for a manuscript. A priority rating of 1 indicates highest priority and a 5 indicates the lowest

priority. The Writing Group Chairperson is responsible for all phases of manuscript preparation, from conception through publication. Members of the Writing Group are responsible for performance of tasks assigned by the Chairperson within the allotted time period. Each member is expected to actively participate in the preparation of the manuscript. Selection of the journal for initial submission of the manuscript is delegated to the Writing Group, with input from the P&P Subcommittee and the Steering Committee.

11.3   Approval of Manuscripts, Abstracts, and Presentations

All manuscripts must be reviewed by the ACCORD P&P Subcommittee and the NHLBI Project Office. Prior to submission for publication, manuscripts must be approved by the P&P Subcommittee and Steering Committee. Manuscripts with NHLBI co-authors must also be approved by NHLBI. The Committees will have 30 days to review and provide comments regarding necessary revisions. After revision, a final copy of the manuscript with the cover letter to the journal should be sent to the chair of the P&P Subcommittee and to the Coordinating Center, in addition to all co-authors.

The ACCORD P&P Subcommittee will maintain a current list of all relevant meetings and their deadlines for submission of abstracts. No abstract shall be submitted to any national or international organization for consideration prior to review by the P&P Subcommittee and the NHLBI Project Office. Additionally, prior to submission, abstracts must be approved by the P&P Subcommittee and the Steering Committee. Abstracts of papers for presentations are expected to be based on active manuscripts. Abstracts should be submitted to the P&P Subcommittee at least two weeks prior to the abstract deadline and will be reviewed within 48 hours. If the P&P Subcommittee review is favorable, the abstract will be sent simultaneously to the Steering Committee and NHLBI Project Office for review. The Steering Committee and NHLBI will have 48 hours to review and to respond to the abstract. If an abstract is approved by the Steering Committee, the Writing Group Chair will be notified by the P&P Subcommittee Chair and will be given clearance to submit the abstract.

Presentations given at national or international scientific meetings or events sponsored by industry need prior clearance by the P&P Subcommittee. Any ACCORD investigator who receives a personal invitation to make a presentation should immediately notify the P&P Subcommittee of the sponsor, date and topic of the presentation. The approval process for these presentations will follow the same guidelines as specified for ACCORD abstracts. If information is to be presented that is not based on previously approved reports, prior approval must be granted by the P&P Subcommittee.

Presentations at local meetings of any previous published or presented ACCORD data do not need prior clearance by the P&P Subcommittee. However, as with all presentations, the P&P Subcommittee should be notified of these presentations.

A standard set of PowerPoint slides presenting the design and the rationale of trial will be developed by the P&P Subcommittee and placed on the ACCORD website for downloading. Presenters are encouraged to use these slides as part of any presentation.

11.4 Recruitment Materials

For purposes of participant recruitment, presentations will use approved materials that will be maintained at the Coordinating Center. Any material to be distributed to the public for recruitment, in addition to approved ACCORD recruitment material, must be approved by the P&P Subcommittee and reviewed by the Project Office. A standard set of PowerPoint slides, developed in collaboration with the ACCORD Recruitment and Retention Subcommittee, will be downloadable from the ACCORD website.

Chapter 12
Quality Control

12.1   Introduction

An important feature of the ACCORD Trial is a concern for the integrity and high quality of the study data. This concern is reflected in the detail provided in the protocol regarding initial screening and recruitment of participants, data acquisition at baseline and follow-up visits, reading and/or interpretation of the results, and their analysis and publication. There are two primary purposes for quality control: to historically document the level of quality and to provide feedback to the clinical and laboratory centers in order to maintain and improve the quality of the study data over the course of the examination. The Measurement Procedures and Quality Control Committee will establish guidelines for quality assurance and quality control while much of the monitoring and analysis will be carried out by the Coordinating Center and the Network Monitoring Centers. The Measurement Procedures and Quality Control Committee will report any areas of concern to the Steering Committee for consideration.

This chapter outlines the type of quality assurance activities that will be conducted in the ACCORD Trial. Two phrases are used. The first, quality assurance, is the collection of manuals and procedures that will be in place to assure the integrity of the data. A subset of these procedures is referred to as quality control, which describes the monitoring and analytic activities that assess performance during data collection and its processing.

12.2   Manual of Procedures

As with any multicenter study, standardization of study procedures is very important in the ACCORD Trial. A Manual of Procedures (MOP) will be developed that will include the detailed descriptions of all trial procedures. This MOP will be used for training purposes and as a reference for all study investigators and staff. The MOP will be an important aspect of efforts to standardize important study procedures across clinical sites in the ACCORD Trial.

Attention has been placed on the standardization of important study procedures, including the use of a central lab and ECG reading center, standard equipment in the clinics for HgbA1c measurement and BP measurement, standard equipment for use by the participants for home glucose monitoring, and standard examinations for visual acuity and foot involvement. Furthermore, attention has been placed on the use of standard event definitions and event validation procedures. Event tracking will include redundancy, such as, questions about multiple types of events and searches of databases (e.g., HCFA, VA, NDI).

12.3   Study Forms and Data Entry Procedures

Attention will be placed on quality assurance concepts during the development of forms. Forms will be printed with question-by-question instructions on the reverse of the preceding page for easy reference. The forms will be translated into web-based data entry screens. These

screens will enable the incorporation of range and logical checks at the time of data entry. These features will contribute to quality assurance.

12.4   Training

As with any multicenter study, training of staff and pilot testing of procedures will be crucial to efforts to standardize procedures and assure data quality. We plan to have two different training models available, central training and the train-the-trainer approach. In the central training aspects of the ACCORD training effort, all relevant staff members from all clinical sites will be convened in a single, centrally administered training session. This approach is cost-efficient and contributes to uniformity of the training experience and thereby to uniformity of data quality across sites. In the train-the-trainer aspect of the ACCORD training effort, clinical center network (CCN) staff will provide training sessions to persons who were unable to attend the central training session and to newly hired staff as turnover occurs. The Vanguard period will serve as a test of feasibility of study procedures; participants recruited during the Vanguard will be retained in the trial. The Steering Committee will organize a central training session prior to the Vanguard and Main trial periods; furthermore, the CCNs will organize CCN training and refresher training sessions, as needed.

12.5   Data Queries

The Coordinating Center will be responsible for data editing, which will include checks for missing data and crosschecks for inconsistencies. The Coordinating Center will produce data query requests that will be distributed directly to the appropriate clinical center. Clinical center staff will be responsible for responding to the data queries in a timely manner. The Coordinating Center will generate a summary indicating the number and types of queries generated by clinic and network. This report will include the number of queries unresolved for more than 30 days. This report will be shared with the Measurement Procedures and Quality Control Subcommittee and Clinical Center Network Monitoring Center investigators and staff for quality control purposes.

12.6   Quality Control Reports

The Measurement Procedures and Quality Control Subcommittee will develop quality indicators that will be tracked in routine quality control reports in the ACCORD Trial. These reports will serve both purposes described above, that is, for historical documentation of the quality of the data collection process and for providing feedback to individual clinic sites. These reports will be generated by the Coordinating Center and distributed to the CCN monitoring centers. Investigators and staff at the CCN monitoring centers will be responsible for disseminating this information to the appropriate investigators and staff at the clinics in their networks. These reports will be used to inform discussions that will take place during regularly scheduled telephone contacts and site visits.

Quality Control reports will focus on measures of process, impact and outcomes. Examples of process measures that will be tracked for quality control purposes include:
1. late submission of data forms
2. the number of participants with missed or late visits

3. proportion of study participants off study medications
4. the number and dose of hypoglycemic and antihypertensive medications
5. adherence to the lipid-lowering assignment.

Examples of impact measures that will be tracked for quality control purposes include:
1. control of glycemia with HgbA1c results (central lab)
2. control of lipid and lipoprotein concentrations (central lab)
3. control of blood pressure with automated BP measurements

Examples of outcome measures that will be tracked for quality control purposes include:
1. Documentation for reported study events
2. Proportion of participants with ECG submitted to central ECG Reading Center
3. Proportion of participants with urine samples submitted for micro/macroalbuminuria assessment

12.6.1 Deviations from protocol

Adherence to the study protocol is crucial to collection of high quality data and to the internal validity of the trial. Thus, the Medical Intervention Subcommittee will define important deviations from the intervention protocol for tracking purposes. A clinic-site-specific report describing important protocol deviations will be disseminated to the CCN monitoring centers for quality control purposes. Copies of these reports and a summary report describing important protocol deviations on a study-wide basis will be shared with the Measurement Procedures and Quality Control Subcommittee and the Steering Committee.

12.6.2 Monitoring the Clinical Centers in the Networks

Within each clinical center network (CCN), the physicians and nurse/study coordinators at the CCN monitoring center will be responsible for monitoring activities and performance at the clinical centers in the network. This team will coordinate the research activities of the study and maintain effective communications with the clinical centers, the coordinating center, the project office, the support centers (lab, ECG, and drug distribution center) as well as the other clinical center networks. The primary role is to support the clinical centers in recruitment and maintenance of the respective clinical center participant cohorts in the trial. The CCN team will assist in solving problems related to quality control, protocol adherence, recruitment and retention for the clinical sites.

12.7 Site Initiation

The initiation of a clinical site to enroll and randomize participants into the ACCORD trial will occur after a series of preliminary tasks are completed. These will include approval from the local or network ethics board, completion of all required FDA forms and letters of agreement, training of staff, development of clinical site recruitment and retention plan, and receipt of study supplies and medication. The individual networks will provide appropriate assistance to the clinical sites as needed with regard to site visits prior, at time of, or following

the clinical site's initial enrollment and randomization of participants to ensure the sites are comfortable with the process.

12.8 Site Visits

During recruitment and follow-up, personnel from the CCN monitoring centers will site visits each clinical center in their network on a regular basis to promote communication, answer questions, and ensure that study procedures are understood and conducted correctly. The site visit program will provide a mechanism to encourage the effective and standardized delivery of recruitment efforts, intervention programs, and the collection of appropriate and valid data within each ACCORD clinic site. Site visits may also be performed if consistent departures from the Protocol and MOP are detected. Refresher training and training of new staff may be done as needed during these visits depending on the availability of staff. Site visits will provide the opportunity for CCN monitoring center investigators and staff to review the operations of clinics in their networks. As needed, representatives from the Coordinating Center, Project Office, other CCNs and the Steering Committee may attend specific site visits. Usual activities at sites visits may include reviews of clinic staffing levels and duties, discussions of clinic flow, inspections of clinic space and records, review of study drug accountability, reviews of the quality control reports described above, reviews of maintenance logs for important study equipment, confirmation of participant's consents, inclusion and exclusion criteria, and source documentation; presence of regulatory documents; review of recruitment and adherence strategies and trouble-shooting of problems. After each site visit, two types of reports will be produced. The first will be a frank discussion at the end of the visit between the site visit team, the clinic PI and key clinic staff. The site visit team will prepare written reports, detailing problems and offering potential solutions regarding the activities of the site. A detailed report of the team's observations and recommendations will be sent to the PI of the site being reviewed, the PI of the Coordinating Center and the Chair of the Measurement Procedures and Quality Control Subcommittee. The Quality Control Committee will regularly review 10% of the site visit reports submitted and recommend reporting changes as needed.

12.9 Laboratory and ECG Center Quality Control

The ACCORD Measurement Procedures and Quality Control Subcommittee will work with the Central Laboratory and the ECG Reading Center to develop quality control procedures to ensure high quality data. The results of quality control procedures performed at the Central Laboratory and the ECG Reading Center will be reported on a regular basis to the Measurement Procedures and Quality Control Subcommittee and the Steering Committee.

Chapter 13
Study Organization

13.1   Overview

The ACCORD organizational structures and responsibilities are similar to those of other, large multicenter clinical trials sponsored by government or industry. Seven Clinical Center Networks and a Coordinating Center are contracted by the National Heart, Lung and Blood Institute to work together through the Steering Committee to successfully design and conduct the trial (see Figure 13.1). In addition, there is a Central Chemistry Laboratory, an ECG Reading Center, and a Drug Distribution Center. Scientific leadership is provided by the Steering Committee (see Figure 13.2).

13.2   Clinical Center Networks and Clinical Sites

The 10,000 ACCORD participants will be recruited, randomized, treated, and followed through a system of seven Clinical Center Networks (CCNs). Each CCN consists of a network of collaborating Clinical Sites, which consist of medical facilities and/or individual practices that will be involved in the evaluation, enrollment and treatment of patients in the trial. CCN investigators will work with their Clinical Sites during the trial on issues related to recruitment, compliance with protocol, and quality control. While these Clinical Sites will interact principally through their CCNs, for matters such as data collection these sites will transmit their data directly to the Coordinating Center and the other central units. Similarly, data queries will be sent directly to the Clinical Sites, with copies to the appropriate CCN.

13.3   The Coordinating Center

The Coordinating Center (CC), with input from the ACCORD Steering Committee, will be responsible for coordinating the protocol writing activities; developing and distributing the Manual of Procedures; training trial personnel in the standardized protocol implementation and data collection; providing rapid feedback to the CCNs and Core Laboratories on the quality of data submitted and proposing corrections; collecting all trial data, including clinical outcomes; and analyzing all data; and preparing reports for the Data and Safety Monitoring Board. The CC will conduct yearly visits to each CCN to monitor and assure high performance throughout the trial. CC investigators and staff are also active members of each of the Steering Committee subcommittees.

During the recruitment phases of the trial, the CC will be responsible for monitoring patient recruitment and will provide weekly reports to the CCNs, the Chair and Vice-chair of the Steering Committee, the NHLBI Project Office, Core Laboratories, and the Drug Distribution Center. Included in the reports will be measures of progress in recruiting women and minorities. These weekly reports will assist the Recruitment and Retention Subcommittee with evaluating

and correcting recruitment problems. The CC will also develop (with the assistance from the Steering Committee) criteria for the certification of new Clinical Sites.

13.4 ECG Reading Center, Central Chemistry Laboratory, and the Drug Distribution Center

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

13.5 NHLBI Project Office and Other Government Representatives

ACCORD is sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The NHLBI Project Office is responsible for the administration and monitoring of the trial. Representatives from this Office participate in the scientific, general organizational, and fiscal management of the trial. Statistical consulting is provided by NHLBI statisticians. The National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) and the Centers for Disease Control and Prevention (CDC) are co-sponsors of ACCORD. In addition to NHLBI personnel, representatives from these agencies actively participate as scientists in the Steering Committee.

13.6 The ACCORD Steering Committee, Committee of Investigators, Subcommittees of the Steering Committee, and Executive Committee

The ACCORD Steering Committee provides the overall leadership for the study and establishes scientific and administrative policy. It is composed of the Principal Investigators from the seven Clinical Center Networks, the Principal Investigator from the Coordinating Center, the NHLBI Project Officer, the Chairs of the three major intervention working groups (glycemia, lipid, and blood pressure), the Steering Committee Chair, and the Steering Committee Vice-Chair. This committee oversees the overall conduct of the trial throughout all Phases. This committee, along with the Committee of Investigators, developed the trial design, prepared the final protocol, and approved the study forms and manual of operations. During the data collection phases of the trial, this committee oversees data collection practices and procedures to identify and correct deficiencies. The committee will also consider and adopt changes in the study protocol or procedures as necessary during the course of the trial.

The Steering Committee is chaired by the Steering Committee Chair, who will serve as the senior executive officer of the investigative group. A Vice-Chair will assist the Chair with his responsibilities. Voting Steering Committee members are the Principal Investigators from the seven Clinical Center Networks, the Principal Investigator from the Coordinating Center, and the NHLBI Project Officer. If a CCN or the CC PI cannot make a meeting at which a vote is taken, then the Co-Principal Investigator may vote (with the understanding that the PI is assured that the Co-PI is fully informed about the issue). The Steering Committee Chair, or Vice-Chair in his

absence, votes only to make or break a tie. Co-investigators, CC staff, NIH staff, consultants, and opinion leaders may also be invited to attend meetings.

All other ACCORD investigators, co-investigators, and senior staff represent the ACCORD Committee of Investigators.

There are nine standing subcommittees of the Steering Committee (Figure 13.2). The charges to these subcommittees are presented in Appendix II. These are the Design and Analysis Subcommittee, the Medical Interventions Subcommittee, the Recruitment and Retention Subcommittee, the Measurement Procedures and Quality Control Subcommittee, the Morbidity and Mortality Subcommittee, the Publications and Presentations Subcommittee, the Health-related Quality of Life/Cost-effectiveness Subcommittee, the Laboratory and Ancillary Studies Subcommittee, and the Operations Subcommittee.

An Executive Committee acts as 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 will meet at least biweekly by conference call to review trial progress and any study issues that may arise. This committee will also develop time lines for the accomplishment of tasks and will develop Steering Committee Meeting agendas.

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

13.7   The Protocol Review Committee

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

13.8   The Data and Safety Monitoring Board

During the recruitment and follow-up phases of the trial, an independent Data and Safety Monitoring Board (DSMB) will monitor data and oversee patient safety. Members of the Board, appointed by the Director of NHLBI, are senior experts in the areas of cardiovascular medicine, diabetes, biostatistics, and bioethics. The Study Chair, the Vice-Chair, the Principal Investigator and senior staff of the Coordinating Center, and representatives from the NHLBI and other

sponsoring Federal agencies and Institutes will participate in DSMB meetings as non-voting members. The DSMB will meet at least once a year to monitor safety, to advise the NHLBI about study progress, including contractor performance, and to make recommendations to the NHLBI regarding study continuation and protocol changes. In addition, the Coordinating Center will provide data to the DSMB Chair at his/her request at regular intervals to ensure early identification of any major adverse outcomes of therapy.

13.9   The Hypoglycemia Monitoring Committee

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

13.10   Role of Industry

Industry may contribute resources to the study and will be acknowledged appropriately. However, the scientific decisions and governance of the trial will be determined by the Steering Committee, as per NHLBI Policy.

13.11   Conflict of Interest Policy

The ACCORD investigators have established a policy regarding Conflict of Interest. This policy is presented in Appendix III. This policy was developed to meet two goals. First, the investigators wished to maintain the confidence that advice was being given, and decisions made, in as unbiased and fully informed manner as possible. Second, the investigators wished that the processes and results of the trial would meet public standards of conduct.

Figure 13.1: ACCORD Organizational Chart
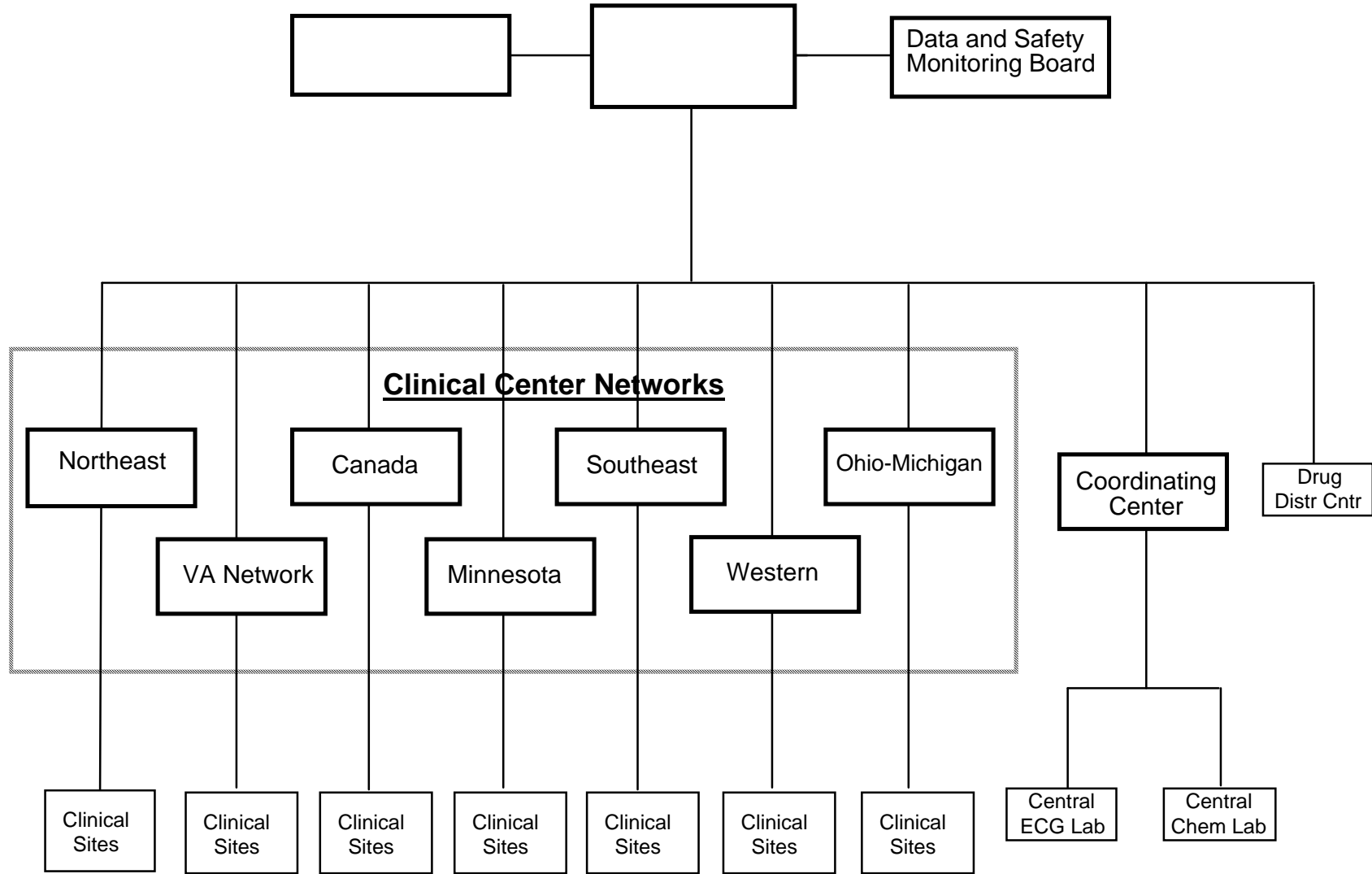
Figure 13.2: ACCORD Committees


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┌──────────────┐      ┌──────────────┐
│  Executive   │──────│   Steering   │
│  Committee   │      │  Committee   │
└──────────────┘      └──────────────┘
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Design & Analysis Subcommittee

Recruitment & Retention Subcommittee

Measurement Procedures & Quality Control Subcommittee

Morbidity & Mortality Subcommittee

Lab & Ancillary Studies Subcommittee

Health Related Quality of Life/ Cost-Effectiveness Subcommittee

Operations Subcommittee

Medical Interventions Subcommittee

Publications & Presentations Subcommittee

Glycemia Working Group

Blood Pressure Working Group

Lipid Working Group

Lifestyle/ Background Working Group

Chapter 14
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Appendix I:
Model Informed Consent Document
(Consent Version Date: May 11, 2005)
ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES (ACCORD)

Principal Investigator(s)_____

You are invited to join in a research study called Action to Control Cardiovascular Risk in Diabetes (ACCORD), which is sponsored by the National Heart, Lung and Blood Institute (part of the U.S. federal government). The investigators listed above are in charge of the study. Other professional persons may help them or act for them.

What are some general things you should know about research studies? Research studies are designed to gain scientific knowledge that may help other people in the future. You may or may not receive any direct benefit from participating. There may also be risks associated with participating in research studies.

Your participation is voluntary. You may refuse to participate, or may withdraw your consent to participate in any study at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your doctor. You do not have to participate in research in order to receive treatment.

Details about this study are discussed below. It is important that you understand this information so that you can decide in a free and informed manner whether you want to participate. You will be given a copy of this consent form. You are urged to ask the investigators named above, or staff members who may assist them, any questions you have about this study at any time.

STUDY PURPOSE

What is the purpose of the study and how long will it last? Type 2 diabetes is very common in North America. People with Type 2 diabetes have a higher chance of getting heart disease or stroke than people without diabetes. The purpose of the ACCORD study is to determine the best approaches to lower the risk of heart disease and stroke in people with Type 2 diabetes.

ACCORD will answer three research questions. In diabetes, the level of sugar in the blood is too high. So the first question is to determine the effects of lowering blood sugar to a level below that normally targeted in current clinical practice, compared with a level that is usually targeted. Many diabetic patients have high blood pressure. So the second question is to determine the effects of lowering blood pressure to a level below that normally targeted in current clinical practice, compared with a level usually targeted. Many diabetic patients also have problems with their blood lipids (like cholesterol, fat-like materials in the blood). So the third question is to determine the effects of treating several components of blood lipids compared with treating only one component. Each of these questions is described in more detail below.

You are being invited to participate in ACCORD because you have Type 2 diabetes along with other factors that increase your chance of having future heart disease and stroke, or you may already have had heart disease or stroke. Your participation in the study will last until 2009. However, study results will be reviewed regularly to see if the trial should be stopped earlier than this. Most participants will be in the ACCORD study between 5 ½ and 8 ½ years.

The total number of participants will be about 10,000 from 77 clinics throughout the United States and Canada. The study will involve approximately ___ patients at the _____ clinical site. ACCORD recruited about 1,200 participants during the Vanguard (pilot) portion of the trial in 2001 and these participants are still being treated and followed.

STUDY SUMMARY

What will happen if you take part in this study? Initial visits will be conducted to determine whether you qualify for the study. These are called "screening" visits. Your medical history, blood pressure, and past blood sugar and cholesterol measurements will be reviewed to determine whether you qualify for the study. You will have a short physical exam, and one tube (about 2 teaspoonfuls) of blood may be collected and tested for creatinine (a measure of kidney function), lipids and liver function. Some urine will also be collected and tested for protein.

If you qualify for the study and volunteer to participate, your study doctor will treat your blood sugar and either your blood pressure or your blood lipids according to the ACCORD study protocol. You and your personal physician are still responsible for other parts of diabetes care, including general preventive measures, foot care, and eye care. If you are not in the blood pressure part of ACCORD, your personal physician will still be responsible for treating your blood pressure. If you are not in the blood lipids part of ACCORD, your personal physician will still be responsible for treating your blood lipids (such as blood cholesterol). In addition, you will still need to see your personal physician(s) for all other medical care.

Blood sugar treatment groups. If you qualify and consent, you will be randomly assigned (like the flip of a coin) to one of the two blood sugar goals. The "intensive" goal is a blood sugar level lower than the current recommended value. The "standard" goal is a blood sugar level similar to the current recommended value. Your current treatment for diabetes (if any) will be changed to study treatment based on the goal to which you are assigned. Your study treatment will use available and approved diabetes treatments (oral medications and/or insulin as may be required).

If you are randomized to the intensive blood sugar goal, it is very likely that you may need one or more of the following: a) at least 2 oral medications; b) 3 or more insulin injections per day; c) frequent self-adjustment of insulin; and d) frequent home glucose monitoring. This means you will probably have to take several pills, give yourself insulin injections with a small needle, and do finger sticks to test your blood sugar up to eight times a day.

The degree of control of blood sugar is best measured by a test called hemoglobin A1c. This test gives an average of your sugar values during the past 2 to 3 months. If you are in the intensive blood sugar treatment group, the goal will be to keep your hemoglobin A1c at less than 6.0% (which is about an average blood sugar of 115 mg/dl (6.4 mmol/L)). This level is much lower than usually achieved in clinical practice. If you are in the standard blood sugar treatment group, the goal will be to keep your hemoglobin A1c value between 7.0% and 7.9% with the average around 7.5% (average blood sugar of 160 mg/dl (8.9 mmol/L)). This level is also lower than that usually achieved in clinical practice. Lowering hemoglobin A1c to this level from higher levels has been shown to reduce complications of diabetes like eye and kidney diseases. Your diabetes medications may be adjusted upwards or downwards, as your study doctors try to reach these blood goals safely.

Compared to the intensive target of a hemoglobin A1c of less than 6.0%, the standard hemoglobin A1c target of 7.5% has a somewhat higher risk for some diabetes complications. These include eye disease (retinopathy), kidney disease (nephropathy), and abnormal nerve function (neuropathy). On the other hand, a hemoglobin A1c of less than 6.0% will increase somewhat the risk for developing serious low blood sugar reactions (hypoglycemia) and weight gain. Whether the lower hemoglobin A1c target gives more or less protection against cardiovascular disease (such as heart attack or stroke) is not known. This is what ACCORD is trying to find out.

In the standard group, ACCORD will take action and recommend treatment to lower your blood sugar if your hemoglobin A1c value becomes greater than 7.9%. If your hemoglobin A1c drops below 7.0% and you are taking insulin or a secretagogue (like glimepiride or repaglinide) , we may reduce your diabetes treatment to try to bring your value above 7.0%. In the intensive group, if your hemoglobin A1c value becomes even slightly greater than 6.0%, we will increase your treatment.

Depending on your initial blood pressure and blood cholesterol results, you will also be asked to participate in either the blood pressure or cholesterol parts of the study. You must participate in one or

the other (based on your qualifications) to participate fully in ACCORD.

Blood pressure treatment groups. Blood pressure lowering can prevent heart disease, stroke, and kidney disease. There is some evidence that lowering blood pressure further than current practice might help prevent heart disease and stroke in people with diabetes. This possibility needs careful testing in a study such as this one.

If you qualify for the blood pressure portion of the study, you will be randomly assigned (like the flip of a coin) to one of two blood pressure goals. The "intensive" goal is a blood pressure level lower than that already proven to reduce heart disease and stroke. The "standard" goal is a blood pressure level similar to that already proven to reduce disease. Your study doctor will choose the medications he/she feels will be best for treating your blood pressure. Therefore, your current blood pressure medication (if any) could be changed or continued. If you do not reach your blood pressure goal, your study doctor will change your treatment until you do.

Blood lipid treatment groups. Lowering blood cholesterol can prevent heart disease and stroke. There is also some evidence that changing other blood lipids by lowering triglycerides (a type of fat in the blood) and raising HDL-cholesterol (the good cholesterol) may prevent heart disease in people with diabetes. This possibility needs careful testing in a study such as this one.

If you are eligible to participate in the blood lipid study, your current cholesterol medication treatment (if any) will be stopped and changed to the study medication. You will be treated with cholesterol-lowering medication commonly known as a "statin". The statin used in ACCORD is called simvastatin.

The dose of simvastatin you are started on will depend on your medical history. If you have had a heart attack, stroke, heart surgery, surgery on your arteries (blood vessels) or angina (chest pain) with changes in an electrocardiogram (ECG or EKG), you will be started on 40 mg of simvastatin. If you have not had any of those, you will receive 20 mg a day of simvastatin.

Regardless of your assigned dose of simvastatin, you will be randomly assigned (like the flip of a coin) to a medication known as a fibrate to lower your triglycerides and raise your HDL-cholesterol, or to a placebo (a pill that does not contain any medicine). The fibrate used in ACCORD is called fenofibrate. Neither you nor your doctor will know which study treatment (placebo or fibrate) you are receiving. If it becomes necessary to know for medical reasons, the information will be made available.

If you begin ACCORD at the 20 mg dose of simvastatin and your cholesterol levels remain higher than the currently recommended level, or if you have a heart attack, stroke, heart surgery, surgery on your arteries (blood vessels) or angina (chest pain) with changes in an electrocardiogram (ECG or EKG) during the study, your dose of simvastatin will be increased to 40 mg per day. If your cholesterol level remains too high despite treatment with the increased dose of simvastatin, you will be taken off the lipid study medications and sent to your personal doctor to get appropriate treatment to reduce your cholesterol level.

Genetic component. Genetic research will be done as part of this study. You may, if you wish, volunteer for the genetic portion of the study. If you volunteer to participate in the genetic portion of ACCORD, your blood will be stored for genetic (DNA) analysis. The genetic portion of ACCORD is described in more detail below. You do not need to agree to participate in the genetic studies to participate in the main ACCORD study.

Visit schedule and measurements. If you qualify for ACCORD and are assigned to the standard blood glucose group and either the lipid trial or the standard blood pressure group, you will be asked to visit the clinic at one month, four months, and every four months thereafter for the duration of the trial. If you are assigned to any of the other groups, you will be asked to come every month for the first four months of the study and then at least every two months thereafter until the end of the study.

At each clinic visit, your health will be reviewed, and any symptoms you may have will be discussed with the study doctor or nurse or other study staff. Your weight, blood pressure, and heart rate will be measured, and your study medications will be reviewed to make sure you are taking them correctly. You

will receive nutrition and physical activity recommendations and will be taught how to follow them. In addition, a member of your ACCORD study care team may contact you by phone between your clinic visits to determine how you are feeling and whether or not further action is required to control your blood sugar or blood pressure levels.

You will have blood specimens (up to five tablespoons) drawn every four months for the first year and once a year thereafter. These tests will measure blood sugar, potassium, kidney function, and liver function. You will also be asked to allow blood and urine specimens to be taken and stored for future non-genetic studies. Also, additional blood samples may be taken occasionally to monitor your treatments for safety, which may require you to come in for additional visits.

Some urine will be collected at the baseline visit and every two years thereafter so that it can be examined for urine protein and creatinine (a measure of kidney function). You will also have an electrocardiogram (a recording of the electrical activity of the heart, also called an ECG or an EKG) at baseline and every two years thereafter. A limited eye exam will be done every other year.

If you are in the cholesterol study, your blood cholesterol will be measured every four months during the first year and every year thereafter until the end of the study. You will also have blood drawn every four months throughout the study to check your kidney function. If you are not in the cholesterol study, you will have your cholesterol measured every year.

As part of diabetes management, you will be expected to check your own blood sugar, as discussed later. If you are assigned to the "intensive" blood sugar goal you will have more frequent blood sugar testing by the clinic. This testing will range from once per month during the first 4 months of treatment to every two months thereafter.

You also have about a 1-in-5 chance of being chosen to complete questionnaires about your quality and activities of life, and your diet and physical activity levels. These questionnaires will be given at the beginning of the study, your 1 year visit, 3 year visit, and 4 year visit. The questionnaires will take about one hour of your time. In addition, you may be chosen to participate in a group where health care costs will be monitored (and you would be asked to give permission to obtain records from any hospitalizations).

Certain medical procedures are recommended for people with diabetes that are not part of the research study. These include annual eye exams by an ophthalmologist, annual foot exams, annual flu and pneumococcal vaccinations, and electrocardiograms (ECGs or EKGs). The study eye examination does not replace the recommended annual eye exams by an experienced eye care professional, such as an ophthalmologist (a doctor who specializes in the diagnosis and treatment of eye diseases).

During the course of the trial, our central Coordinating Center at Wake Forest University School of Medicine, or its representatives may contact you, about your participation in the trial. For example, you may be asked if you are having any trouble taking any of your medications. You may also be asked how you are feeling and whether you have been in the hospital for any reason, why and where you were hospitalized.

POTENTIAL RISKS OF PARTICIPATING IN THE ACCORD STUDY

What are the possible risks and discomforts? Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are considered to be abstinence (not having sex), oral contraceptives (the pill), intrauterine device (IUD), DepoProvera, Norplant, tubal ligation (tubes tied), or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable method, involves the careful use of condoms and/or a spermicidal foam or gel along with a diaphragm, cervical cap, or sponge. We encourage you to discuss this issue further with your doctor if you have any questions.

If you are a pregnant woman, you cannot participate in this study. Because some methods of birth

control are not 100% reliable, a negative pregnancy test is required at least 10 days after your last normal menstrual period if you are a sexually active woman of childbearing potential.

This study requires that blood be drawn from a vein in your arm several times during the study. Drawing blood may result in pain at the point of puncture, a feeling of faintness, irritation of the vein, and bruising or bleeding at the site of the needle stick. There is also a very slight possibility of an infection at the needle puncture site. The study visits, procedures, and lab work might be more often than your medical conditions usually require, but they are very important for the study.

This study requires daily finger-stick measurements of your blood sugar level. You probably have experience testing your blood sugar by finger-stick before coming into the study. You need to test your blood sugar daily because it is very important for the study that you keep your blood sugar values at the assigned goal. If you are assigned to the intensive blood sugar goal, there is a good chance that at some point you will be asked to do up to eight finger sticks a day to properly correct your blood sugar. Your blood sugar checks will be reviewed by clinic personnel and will be used to figure out your treatment plan. Clinic personnel, or others working for ACCORD, may contact you to discuss your blood sugar results.

Treating blood sugar in persons with diabetes can sometimes cause blood sugar to be too low. This condition, called "hypoglycemia", can result from changing diet, exercise, or medication. Symptoms are usually mild but sometimes can be more serious.

Mild symptoms of hypoglycemia include hunger, anxiety, dizziness, or light-headedness. Sometimes there is sweating, fatigue or mild confusion, tremors (shaking) or palpitations (feeling your heart beating in your chest). Hypoglycemia may cause loss of consciousness. If this occurs while operating machinery such as driving a car, it can result in injury or even be life threatening.

In rare cases, hypoglycemia can be very severe and require emergency treatment or hospitalization. Severe hypoglycemia may cause brain damage, coma, or death. Severe hypoglycemia can occur in any patient taking medication to lower blood sugar. It is more likely to occur in those treated with insulin to achieve lower glucose targets, as in the intensive treatment group of this study.

A sugar-containing drink such as fruit juice usually quickly relieves the milder symptoms. You may be given sugar pills to raise your blood sugar if you have symptoms. Medications are sometimes needed to treat severe hypoglycemia. These may include intravenous (I.V.) fluids or injections of glucagon, a medication that rapidly increases blood sugar.

Regardless of which blood sugar treatment group you are assigned to, safety will always be of first importance when changes in the management of your blood sugar are made. Based on data from previous studies it is estimated that, in the intensive group, about six out of 100 participants will have a serious complication (such as hospitalization or emergency room visit for hypoglycemia) every year. In the standard group about 2 participants may have such a complication every year. In either group, ACCORD doctors and nurses will take action to lessen the risk of hypoglycemia should it occur too often or in a severe form. On the other hand participants in the standard group may have a somewhat higher risk of complications related to diabetes (like eye, kidney disease or abnormal nerve function). It is estimated that, in the intensive group, about one out of 100 participants will have such a complication every year. In the standard group about 1.5 participants may present such a complication every year.

If you are assigned to the intensive blood pressure group, you may experience blood pressure that is too low. Symptoms of low blood pressure may be mild, such as feeling a little lightheaded, or less often may be more severe, such as dizziness, fatigue, or fainting. Sitting or lying down often relieves these symptoms. You should notify your clinic doctor or nurse if you have these symptoms. Clinic staff will follow you closely to lower your chances of having too-low blood pressure.

What are the side effects of the medicines used in the study? All drugs have a potential risk of an allergic reaction, which if not treated quickly, could become life threatening.

You may have side effects from the specific medications chosen as treatments. Medications that may be

used at this time in ACCORD are listed below. Additional medications may be chosen in the future. The ACCORD staff will tell you about any new medicines that they may give you.

Possible side effects for the classes of medications include the following. Your doctors have ways to manage these effects.

<u>Blood sugar treatments</u>

Sulfonylureas [<u>glimepiride</u>]: The most common side effects associated with this family of medicines include hypoglycemia (low blood sugar), weight gain, and allergies. Very rarely, blood cell abnormalities may occur. Your doctor has ways of managing the blood cell abnormalities.

Biguanides [<u>metformin</u>]: Common side effects associated with this drug class include nausea, vomiting, diarrhea, bloating, loss of appetite, or metallic taste in the mouth. These usually get better after the first few weeks of treatment. If these treatments are stopped, the side effects will go away over a day or two. Very rarely, people can have a severe reaction known as lactic acidosis (a condition that occurs when your body fluids and tissues have too much acid in them). Lactic acidosis almost always occurs in people with advanced kidney disease, liver disease or heart failure, and in people who drink alcohol heavily. Every effort will be made to avoid using this drug in people with those conditions.

Thiazolidinediones (TZDs) [<u>rosiglitazone, pioglitazone</u>]: The most common side effects related to this group of medicines include fluid retention (a condition that occurs when your body holds in too much water) and weight gain. Although the 4 mg/day dose of rosiglitazone (the TZD to be used in ACCORD) is the only dose of rosiglitazone that has been approved by the U.S. FDA for use with insulin, higher doses of rosiglitazone, which you may be placed on, have been combined with insulin in medical practice. The use of drugs like rosiglitazone together with insulin may cause fluid retention, which could lead to or worsen heart failure. Heart failure is a decreased ability to pump enough blood throughout the body. Symptoms of heart failure include shortness of breath, cough, fatigue, tiredness, ankle swelling, or weight gain. If your doctor prescribes insulin together with rosiglitazone, you will be monitored closely for these symptoms, so that the medications can be adjusted or, if necessary, stopped.

Although there has been no report of liver difficulties with rosiglitazone, a related medication was removed from the market due to rare, severe liver reactions. Thus, if you require this medication, you will need to have blood tests looking for liver problems every two months for the first year after you begin the medication and once a year thereafter.

Insulin [<u>various short-, intermediate-, or long-acting forms, including aspart and glargine</u>]: Potential side effects related to insulin use include: low blood sugar, low potassium in the blood, allergies or skin changes.

Meglitinides [<u>repaglinide</u>]: Common side effects include headache, upper respiratory infections, nausea, vomiting, constipation, and diarrhea. The most serious side effect is hypoglycemia.

Alpha-Glucosidase Inhibitors [acarbose]: Side effects include flatulence (gas), diarrhea and abdominal discomfort These are generally mild to moderate in severity and usually diminish in frequency and intensity with time. Very rarely, this medication may cause skin reactions, hepatitis, and/or jaundice (yellowing of the skin or whites of the eyes, indicating possible liver problems).

<u>Blood pressure treatments</u>

Angiotensin Converting Enzyme Inhibitors (ACE-I) [<u>benazepril, lisinopril, ramipril</u>]: Potential side effects associated with this type of medicine include: dizziness, headache, fatigue, nausea, diarrhea, cough, rash, high potassium in the blood, low blood pressure upon standing, harm to kidney function and rarely angioedema (swelling of the face, lips and tongue that can result in difficulty breathing or in rare cases, death).

Diuretics [<u>chlorthalidone, hydrochlorothiazide</u>]: Potential side effects associated with this class of medication also known as "water pills" include: muscle cramps, nausea, vomiting, diarrhea, dizziness, rash, weakness, low blood pressure, low potassium, high blood sugar, partial or total lack of ability to

perform sexual function, and gout (a painful joint condition that occurs when too much acid and salt build up in the blood stream and joints).

Beta Blockers [metoprolol]: The most common side effects associated with this group of medicines include: dizziness, fatigue, stomach upset, depression, cold hands and feet, low blood pressure, changes in heart rhythm and heart rate, and decrease in sexual function. Beta-blockers may also hide some of the symptoms but not the hazards of low blood sugar. If you begin taking these medications, you should not stop taking them without talking to your study doctor first.

Calcium Channel Blockers [isradipine, diltiazem, amlodipine, nifedipine]: The most frequent side effects associated with these medications are: ankle or foot swelling, dizziness, flushing, palpitations (awareness of your heartbeat), headache, fatigue, nausea and abdominal discomfort. Occasionally, severe hypotension (abnormally low blood pressure) may occur when starting these medications or adjusting their dose. Rarely, increased angina (chest pain) and myocardial infarctions (heart attacks) may occur in people with severe coronary artery disease. When combined with a Beta Blocker, the medication nifedipine may cause congestive heart failure (a decreased ability to pump enough blood through the body), which can be serious but is very rare.

Alpha Blockers [terazosin]: Potential side effects associated with this category include: fainting, dizziness, fatigue, swelling, low blood pressure, partial or total lack of ability to perform sexual function, changes in heart rhythm and certain blood cell abnormalities.

A-II Receptor Blockers [candesartan, valsartan]: The most common side effects are dizziness, headache, fatigue, diarrhea, muscular-skeletal pain. More serious side effects are angioedema (swelling of the face, lips and tongue that can result in difficulty breathing or in rare cases, death) and severe hypotension. This family of drugs may also affect your kidney function. Your doctor may do blood tests to see if your kidneys are performing properly.

Loop Diuretic [furosemide]: rare side effects include thrombocytopenia (low platelet count), rash, pancreatitis (inflammation of the pancreas), and jaundice (yellowing of the skin or whites of the eyes, indicating possible liver problems). Serious side effects include abnormalities in blood cells.

Sympatholytics [reserpine]: The most common side effects include dizziness, dry mouth, nausea, vomiting, nasal congestion, peripheral edema (too much fluid in the body's tissues), stomach cramps, headache, impotence, depression, nervousness, shortness of breath, nightmares, difficulty with urination, shaky hands, and anorexia (poor appetite). More serious side effects include dysrhythmias (heart rhythm abnormalities), black tarry stools, hematemesis (vomiting blood), bradycardia (slow heart rate), chest pain, and thrombocytopenia (low platelet count).

Vasodilators [hydralazine]: Side effects include headache, tachycardia (fast heart rate), angina (chest pain), and palpitations. Rare but more serious side effects include abnormalities in blood cells and lupus-like syndrome.

Potassium Sparing Diuretics [triamterene]: The most common side effects include diarrhea, nausea, vomiting, gastrointestinal distress, dizziness, dry mouth, pruritis (itching), rash, sensitivity to light, weakness, hypotension, muscle cramps, blood chemical imbalances (such as too much potassium), impaired kidney function, elevated uric acid, blood cell abnormalities and reduced folic acid stores. More serious possible side effects include increased acid in the blood and shock due to an allergic reaction to the medication.

Alpha-beta blockers [carvedilol]: The most common side effects are dizziness and fatigue. The more serious side effects include AV block (a heart rhythm disturbance), bradycardia (slow heart rate), thrombocytopenia (low platelet count), and bronchospasm (tightening of breathing airways). Alpha-beta-blockers may also hide some of the symptoms but not the hazards of low blood sugar.

Lipid treatments

HMG-CoA Reductase Inhibitors (statins) [simvastatin]: Common side effects associated with this class of cholesterol-lowering medications include: headache, dizziness, stomach upset. Rare, but more

serious side-effects are muscle aches, rash and elevated liver enzymes (indicating possible liver problems) in the blood. (Also, see 'Drug Interactions' discussed below.)

Fibrates [fenofibrate]: Potential side effects associated with these medications include: abdominal pain, stones in the gall bladder, jaundice (yellowing of the skin and/or whites of the eyes, indicating possible liver problems), headache, change in taste, elevated liver and kidney function tests, and certain abnormalities in blood cells. Your study doctor has ways to manage these blood cell abnormalities.

Fenofibrate could possibly harm the kidney. Blood tests will be done regularly to look at your kidney functioning. If your results are not normal your dose of fenofibrate or placebo (whichever you are on) will be reduced. If your values do not improve, the medication will be stopped entirely. After your dose is reduced or stopped, your study doctor will continue to monitor your kidney function. (Also, see 'Drug Interactions' discussed below.)

Drug Interactions

What are some of the ways the study drugs can interact? The Food and Drug Administration (FDA) has approved all drugs that will be used in ACCORD. Most have been used for many years. Therefore, we know much about the way these drugs work and how they interact with other drugs - especially other treatments that will be used in this study.

Researchers know that using a sulfonylurea (a type of drug that lowers blood sugar) with certain other drugs should be avoided. Your study doctor will make sure that you do not take these kinds of medicines together.

Researchers also know that using statins and fibrates together may increase the chance for certain side effects such as liver problems and muscle pain and inflammation. These side effects are rare, but are more likely at higher statin doses. If your dose of simvastatin is increased to 40 mg per day, your chance of side effects may be increased. Many doctors use simvastatin and fenofibrate together, and the ACCORD trial will use caution whenever you are given this combination. Additionally, the ACCORD clinic will be checking your blood to make sure that the study medications are not harming your liver or muscles. These tests will be done at 1, 4, 8, and 12 months after you begin the medications, and every year after that. If your study doctor thinks that the statin and fibrate medicines are causing problems for you, then he/she may take you off one or both these medicines.

If you are eligible to be in the lipid portion of ACCORD and if you are on warfarin (also called Coumadin), your personal doctor will be informed both by phone and in writing that you may be on fenofibrate. Because the use of fenofibrate generally means that your dose of warfarin should be reduced to avoid excessive risk of bleeding, you will be tested to see how fast your blood clots. This blood test can be done by either the ACCORD clinic or by your private doctor. You will not be randomized until the ACCORD clinic staff speaks with your private doctor about monitoring the appropriate dose of warfarin for you. If you are placed on warfarin during the study, you will need to make sure that your private doctor is reminded that you may be on fenofibrate.

POTENTIAL BENEFITS

What are the possible benefits? The ACCORD treatment may or may not be of personal benefit to you. The information gathered from the study will be very important for the treatment of diabetes in the future. There will be no charge to you for any of the required tests and procedures performed during your participation in this study. Clinic visits, physical exams, laboratory tests, electrocardiograms and any other procedures associated with the research aspects of this study are paid for by the study. In addition, your medications for the blood sugar control as well as for the blood pressure control portion or blood lipid control portion of ACCORD (whichever part you are in) will be provided to you free of charge. You will not be paid for your participation in this study.

ALTERNATIVE TREATMENTS

If you chose not to participate, what other options do you have? You do not have to participate in this research study in order to receive treatment. A number of treatments are available for diabetes, high blood pressure, or high cholesterol. These treatments include drugs, diet, exercise, and weight loss. If you decide to stop participating in this study, your personal doctor should manage your medical care.

NEW INFORMATION

What if we learn about new risks during the study? You will be given any new information gained during the course of the study that might affect your health, welfare, or willingness to stay in the ACCORD study. Results of your laboratory tests and clinical measurements will be provided to you to share with your personal physician.

PRIVACY

How will your privacy be protected? Any information obtained about you during this study will be treated as strictly confidential to the full extent permitted by applicable law. To ensure confidentiality, a code number will be assigned to you. Your name and any other potentially identifying information will not be used on any data or samples you provide. However, your name and Social Security and Medicare numbers will be recorded and stored centrally to help the study keep track of any illnesses you may experience. Also, in order to receive supplies (glucose strips) to measure your own blood glucose during the trial, you will need to provide the information that will permit billing for Medicare (if you are covered) and/or other insurance you may have (if you have it.) You will not be identified in any report or publication about this study.

Your records for this study may be reviewed by authorized representatives from the National Heart, Lung, and Blood Institute, the Food and Drug Administration (FDA) and monitoring personnel from the _____ Clinical Center Network Office for the study at _____and by the committee in charge of protecting research participants at_____.

At the end of the study, all forms with your name or other identifying information will be kept in a locked room for a period of five years. Only your study doctor or co-workers assisting the doctor will have access to these forms. After five years, the forms will be destroyed.

Also at the end of the study, the Coordinating Center will provide the National Heart, Lung, and Blood Institute (NHLBI) data from the study, without personal identifying information such as your name, address, Social Security number, or Medicare number. Blood, urine, and/or tissue samples or other materials taken from you during the study will be considered donated by you to medical research. These materials may also be provided to the NHLBI at the end of the study, again without personal identifying information. The data and/or materials may be shared with other scientists who meet NHLBI requirements including treating the data or materials as medically confidential, obtaining approval from their Human Subjects review boards, and agreeing not to share the data or materials with other parties. Drug companies that have contributed drugs, and in some cases money, to the ACCORD study also will be provided study data without any personal identifying information.

U.S. Federal Certificate of Confidentiality. It is particularly important to you to know that ACCORD has been granted a Certificate of Confidentiality from the United States Federal Government to make sure we can best protect your privacy. This certificate means that the ACCORD researchers cannot be forced to tell anyone not connected with the study about your participation. This includes courts and police. The researchers will only release information if you request it.

There are some limits to the researcher's ability to maintain your confidentiality. If we learn that keeping information private would immediately put you in danger, or put someone else we know about in danger, then we will have to tell the appropriate agencies to protect you or the other person.

INJURY

What will happen if you become ill during the study or suffer a complication related to the treatment that you are receiving as part of the study? While it is not likely that you will suffer major health problems as a result of your participation in this study, the medical treatment that is a part of this study carries a small risk of serious health problems. Of course, should a problem occur, or should you need emergency medical help, necessary emergency care would be provided and the investigator working with you would help you find a doctor to continue your care if needed. Any cost of medical care that results from such a health problem will be your responsibility and will not be paid for by the National Heart, Lung, and Blood Institute, the study investigators, or the hospital or clinic conducting this study.

QUESTIONS ABOUT THE STUDY AND YOUR RIGHTS

What if you have questions about this study? For questions about the study or in the event of a research-related injury, contact the study investigator, _____, at _____ [INCLUDE AFTER-HOURS NUMBER].

What if you have questions about your rights as a participant? For questions about your rights as a research participant, you may contact the Chairman of the Institutional Review Board, which is a group of people who review the research to protect your rights as a research participant, at _____. You will be given a copy of this consent form.

What if you want to stop before your part in the study is complete? Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your study doctor also has the right to stop your participation in this study at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

GENETIC STUDIES

What is the goal of the genetic studies? One goal of ACCORD is to examine your genetic material (DNA) and its relationship to the effects of the treatments. If you volunteer to participate in the genetic studies you will be asked for a sample of blood (about 1 teaspoon) to obtain DNA from your blood cells. Information gained from research on your DNA may be used to develop new ways to detect or treat major diseases.

Will the DNA samples be shared with other institutions? If you agree to participate in the genetics portion of the study, the ACCORD Central Laboratory may share DNA samples with researchers participating in ACCORD. If you give permission, samples may also be shared with other research laboratories studying the genetics of type 2 diabetes and the development of heart and blood vessel diseases, other major diseases, health conditions, or risk factors. The scientists from these laboratories would be given the DNA without any information to identify you.

How will genetic information be kept private? Only the ACCORD Central Laboratory will have access to the samples. No other individual, including your spouse, parents, children, physician or employer will have access to the stored sample or information gained from your stored sample. At the end of the study, your samples may be provided to other investigators under certain conditions, without any personal identifying information (See Privacy section above).

How long will the DNA samples be kept? Your sample may be kept until it is no longer of scientific value. If, at any time during the study, you decide that you do not wish to have your DNA sample stored any longer, you may notify your ACCORD study coordinator and the sample will be destroyed.

Who owns the samples? By checking "yes" at the end of this document, you volunteer to provide

genetic samples for medical research purposes. Your DNA will not be sold to anyone or to institutions or companies for financial gain or commercial profit without your consent. Also, neither you nor your heirs will receive money from any discoveries or inventions made using the information and/or specimens you provide. There is no cost to you or your insurance company for the storage and use of the samples.

Will you receive study results of research involving your samples? You will not be informed of the results of the research performed on your genetic blood sample, although genetic tests may be developed after a study of samples in the ACCORD study. If there is any new information about genetic testing for type 2 diabetes and its relationship to heart and blood vessel diseases or other health conditions, you will be informed by your study doctor if this information may be important to you or your family.

PARTICIPANT'S AGREEMENT FOR THE GENETIC PORTION OF ACCORD

*Please check **one** of the following choices:*

       ____ **Yes**, I agree to participate in the genetic portion of ACCORD

       ____ **No**, I do not agree to participate in the genetic portion of ACCORD

If you agreed to participate in the genetic portion of ACCORD, please check one of the following regarding diseases to be studied:

       ____ I agree to allow my genetic sample to be studied for genes related to any major disease or health condition or risk factors.

       ____ I agree to allow my genetic sample to be studied **ONLY** for genes related to diabetes, blood pressure, blood cholesterol abnormalities, heart disease, other cardiovascular diseases, kidney diseases, or other risk factors for heart disease or for diabetes.

If you agreed to participate in the genetic portion of ACCORD, please check one of the following regarding investigators who will have access to the genetic samples:

       ____ I agree to allow my genetic samples to be used for research by ACCORD investigators as well as by other researchers who meet NHLBI standards and procedures.

       ____ I agree to allow my genetic samples to be used **ONLY** for research by ACCORD investigators.

PARTICIPANT'S AGREEMENT FOR ACCORD STUDY

I have read the information provided above. I voluntarily consent to participate in the ACCORD study.

_____   _____

Participant's signature   Date

_____

Printed name of participant

_____   _____

Signature of person obtaining consent   Date

_____

Printed name of person obtaining consent

Appendix II:
Charges to the Subcommittees
of the ACCORD Steering Committee

During the protocol development phase of ACCORD, the Subcommittees of the Steering Committee were responsible for developing specific portions of the protocol and for making recommendations to the ACCORD Steering Committee for approval. During the data collection phases of the trial, the Subcommittees will be responsible for monitoring specific portions of the conduct of the trial and will provide periodic status reports to the Steering Committee.

Medical Interventions Subcommittee

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

Recruitment and Retention Subcommittee

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

Measurement and Quality Control Subcommittee

This subcommittee developed the general data collection forms for use in the trial (in conjunction with other ACCORD subcommittee recommendations) and identified (with input from other subcommittees) clinical laboratory data to be collected. This subcommittee will also establish criteria under which the clinics, the Coordinating Center, and Core Units are expected to perform. This subcommittee will review all aspects of quality control monitoring and will act on these reports. Deviations from performance levels will be brought to the attention of this

subcommittee by the Coordinating Center. The monitoring activities will include, but not be limited to, monitoring data quality, timeliness, completeness; monitoring alert levels; monitoring data entry, and, with respect to the core labs, reviewing the processing of samples. Reports from the Site Visitors to the Clinical Center Networks and to the Core Labs will be reviewed by this Subcommittee to determine whether action should be taken.

Design and Analysis Subcommittee

This subcommittee reviewed alternative designs for the trial, including the impact of various designs on sample size, statistical power, and patient recruitment. This subcommittee will of necessity work closely with the Medical Interventions Subcommittee and the Recruitment and Retention Subcommittee on the development of analysis plans for recruitment and adherence monitoring.

Health-related Quality of Life/Cost-Effectiveness Subcommittee

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

Operations Subcommittee

Selected staff of the CCNs will meet as an Operations Subcommittee to discuss and review the progress of the trial. The purpose of this group is to assure communication among the study sites with respect to overall study coordination. Also attending these meetings will be representatives from the Coordinating Center and the Project Office, who will inform and train the Project Coordinators on trial procedures. The CCN Project Coordinators, who are most aware of the day-to-day issues at the sites, will be an invaluable resource to the trial and will be invited to make recommendations regarding the conduct of the trial to the Steering Committee for review and consideration.

Morbidity and Mortality Subcommittee

This subcommittee recommended the definitions to be used for the classification of study events that comprise the primary and secondary ACCORD outcome measures. This Subcommittee will develop the procedures for collecting the relevant information from the clinical centers, develop the procedures to classify each applicable event, and develop quality control procedures for the ascertainment and classification of these clinical events. During the data collection phases of the trial, this subcommittee will oversee 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 will 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.

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 approving analyses/papers/presentations, soliciting writing group members, and monitoring the progress of all proposed papers to ensure their prompt completion and publication.

Laboratory and Ancillary Studies Subcommittee

This subcommittee will review procedures regarding the collection and storage of body fluids and specimens, provide appropriate recommendations to the Steering Committee regarding the collection and storage, and develop policies regarding access to the stored fluids and specimens. The subcommittee will also be responsible for reviewing ancillary study proposals, providing feedback to the Principal Investigator of the proposal, and making recommendations to the Steering Committee regarding the proposals.

Appendix III:
ACCORD Conflict of Interest Policy
(Revised 08/24/01)

General Principles

1.   This full policy is to be made public on our Website and in publications when possible.

2.   The primary concerns are twofold. First, that the ACCORD investigators maintain the internal integrity of the study by which we mean the confidence among ourselves (investigators and staff) as we develop and modify the detailed protocol, that advice is being given and decisions are being made in as unbiased and fully informed manner as possible. Second, that we maintain the external integrity of the study by which we mean the acceptance of our process and results as having met public standards of conduct.

3.   To meet these goals we will obtain full disclosure by all of the key members of the study (defined below) of their, and their immediate family's, financial relationships with all pharmaceutical and biomedical companies judged to have an active or potential interest in the conduct and outcome of the study. These are to be reported on a standard form, each of which will be reviewed on at least an annual basis, or more frequently if there is a significant change from the last report, by a small subset of the Executive Committee (termed the Oversight Committee). The Oversight Committee will be comprised of the Chair of the Steering Committee, the PI of the Coordinating Center, and the NHLBI Project Officer. The information to be reported will be detailed, but will not include specific dollar amounts, although the definitions below require that certain relationships be segregated by those above and below certain dollar thresholds.

4.   All of the study PIs, Co-PIs, and the Steering Committee and its various subcommittees' members are covered by this policy.

5.   A conflict of interest will not necessarily exclude any member of the study from participating in study discussions, unless required in individual cases by the Oversight Committee. However, full disclosure of all potential conflicts of interest will be made at each meeting to all attendees in an effective, but non-cumbersome manner. This includes the full Steering Committee as well as each of its subcommittees.

6.   A significant financial conflict of interest, defined below, will cause a person to recuse himself or herself from voting on all issues related to the conflict. All such actions will be recorded and kept as part of the study record in the Coordinating Center. This policy applies most especially to the subcommittees making recommendations to the full Steering Committee during the protocol design phase, as well as to the Steering Committee itself.

7.   All financially relevant relationships are to be reported. Only those relationships that are between the individual and the specific company (rather than between the individual's

parent institution and the specific company, for example) present the potential for a significant financial conflict of interest, defined under paragraphs 9a and 9b below. Specifically, research funding for contracts or grants to the parent institution which provide support to the individual, his/her laboratory or his/her close scientific collaborators is not ordinarily judged to present the potential for a financial conflict of interest, although such awards are to be fully disclosed as a part of this policy.

8. Those financially relevant relationships that are to be reported include employment, consultancies, board memberships, honoraria, stock ownership or options, grants, contracts, patents received or pending, and royalties. The Oversight Committee will decide, with #9 below as a guideline, whether any of these and other relationships in each individual case are significant enough to warrant recusal from voting or discussions.

9. A significant financial relationship is defined to exist:

    a. when the dollar amount awarded on an annual basis, or expected-to-be awarded on an annual basis, with regard to each related corporate relationship exceeds $25,000. The Oversight Committee may also judge lower dollar amounts as significant in specific/individual circumstances.

    b. or when there is any equity holding in a related company (excluding mutual funds and blind trusts). Again the Oversight Committee may decide in individual circumstances that the equity holdings are relatively minor enough to not present a real conflict of interest.

10. Significant financial relationships in existence since October 1, 1999 between ACCORD investigators and all pharmaceutical and biomedical companies judged to have an active or potential interest in the conduct and outcome of the study will be described in all study reports and publications. Similar relationships, but which are not significant, as well as actions taken early in the design phase of ACCORD that end significant financial relationships (e.g., stock divestment) will all be described on the ACCORD web site, but will not ordinarily be listed in study reports or publications. In addition we will obviously meet or exceed the reporting standards of the journals publishing our manuscripts.

Action to Control Cardiovascular Risk in Diabetes

ACCORD

Approved Amendments to ACCORD Protocol
(Original Post-Vanguard Protocol is dated 10/16/00)

Major Changes Between October 16, 2000 and September 13, 2001 Versions of ACCORD ("Action to Control Cardiovascular Risk in Diabetes") Protocol

(Report Date: September 21, 2001)

This document describes the nine amendments approved by the ACCORD Steering Committee between the October 16, 2000 and September 13, 2001 versions of the ACCORD Protocol.

AMENDMENT 1:
Adding a centrally measured CPK test at the 2 month follow-up visit for participants in the Lipid Trial who are on both simvastatin and the blinded fenofibrate/placebo study medication.

From October 16, 2000 Protocol

The first post-randomization CPK measurement is scheduled in Table 2.2 as occurring at the 4 month follow-up visit.

Change to September 13, 2001 Protocol

For the purpose of safety monitoring, an additional CPK measurement is added at the 2 month follow-up visit for these participants.

This change appears in Table 2.2 (*Scheduled Examination Components by Visit*) and in Sections 3.3b (*Lipid Intervention-Research Design*) and 4.3 (*Adverse Reactions and Discontinuation of Study Drug*).

AMENDMENT 2:
Adding a centrally measured lipid profile at the 2 month follow-up visit for participants in the Lipid Trial

From October 16, 2000 Protocol

The first post-randomization lipid profile for participants in the lipid trial is scheduled in Table 2.2 (*Scheduled Examination Components by Visit*) as occurring at the 4 month follow-up visit.

Change to September 13, 2001 Protocol

For the purpose of reaching the LDL-C treatment targets sooner, an additional lipid profile is added at the 2 month follow-up visit for these participants.

This change now appears in Table 2.2 (*Scheduled Examination Components by Visit*), in Section 3.3.b (*Lipid Intervention-Research Design*), and in Appendix I (*Model Informed Consent,* in the eighth paragraph under STUDY SUMMARY)

AMENDMENT 3:
Stepping-down blood pressure therapy among standard blood pressure group participants

From October 16, 2000 Protocol

Referring to participants in the standard blood pressure group, the last sentence of Section 3.4.f (*Achieving and Monitoring Blood Pressure Control*) of the October 16, 2001 version of the protocol states: "Step-down is allowed at the discretion of the ACCORD therapist, after consultation with the participant, when the SBP has been <135 mm Hg on two successive clinic visits. "

Change to September 13, 2001 Protocol

To improve the ability to reach but not exceed the blood pressure goals in the standard blood pressure group, the last sentence of Section 3.4.f (*Achieving and Monitoring Blood Pressure Control*) now states: "Step-down is allowed at the discretion of the ACCORD therapist, after consultation with the participant, when the SBP has been < 135 mm Hg on two successive clinic visits or is < 130 mm Hg at the current visit."

This change is also noted in Figure 3.7 (*Treatment Algorithm for Standard Blood Pressure Group*), which is a revision of Figure 3.5 of the October 16, 2000 Protocol.

AMENDMENT 4:
Blood Pressure Milepost Follow-up Visits

From October 16, 2000 Protocol

Referring to participants in the blood pressure trial, the first sentence of the second paragraph of Section 3.4.f (*Achieving and Monitoring Blood Pressure Control*) states: "At the point of randomization, all participants in the hypertension study will automatically be assigned a series of milepost dates." However, Section 3.4.d (*Antihypertensive Classes*) correctly states that Milepost Visits are for the intensive blood pressure group participants.

<u>Change to September 13, 2001 Protocol</u>

For the purpose of correcting inconsistencies in the protocol, Section 3.4.f (*Achieving and Monitoring Blood Pressure Control*) now states that the Milepost Visits are for the intensive blood pressure group participants.

AMENDMENT 5:
What to do if a Lipid Trial participant is already on the maximum dose of 20 mg and the LDL-C goes above 130 mg/dl (3.36 mmol/l) on 2 consecutive visits

<u>From October 16, 2000 Protocol</u>

The second sentence of the fourth paragraph of Section 3.3.d (*Lipid Goals*) states:

"If the participant is already on the maximum dose of 20 mg and the LDL-C goes above 130 mg/dl on 2 consecutive visits (even after compliance review and dietary counseling), the investigator will be notified by the Coordinating Center to take the participant completely off his/her ACCORD lipid study medications and to notify the participant's personal physician of the elevated LDL-C values so that appropriate lipid-lowering therapy may be initiated."

<u>Change to September 13, 2001 Protocol</u>

For the purpose of assuring participant safety, this description in Section 3.3.d (*Lipid Goals*) (beginning as the second sentence in the fifth paragraph) is expanded to:

"If the measured LDL-C goes above 130 mg/dl (3.36 mmol/l) for a participant who has already had his/her statin dose doubled once or twice, and has reached a dose of 20 mg/day, the Coordinating Center will notify the clinical site. In this instance, the clinic staff ought to confirm compliance with the study statin, refer the participant to a nutritionist for dietary instruction/reinforcement (if appropriate), and schedule a blood draw for the next regularly scheduled visit. This blood specimen needs to be sent to the ACCORD Central Chemistry Laboratory for lipid analysis.

If the participant is already on the maximum dose of 20 mg and the LDL-C goes above 130 mg/dl (3.36 mmol/l) on 2 consecutive visits (even after compliance review and dietary counseling), the following will occur:

- The investigator will be notified by the Coordinating Center to take the participant off the fibrate/placebo pills.
- The participant will remain on simvastatin 20 mg/day until placed on nonstudy statin by his/her primary caregiver.
- The site staff will make an appointment with the participant's doctor for follow-up.

- The site staff will also provide a letter for the participant to take to his/her physician for the follow-up visit. This letter will include the blood lipid values and describes the medication regimen the patient was on when the blood was drawn.
- The site staff will confirm that the participant had visited their physician.
- From that point on, the participant would be treated for their lipids by their personal physician and given results of any ACCORD lipid determinations to share with their physician."

AMENDMENT 6:
What to do if a Lipid Trial participant exceeds triglyceride 750 mg/dl (8.47 mmol/l)

From October 16, 2000 Protocol

The seventh paragraph of Section 3.3.d (*Lipid Goals*) states:

"If the triglyceride exceeds 750 mg/dl on two consecutive measurements, even after the above measures have been conducted, the Coordinating Center will notify the Clinical Site Investigator. The participant should be taken off his/her lipid study medications and the participant's private physician notified of the elevated triglyceride levels so that open-labeled lipid therapy may be started. "

Change to September 13, 2001 Protocol

For the purpose of assuring participant safety, this description is expanded as the ninth paragraph of Section 3.3.d (*Lipid Goals*), which now states:

"If the triglyceride exceeds 750 mg/dl (8.47 mmol/l) on two consecutive measurements, even after the above measures have been conducted, the following will occur:

- The participant will be taken off simvastatin and the fibrate/placebo medication.
- The participant will be dispensed 200 mg/day of fenofibrate or 600 mg BID of gemfibrozil until placed on nonstudy fibrate by his/her primary caregiver.
- The site staff will make the appointment for follow-up by the participant's physician and will confirm that the appointment was kept.
- The site staff will also provide a letter for the participant to take to their physician for the follow-up visit. This letter will include the blood lipid values and describes the medication regimen the patient was on when the blood was drawn.
- From that point on, the participant will be treated for their lipids by their personal physician and given results of any ACCORD lipid determinations to share with their physician."

AMENDMENT 7:
Lowering the LDL-C threshold level for increasing the dose of simvastatin for participants in the Lipid Trial.

From October 16, 2000 Protocol

Section 3.3.d (*Lipid Goals*) describes that the initial LDL-C threshold value for increasing the dose of simvastatin as being 120 (3.10 mmol/l) and that a higher threshold of 130 mg/dl (3.36 mmol/l) would be used subsequently.

Change to September 13, 2001 Protocol

To simplify the process, the LDL-cholesterol level that triggers the initial and all subsequent up-titrations will be 120 mg/dl (3.10 mmol/l).

This change appears in the third paragraph of Section 3.3.d (*Lipid Goals*).

AMENDMENT 8:
LDL-C Reporting to the Clinics in the Lipid Trial

From October 16, 2000 Protocol

The second paragraph of Section 3.3.d (*Lipid Goals*) indicates that the Coordinating Center will notify the Clinical Sites when an adjustment in the dose of simvastatin is required. The Coordinating Center only reported on those patients that needed a dose adjustment. No LDL-C value was given to the clinics.

Change to September 13, 2001 Protocol

To clarify whether or not a dose adjustment was needed and to accelerate the process of notification, the Central Lab will report directly to the sites and tell them whether the LDL-cholesterol is ≤ or > 120 mg/dl (3.10 mmol/l).

This change appears in the second paragraph of Section 3.3.d (*Lipid Goals*).

AMENDMENT 9:
Allowing the use of prn ('as needed') lipid determinations (measured centrally) for participants in the Lipid Trial to follow-up lipid values measured outside the study.

From October 16, 2000 Protocol

No allowance is currently made for prn ('as needed') lipid determinations for the purpose of confirming values measured outside the study. Currently, a lipid profile is obtained only at the 2nd (per Amendment #2), 4th, 8th, 12th, and subsequent annual follow-up clinic visits.

Change to September 13, 2001 Protocol

It is now permissible to obtain a prn blood specimen and have it centrally analyzed by the ACCORD Central Lab.

The fourth paragraph of Section 3.3.d (*Lipid Goals*) now states that 'If needed, prn Central Laboratory LDL-C analyses (reported directly by the ACCORD Central Laboratory to the clinical sites as either $\leq$ or $>$ 120 mg/dl [3.10 mmol/l]) are allowed between regular visits for the purpose of possible up-titration.'

**Major Changes Between September 13, 2001 and November 14, 2002
Versions of ACCORD ("Action to Control Cardiovascular Risk in Diabetes")
Protocol**
(Report Date: November 14, 2002 v5)

This document describes the fourteen amendments (Protocol Amendments 10 through 23) approved by the ACCORD Steering Committee between the September 13, 2001 and November 14, 2002 versions of the ACCORD Protocol.

Amendments 1 through 9 were previously incorporated into the September 13, 2001 Protocol (see Report Date: September 21, 2001).

Amendments 10 through 23 are incorporated into the November 14, 2002 Protocol.

AMENDMENT 10:
The ACCORD glycemia hypothesis is reworded as: does a therapeutic strategy that targets a HbA1c of < 6.0% reduce the rate of CVD events more than a strategy that targets a HbA1c of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%)?

From the September 13, 2001 Protocol:

The glycemia hypothesis was originally worded as: does a therapeutic strategy that targets a HbA1c of < 6.0% reduce the rate of CVD events compared to a strategy that targets a HbA1c of $\leq$ 7.5% ?

Change to the November 14, 2002 Protocol:

The original intent of the ACCORD design was to achieve a standard group HbA1c level of approximately 7.5%. However, during the vanguard phase it became apparent that some clinical sites were interpreting the September 13 wording as a directive to target to any HbA1c level of 7.5% or less. This contributed to a lower than desired HbA1c level in the standard glycemia treatment group after 12 months of therapy and a smaller than desired overall difference in HbA1c between the treatment groups.

The new wording was designed to explicitly describe the ACCORD goal of achieving a standard group median HbA1c level of approximately 7.5% and to remove any scientific or therapeutic ambiguity. This level minimizes the risk of severe hypoglycemia, substantially reduces the risk of microvascular events, and is expected to yield a sufficiently large HbA1c contrast to clearly answer the research question.). Moreover,

7.5% is lower than the HbA1c usually achieved in most people with type 2 diabetes and lower than the median HbA1c noted at baseline in the ACCORD Vanguard Phase.

This change appears in the *Abstract*, and in Sections 1.5 (*Specific ACCORD Hypotheses*) and 3.2.a (*Glycemia Research Question*).

AMENDMENT 11:
The participants randomized to the ACCORD Standard Glycemia treatment group will now be treated according to the revised Protocol Figure 3.2 treatment algorithm (see Protocol Figure 3.2 on Next Page).

From the September 13, 2001 Protocol:

The original standard group treatment algorithm did not permit a reduction in therapy unless clinically warranted, even if the participant was far below the standard group HbA1c goal.

Change to the November 14, 2002 Protocol:

A reduction in therapy for standard group participants is now permitted under the following circumstances, which are outlined in the revised Protocol Figure 3.2 (reproduced on next page):
1. any severe hypoglycemia
2. more than 1 episode of symptomatic hypoglycemia per week
3. $\geq$ 50% of SMBG levels < 90 mg/dl (5 mmol/l)
4. adverse effects of antihyperglycemic drugs
5. HbA1c < 6.5% on one occasion or 6.6-6.99% on 2 consecutive occasions and either on insulin or a secretagogue, a history of 1 or more episodes of symptomatic hypoglycemia since the previous visit, or 1 or more SMBG levels below 90 mg/dl (5 mmol/l) since the previous visit.

This change is also specified in Protocol Section 3.2.K (*Adjustment of Glycemic Therapy*).

Figure 3.2:
Treatment Group Algorithm for Standard Glycemia Therapy Group (Goal: HbA1c 7% to 7.9%)
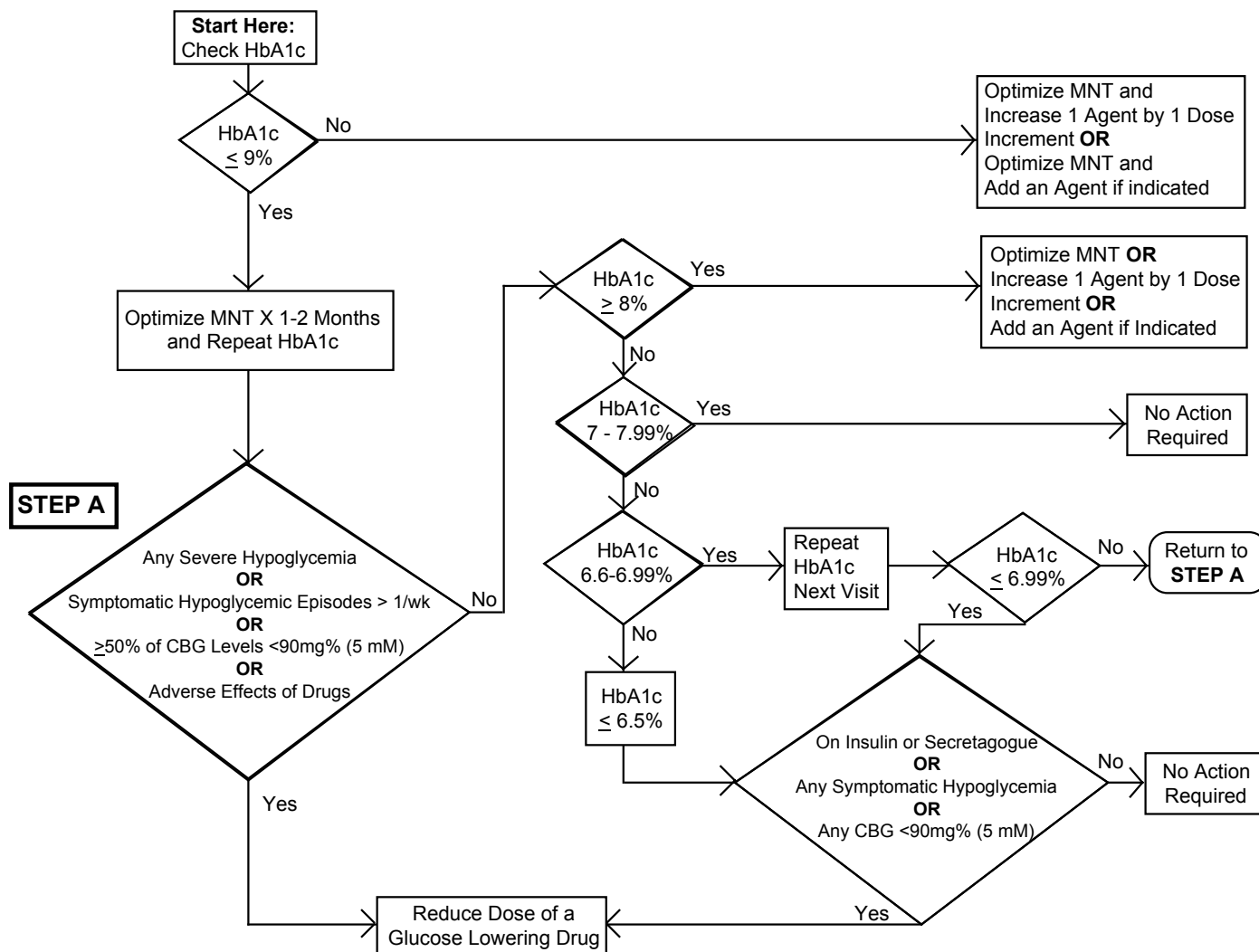
AMENDMENT 12:
The ACCORD lipid hypothesis is reworded as: in the context of good glycemic control, does a therapeutic strategy that uses a fibrate to raise HDL-C/lower triglyceride levels and uses a statin for treatment of LDL-C reduce the rate of CVD events compared to a strategy that only uses a statin for treatment of LDL-C?

From the September 13, 2001 Protocol:

The lipid hypothesis was originally worded as: does a therapeutic strategy that raises HDL-C and lowers triglyceride levels in the context of desirable levels of LDL-C and good glycemic control reduce the rate of CVD events compared to a strategy that only achieves desirable levels of LDL-C and glycemic control?

Change to the November 14, 2002 Protocol:

This change clarifies the original intent of the ACCORD Steering Committee and specifies that the HDL-C and triglyceride changes are to be effected by use of a fibrate (specifically, fenofibrate) and that the LDL-C will be treated by a statin (specifically, simvastatin).

This change appears in the *Abstract*, and in Sections 1.5 (*Specific ACCORD Hypotheses*) and 3.3.a (*Lipid Research Question*).

AMENDMENT 13:
All participants in the ACCORD Lipid Trial will receive 20 mg of simvastatin with no titration.

From the September 13, 2001 Protocol:

Under this protocol, participants in the lipid trial were randomized to either a fibrate (specifically, fenofibrate) or placebo. Also, depending upon the entry level LDL-C, participants may have been placed on a statin (specifically, simvastatin), and if on the statin, the dose of simvastatin was titrated (up to 20 mg simvastatin) to achieve at an LDL-C of < 120 mg/dl (< 3.10 mmol/l).

Change to the November 14, 2002 Protocol:

Based on the recently published results of the Heart Protection Study (Lancet 2002;360:7-22) , in which high risk participants, many with diabetes, benefited from 40 mg of simvastatin irrespective of their initial LDL cholesterol levels (including a significant number with baseline LDL cholesterol <100 mg/dl), all ACCORD patients in the lipid trial will now receive simvastatin. Because of the

reported association between adverse events (specifically, myositis) and the combination of fibrate+high dose statin and because half of the participants will be receiving fenofibrate in this masked study, 20 mg simvastatin was selected as the highest permissible dose.

The change regarding the use of 20 mg simvastatin by all lipid trial participants appears in section 3.3.b (*Research Design*).

AMENDMENT 14:
All Vanguard participants will be asked to provide re-consent, and treated and followed according to the revised protocol.

The intention behind this protocol change is that all participants in ACCORD, both those recruited during the Vanguard Phase and those recruited under this revised Protocol, will be treated and followed in an identical manner from this point on.

The new Section 4.7 (*Vanguard Participants*) specifically states that "The Vanguard Phase participants will be asked to provide consent to be treated and followed according to this revised main trial protocol."

AMENDMENT 15:
The general age inclusion criteria will no longer be based on race/ethnicity, but rather on a history of clinical cardiovascular disease:
> 40 yrs of age if there is a history of clinical cardiovascular disease.
> 55 yrs of age if there is no history of clinical cardiovascular disease.

From the September 13, 2001 Protocol:

The original age eligibility criteria (described in Section 2.1.a *Inclusion Criteria*) was based on the concept that diabetes first manifested itself at different ages in different race/ethnic groups. Specifically, the ACCORD age inclusion criteria was:
- ≥ 55 years for Caucasian and African American
- ≥ 50 years for Asians and Hispanics
- ≥ 45 years for Native Americans.

Change to the November 14, 2002 Protocol:

The revised age criteria are considered to be simpler to apply in the clinics and to explain/generalize from in future publications, while simultaneously providing the trial with a population with a high enough event rate to provide adequate power.

The new age criteria appear in Section 2.1.a (*Inclusion Criteria*).

AMENDMENT 16:
New general exclusion criterion: living in the same household as an already randomized ACCORD participant.

From the September 13, 2001 Protocol:

This criterion did not exist in the original protocol.

Change to the November 14, 2002 Protocol:

This addition to the list of exclusions is designed to prevent the situation in which 2 or more people in the same household get randomized to different treatment groups. Each treatment group demands adherence to specific medication regimens and schedules, and having people in a household participating in different protocols may adversely affect adherence to one or more of these protocols.

This change appears as Exclusion #15 in Section 2.1.b (*Exclusion Criteria*).

AMENDMENT 17:
New Lipid Trial inclusion criterion: the lower LDL-C entry criterion will be ≥ 85 mg/dl (2.20 mmol/l).

From the September 13, 2001 Protocol:

There was no lower LDL-C entry criterion under this protocol.

Change to the November 14, 2002 Protocol:

Because all participants in the lipid trial would be on 20 mg of simvastatin, a lower entry level was established to reduce the likelihhood of having LDL-C being reduced to an unacceptably low level.

This change appears in Section 2.1.c (*Additional Eligibility Criteria for Participants in the Lipid Component of ACCORD*).

AMENDMENT 18:
For participants in the Lipid Trial, if a participant's LDL-C ever goes below 40 mg/dl (1.02 mmol/l) on 2 consecutive measurements, the Coordinating Center will notify the clinic site to take the participant off simvastatin. The participant will remain on the masked fibrate/placebo medication.

<u>From the September 13, 2001 Protocol:</u>

In seventh paragraph of Section 3.3d (Lipid Goals) of this protocol, it was stated that: "If the centrally measured LDL-C is ever less than 50 mg/dl during follow-up, the Coordinating Center will notify the clinical site and the statin dose may be down-titrated by one level (at investigator's discretion)."

<u>Change to the November 14, 2002 Protocol:</u>

Whereas the investigator was previously permitted to choose what action to take, this amendment requires that the ACCORD-specified LDL-C treatment (simvastatin, which all lipid trial participants will be on) be stopped if the LDL-C is consistently low, with 'low' now defined as < 40 mg/dl (1.02 mmol/l) on 2 consecutive measurements (which will ensure that this is not a random occurrence).

AMENDMENT 19:
New Blood Pressure Trial inclusion criterion: the systolic blood criteria will be:
130 - 160 mmHg on 0 - 3 meds, <u>or</u>
161 - 170 mmHg on 0 - 2 meds, or
171 - 180 mmHg on 0 - 1 med

<u>From the September 13, 2001 Protocol:</u>

The original blood pressure inclusion criteria were:

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

<u>Change to the November 14, 2002 Protocol:</u>

After review of the Vanguard data, it was concluded that the population recruited for the blood pressure (BP) trial had, on average, blood pressure levels that were lower than expected. This made it more difficult to employ BP-reducing strategies that would result quickly in the targeted difference in post-randomization blood pressures between the two randomized arms. This change to the protocol would increase the generalizability of the findings, as well as improve the ability of the study to achieve the targeted between-group differences while maintaining a BP level in the standard group below that proven

to have cardiovascular benefits. The BP targets for the randomized groups have not changed.

This change appears in Section 2.1.d (*Additional Eligibility Criteria for Participants in the Blood Pressure Component of ACCORD).*

AMENDMENT 20:
If SBP > 120 mm Hg for a participant in the intensive BP therapy group, visits should be at least monthly until the blood pressure is controlled or a decision is made not to increase therapy further.

From the September 13, 2001 Protocol:

This rule did not exist in this version of the protocol. The blood pressure strategy originally described in Section 3.4.f (*Achieving and Monitoring Blood Pressure Control*) overestimated protocol adherence and underestimated the need for additional visits beyond 4-6 months

Change to the November 14, 2002 Protocol:

This change will make it easier to achieve the intensive blood pressure goal more quickly.

It is described in the revised Section 3.4.f (*Achieving and Monitoring Blood Pressure Control*) and is added to the revised Figure 3.4.

AMENDMENT 21:
The visit and procedure/evaluation schedules are changed, as described in revised Protocol Table 2.2.

From the September 13, 2001 Protocol:

This table originally only had one matrix, and encompassed all treatment groups in one table.

Change to the November 14, 2002 Protocol:

The revised table is divided into 6 parts, one part for each of the six types of participants that would be seen in the ACCORD clinic: These are participants who are randomized to the:
- Intensive Glycemia and Intensive Blood Pressure Groups
- Intensive Glycemia and Standard Blood Pressure Groups
- Intensive Glycemia Group and in the Lipid Trial

- Standard Glycemia and Intensive Blood Pressure Groups
- Standard Glycemia and Standard Blood Pressure Groups
- Standard Glycemia Group and in the Lipid Trial.

This new 6-part table, being treatment group-specific, will make it easier for the clinics to follow and to carry out the correct procedures and evaluations.

On the next page is a summary comparison of the visit schedules under the September 13, 2001 and November 14, 2002 ACCORD Protocols.

The visit frequency in this new schedule differs from the frequency required under the September 13, 2001 Protocol. Originally, both glycemia treatment groups had the same regularly scheduled visits through Month 8 (at Baseline, and Months 1, 2, 3, 4, 6, and 8). From Month 8 through Month 24, the Intensive group was seen every 2 months and the Standard Group seen every 4 months. Thereafter, the Intensive group was seen every 3 months, while the Standard Group was continued to be seen every 4 months.

Under the new schedule, the Intensive Group is seen more frequently throughout the course of the trial, while the Standard Group has slightly fewer visits (the frequency of visits still meets the desired requirement that diabetic patients be followed on a close schedule). This new differential in visit frequency between the treatment groups (especially in the early post-randomization period) is designed to increase the likelihood of achieving an adequate HbA1c difference between the treatment groups.

For the purpose of event ascertainment, all participants in all treatment groups will be queried regarding the occurrence of a possible event on the same schedule, specifically every 4 months. Also, additional visits can always be scheduled as needed to monitor and assure appropriate implementation of the study interventions.

COMPARISON OF ACCORD TREATMENT GROUP-SPECIFIC REGULAR CLINIC VISIT SCHEDULES BY PROTOCOL

Under September 13, 2001 Protocol (Described in Table 2.2)

	BL	1	2	3	4	6	8	10	12	14	16	18	20	22	24	Q2	Q3	Q4	prn
Group 1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Group 2	X	X	X	X	X	X	X		X		X		X		X			X	

Group 1 = Intensive Glycemia Group (regardless of blood pressure trial or lipid trial assignment) [N = 5000]
Group 2 = Standard Glycemia Group (regardless of blood pressure trial or lipid trial assignment) [N = 5000]

Under November 14, 2001 Protocol (Described in Tables 2.2A through F)

	BL	1	2	3	4	6	8	10	12	14	16	18	20	22	24	Q2	Q3	Q4	prn
Group 1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Group 2	X	X			X		X		X		X		X		X			X	X

Group 1 = Intensive Glycemia Group (regardless of blood pressure trial or lipid trial assignment)   and
Standard Glycemia Group if in Intensive BP Group [N = 6050]
Group 2 = Standard Glycemia Group if in Standard BP Group or Lipid Trial [N = 3950]

AMENDMENT 22:
The Steering Committee will be composed of the Principal Investigators from the seven Clinical Center Networks, the Principal Investigator from the Coordinating Center, the NHLBI Project Officer, the Chairs of the three major intervention working groups (glycemia, lipid, and blood pressure), the Steering Committee Chair, and the Steering Committee Vice-Chair. Voting Steering Committee members are the Principal Investigators from the seven Clinical Center Networks, the Principal Investigator from the Coordinating Center, and the NHLBI Project Officer. The Steering Committee Chair, or Vice-Chair in his absence, votes only to make or break a tie.

From the September 13, 2001 Protocol:

The original description of the Steering Committee (in Section 13.6, *The ACCORD Steering Committee and Executive Committee*) did not specifically identify what actually constituted the Steering Committee.

Also, the voting members were originally identified in this Section as of the Principal Investigators from the seven Clinical Center Networks, the Principal Investigator from the Coordinating Center, and the NHLBI Project Officer.

Change to the November 14, 2002 Protocol:

This administrative change specifies exactly who is officially on the Steering Committee and notes that the Steering Committee Chair, or Vice-Chair in his absence, may vote (only to make or break a tie).

This change appears in the revised Section 13.6 (*The ACCORD Steering Committee and Executive Committee*),

AMENDMENT 23:
The Model Informed Consent (Appendix I of the Protocol) has been rewritten.

The model informed consent was revised to describe more clearly to participants what would be required of them, as well as to reflect the other protocol changes. The major changes to the Model are as follow.

1. There is now a description that if a patient is randomized to the intensive blood sugar goal, there is a high likelihood that the person may require insulin, frequent adjustment of insulin by injection, and frequent home glucose

monitoring. This is described in the fourth paragraph in the section entitled "Study Summary" (beginning on the bottom of the second page of the Model).

2. There is now a description that notes that the patients who are randomized to the standard glycemia group have a HbA1c target of 7.5%, which has a somewhat higher risk for some diabetes complications (including eye, kidney, and nerve function diseases) compared to the 6.0% target in the intensive group. The description continues, however, to note that participants in the intensive group will have a somewhat higher risk for hypoglycemia and weight gain. In balance, the description concludes by noting that ACCORD was designed to determine which of these targets would reduce the risk of clinical cardiovascular disease. These descriptions are in sixth paragraph in the section entitled "Study Summary" (on the third page of the Model).

3. The description of the side effects of rosiglitazone has been expanded, including a mention that although liver problems have not been reported with rosiglitazone, another medication of the same class was removed from the market due to rare, severe liver problems. Because of this, it is noted that if the participant is placed on rosiglitazone, liver function tests will be conducted every other month for the first year after the initiation of the drug, and annually thereafter. Also, it is noted that the use of rosiglitazone with insulin may cause fluid retention, which could lead to or worsen heart failure. If the participant is placed on this combination, it is noted that the participant will be monitored closely, and if necessary, the medications adjusted or stopped. These descriptions are in the paragraph entitled "Thiazolidinediones", which is under Blood Sugar Treatments in the section entitled "Potential Risks of Participating in the ACCORD Study" (beginning on the bottom of the seventh page of the Model). (Questions regarding edema, rales, congestive heart failure, etc have also been added to the follow-up forms, which will be completed by all ACCORD participants.)

In addition to these major changes, the document now reflects all of the protocol changes.

Overview of Major Changes Made to November 14, 2002 Version of ACCORD ("Action to Control Cardiovascular Risk in Diabetes") Protocol
(Report Date: November 21, 2003)

This document describes the three amendments (Protocol Amendments 24 through 26) approved by the ACCORD Steering Committee since the adoption of the November 14, 2002 version of the ACCORD Protocol and approved by the ACCORD Data and Safety Monitoring Committee at its September 24, 2003 meeting.

These amendments are incorporated into November 21, 2003 version of the Protocol.

AMENDMENT 24:
The ACCORD age eligibility criteria in Protocol Section 2.1.a is reworded to be:

Age at Randomization:
- **40 to 79 years (inclusive) for anyone with a history of clinical cardiovascular disease, or**
- **55 to 79 years (inclusive) for anyone without a history of clinical cardiovascular disease**

As Currently Stated in the November 14, 2002 Protocol:

The age eligibility criterion in Section 2.1.a was defined as:
- ≥ 40 years for anyone <u>with</u> a history of clinical cardiovascular disease …
- ≥ 55 years for anyone <u>without</u> a history of clinical cardiovascular disease …

Reason for Change to the Protocol:

Because of suggestions in the developing data that participants 80+ years of age may be experiencing more severe hypoglycemia events than participants less than 80, the ACCORD Steering Committee voted on June 27, 2003 to suspend the randomization of participants 80+ years of age.

Also, it is clarified that the age eligibility criterion refers to the age at the time of randomization.

AMENDMENT 25:
Protocol Section 5.2 will now define two microvascular secondary outcomes:

- **"The main microvascular outcome of the ACCORD study is the primary outcome of the ACCORD Eye Sub-study, namely: 'the combined outcome of progression of diabetic retinopathy of at least 3 stages on the ETDRS scale, photocoagulation, or vitrectomy'. This Sub-study will only take place in approximately half of the ACCORD study population.**
- **A second composite microvascular endpoint will be examined in the entire ACCORD population: fatal or non-fatal renal failure or of retinal photocoagulation or vitrectomy for diabetic retinopathy This endpoint essentially replicates the composite microvascular endpoint in the UKPDS."**

Fatal or no-fatal renal failure is now defined in Section 5.4.a.3 as: "Development of renal failure as defined by renal transplantation or initiation of dialysis or a rise in serum creatinine $\geq$ 3.3 mg/dl in the absence of an acute reversible cause"

<u>As Currently Stated in the November 14, 2002 Protocol:</u>

In Section 5.2 of the November 14, 2002 Protocol, the ACCORD microvascular secondary outcome measure was defined as: "A composite microvascular disease outcome, specifically kidney disease (defined in Section 5.4.a) and eye disease complications (defined in Section 5.4.b)."

Kidney disease was defined in Section 5.4.a as

<u>"5.4.a Development of nephropathy</u>
5.4.a.1 Doubling of serum creatinine
5.4.a.2 Severe microalbuminuria (albumin/creatinine ratio >28 mg/mmol in random urine sample) (HOPE 2000)
5.4.a.3 Dialysis
5.4.a.4 Kidney transplant"

And eye disease complications were defined in Section 5.4.b as

<u>"5.4.b Development of diabetic eye complication</u>
5.4.b.1 Use of retinal photocoagulation or vitrectomy for diabetic retinopathy
5.4.b.2 Cataract extraction
5.4.b.3 Three-line change in visual acuity using Log MAR visual acuity chart
5.4.b.4 Severe vision loss due to diabetes retinopathy (< 5/200)"

<u>Reason for Change to the Protocol:</u>

To identify a primary microvascular outcome and also to permit the comparison of the ACCORD microvascular effects with the effects reported from other diabetes trials (e.g., UKPDS). The ACCORD Steering Committee voted on June 27, 2003 to accept these changes to the protocol.

AMENDMENT 26:
The ACCORD Health-related Quality of Life (HRQL) and Cost-Effectiveness Analysis (CEA) hypotheses in Protocol Section 6.1 are reworded to be:

6.1.a.1 Primary HRQL Hypotheses (Main Effects Comparisons)

(1) Intensive control of blood glucose compared with less intensive control in patients with diabetes will:
> **a) decrease symptoms and side effects as assessed by the _Symptoms Distress In Diabetes Questionnaire_.**
> **b) decrease symptoms and disability associated with cardiovascular events as assessed by the _SF-36v2_ and the _Health Utilities Index III_.**
> **c) improve self-reported treatment satisfaction (and consequently treatment adherence and drop-outs) as assessed by the _Diabetes Treatment Satisfaction Questionnaire_ (DTSQ).**

(2) Treatment of lipids with statins and fibrates (to lower LDL-C and triglycerides and raise HDL-C) compared with treatment of lipids with statins alone (to lower LDL-C) will:
> **a) decrease symptoms and side effects as assessed by the _Symptoms Distress In Diabetes Questionnaire_.**
> **b) decrease symptoms and disability associated with cardiovascular events as assessed by the _SF-36v2_ and the _Health Utilities Index III_.**
> **c) improve self-reported treatment satisfaction (and consequently treatment adherence and drop-outs) as assessed by the _Diabetes Treatment Satisfaction Questionnaire_ (DTSQ).**

(3) Intensive control of blood pressure compared with less intensive control in patients with diabetes will:
> **a) decrease symptoms and side effects as assessed by the _Symptoms Distress In Diabetes Questionnaire_.**
> **b) decrease symptoms and disability associated with cardiovascular events as assessed by the _SF-36v2_ and the _Health Utilities Index III_.**
> **c) improve self-reported treatment satisfaction (and consequently treatment adherence and drop-outs) as assessed by the _Diabetes Treatment Satisfaction Questionnaire_ (DTSQ).**

_. . ._

6.1.b.1 Primary Cost-Effectiveness Hypotheses (Main Effects Comparisons)

(1)   The incremental cost effectiveness ratio of intensive control of blood glucose, in the presence of lipid therapy or blood pressure control, will not be larger than the maximum acceptable "ceiling" level of the cost per cardiovascular disease free year gained and cost per quality

adjusted life-year (QALY) gained when compared to less intensive control.

(2) The incremental cost effectiveness ratio of intensive lipid treatment (adding a fibrate to a statin), in the presence of control of glucose, will not be larger than the maximum acceptable "ceiling" level of the cost per cardiovascular disease free year gained and cost per quality adjusted life-year (QALY) gained when compared to less intensive control.

(3) The incremental cost effectiveness ratio of intensive blood pressure control, in the presence of control of glucose, will not be larger than the maximum acceptable "ceiling" level of the cost per cardiovascular disease free year gained and cost per quality adjusted life-year (QALY) gained when compared to less intensive control.

<u>As Currently Stated in the November 14, 2002 Protocol:</u>

The objectives of the Health-Related Quality of Life and Cost-Effectiveness analyses, as stated in Section 6.1 of the November 14, 2002 Protocol, are currently:

"(1) To measure changes in health-related quality of life (HRQL) associated with diabetes symptoms and side effects produced through intensified control of blood glucose, in the presence of intensified lipid therapy or intensified blood pressure control, compared to standard control. (*Null Hypothesis: Intensified control of blood glucose, in the presence of intensified lipid therapy or intensified blood pressure control, will not decrease glycemic symptoms or increase side effects compared to less intensive control in patients with diabetes as assessed by the Symptoms Distress In Diabetes Questionnaire.*

(2) To measure the effect of intensified control of blood glucose, in the presence of intensified lipid therapy or intensified blood pressure control, on HRQL associated with cardiovascular events and other diabetes complications (microvascular, cognitive, neuropathic etc.) (*Null Hypothesis: Intensified control of glucose, in the presence of intensified lipid therapy or intensified blood pressure control, compared to standard will not delay the onset of symptoms and disability associated with cardiovascular events as assessed by the SF-36v2 and the Health Utilities Index III.*)

(3) To measure the effect of intensified control of blood glucose, in the presence of intensified lipid therapy or intensified blood pressure control, compared to standard control on self-reported treatment satisfaction. (*Null Hypothesis: Intensified control of glucose, in the presence of intensified lipid therapy or intensified blood pressure control, will not change self-reported treatment satisfaction (and consequently treatment adherence and drop-outs) from less intensive therapy.*)

(4) To measure the incremental cost effectiveness and cost utility of intensified control of glucose, in the presence of intensified lipid therapy or intensified blood pressure control, compared to less intensive control. (*Null Hypothesis: The incremental cost effectiveness ratio of intensified control of glucose, in the presence of intensified lipid therapy or intensified blood pressure control, will be larger than the maximum acceptable "ceiling" level of the cost per cardiovascular disease free year gained and cost per quality adjusted life-year (QALY) gained when compared to less intensive control.)"*

Reason for Change to the Protocol:

The HRQL and CEA hypotheses were rewritten to incorporate main effect comparisons in order to be consistent with the main trial hypotheses. In addition, the changes were made so that the HRQL and CEA hypotheses would be parallel.

Major Changes Made to November 21, 2003 Version of ACCORD
("Action to Control Cardiovascular Risk in Diabetes") Protocol
(August 31, 2004)

This document describes the four amendments (Protocol Amendments 27 and 30) approved by the ACCORD Steering Committee since the adoption of the November 21, 2003 version of the ACCORD Protocol. These changes are now incorporated into the August 31, 2004 version of the Protocol.

AMENDMENT 27:
"Congestive Heart Failure Death or Hospitalization for Congestive Heart Failure" is to be added as a secondary outcome measure in ACCORD.

As Currently Stated in the November 21, 2003 Protocol:

Currently, "Hospitalization for congestive heart failure" is listed in Protocol Section 5.3 as an "Other ACCORD Outcome." Death due to congestive heart failure is a component of the ACCORD primary outcome (in Section 5.1) and is also part of the cardiovascular mortality secondary outcome (in Sections 5.1.a and 5.2).

Rationale for Change to the Protocol:

Congestive heart failure (CHF) is a major complication of hypertension and diabetes and is prognostic of subsequent additional morbidity and mortality. It also adds to the economic/financial burden of diabetes.

CHF is not currently a major outcome measure for ACCORD and this amendment elevates it to a secondary outcome. Also, to be more inclusive, this new outcome is the combination of death due to heart failure, as well as having CHF as the admission diagnosis for hospitalization.

This change is now incorporated into Section 5.2 of the August 31, 2004 Protocol.

AMENDMENT 28:
The ACCORD Lipid Trial LDL-C and HDL-C eligibility criteria in Protocol Section 2.1.c is reworded to be:

- "60 mg/dl $\leq$ LDL-C $\leq$ 180 mg/dl (1.55 to 4.65 mmol/l) if not on a lipid-lowering agent during screening, or, if on a lipid-lowering agent, the LDL-C needs to be between the drug/dose-specific cut points <u>inclusive</u> found in Table 2.1.

    and

- HDL-C less than 55 mg/dl (1.42 mmol/l) for women or Blacks/African-Americans, or HDL-C less than 50 mg/dl (1.29 mmol/l) for all other gender-race groups"

<u>As Currently Stated in the November 21, 2003 Protocol:</u>

The current LDL-C and HDL-C eligibility criteria are:

- "85 mg/dl $\leq$ LDL-C $\leq$ 170 mg/dl (2.20 to 4.40 mmol/l) if not on a lipid-lowering agent during screening, or, if on a lipid-lowering agent, the LDL-C needs to be between the drug/dose-specific cut points <u>inclusive</u> found in Table 2.1.

    and

- HDL-C less than 50 mg/dl (1.29 mmol/l) for all gender-race groups" …

<u>Rationale for Change to the Protocol:</u>

a) <u>Lowering the lower LDL-C entry criterion from ≥85 mg/dl to ≥60 mg/dl</u>

Lowering the lower LDL-C limit for enrollment from ≥85 mg/dl to ≥60 mg/dl would allow for greater enrollment into the lipid trial without increasing the risk of developing hypolipidemia because ACCORD already has in place a procedure whereby participants with LDL cholesterol levels below 40 mg/dl are taken off simvastatin. There was no lower LDL-C entry criterion in the Vanguard Protocol.

This change is now incorporated into Section 2.1.c of the August 31, 2004 Protocol.

b) <u>Raising the upper LDL-C entry criterion from <170 to <180 mg/dl</u>

Raising the upper LDL-C limit for enrollment from $\leq$170 mg/dl to $\leq$180 mg/dl would allow for greater enrollment into the lipid trial without increasing the risk that many randomized participants would need more than 40 mg of simvastatin per day, which would now be permitted under **Amendment 29** below.

This change is now incorporated into Section 2.1.c of the August 31, 2004 Protocol.

c) Modifying the HDL-C Criterion So that Women and Blacks/African-Americans have a higher HDL-C Eligibility Criterion.

This protocol change should have the overall effect of improving recruitment into the lipid trial without negatively impacting on the trial question, while simultaneously increasing the proportions of women and Blacks/African-Americans in the lipid trial and in the overall ACCORD trial.

Currently, to be eligible for the lipid portion of ACCORD, a screenee must have an HDL-C <50 mg/dl, regardless of gender-race group. However, women and Blacks/African-Americans in general have higher HDL-C levels than do the other gender-race groups, and women and Blacks are disproportionately not being recruited into the lipid trial

This change is now incorporated into Section 2.1.c of the August 31, 2004 Protocol.

AMENDMENT 29:
Among participants in the Lipid Trial, the daily dose of simvastatin will be increased from 20 mg to 40 mg if the LDL-C is greater than 100 mg/dl on two consecutive follow-up visits.

In conjunction with the overall increase in aggressive treatment of LDL-C levels, the level of LDL-C at which the participant will be referred to their own physician for individualized treatment will be lowered from 130 mg/dl to 120 mg/dl after two consecutive measurements following titration of simvastatin to 40 mg/day.

As Currently Stated in the November 21, 2003 Protocol:

Currently, all participants in the Lipid Trial are placed on 20 mg of simvastatin, with no provision for up-titration, although down-titration is required "if the centrally measured LDL-C is ever less than 40 mg/dl (1.03 mmol/l) on two consecutive measurements" (described in the sixth paragraph of Section 3.3.c).

The protocol also states in the fifth paragraph of this section that the participant is to be referred to his/her own physician for treatment instead of receiving treatment by the ACCORD study "if the participant has an LDL-C above 130 mg/dl (3.36 mmol/l) on two consecutive occasions."

Rationale for Change to the Protocol:

a) Increasing the dose of simvastatin from 20 to 40 mg/day among participants whose LDL-Cs are consistently over 100 mg/dl.

This change will make the ACCORD lipid treatment more consistent with the recent recommendations from the National Cholesterol Education Program. In addition, there is a perception among many practicing physicians, based upon the results of the Heart protection Study and others, that 40 mg is the correct dose of simvastatin, particularly if LDL-C is not <100 mg/dl. The change in protocol is expected to make the lipid trial protocol more consistent with national guidelines and more acceptable to private physicians of ACCORD screenees (from whom we would like to recruit patients for our lipid trial) and participants (from whom we would need their continued support of our protocol).

Also, approval of the possible use of 40 mg simvastatin would allow recruitment of individuals with screening LDL-C up to 180 mg/dl (as recommended in **Amendment 28** above).

This change is now incorporated into Sections 3.3.b and 3.3c of the August 31, 2004 Protocol.

<u>b) Lowering the LDL-C Threshold Level at which participants are referred to their own physician for treatment instead of being treated by the ACCORD study from >130 to >120 mg/dl</u>

In conjunction with a more aggressive treatment of LDL-C levels, the level of LDL-C at which lipid treatment by ACCORD will be stopped and the participant referred to their own physician for individualized treatment will be lowered from >130 mg/dl to >120 mg/dl (on two consecutive measures after titrating simvastatin to 40 mg/day). Again, this change should make the lipid trial protocol more acceptable for physicians and enable treatment consistent with national guidelines.

NOTE: based upon this change, the 5th paragraph of Protocol Section 3.3.c will now be changed to read as follows:

> "If the participant has an LDL-C above 120 mg/dl (3.10 mmol/l) on two consecutive visits after titrating simvastatin to 40 mg/day (even after compliance review and dietary counseling), the following will occur:
> - The investigator will be notified by the Coordinating Center to take the participant off the fibrate/placebo pills.
> - The participant will remain on simvastatin 40 mg/day until placed on nonstudy statin by his/her primary caregiver.
> - The site staff will make an appointment with the participant's doctor for follow-up.
> - The site staff will also provide a letter for the participant to take to his/her physician for the follow-up visit. This letter will include the blood lipid values and describes the medication regimen the participant was on when the blood was drawn.
> - The site staff will confirm that the participant had visited their physician.
> - From that point on, the participant would be treated for lipids by his/her personal physician and given results of any ACCORD lipid determinations to share with this physician."

This change is now incorporated into Section 3.3.c of the Protocol.

AMENDMENT 30:
Among participants in the lipid trial, the starting dose of masked fenofibrate/placebo medication will be determined by the calculated glomerular filtration rate (GFR) using the baseline creatinine level and the MDRD equation. Those participants with a baseline GFR >50 ml/min/1.73^2 will begin at a starting dose of 160 mg of fenofibrate or identical placebo tablet. Those with a calculated GFR between 30 and 50 will start at the reduced dose of 54mg/day fenofibrate or placebo or will be placed on 160 mg tablet every other day.

Participants will have masked study medication dosage adjusted throughout the trial based on GFR. The dose of the masked medication will be down-titrated if the participant's estimated GFR falls between 30 and <50 mL/min/1.73m^2 on two consecutive measurements taken 4 months apart. For participants randomized to the fenofibrate group, the dose of the fibrate tablet will be titrated from 160 mg to 54 mg/day or placed on 160 mg tablet every other day. Participants randomized to placebo will be instructed to go on the masked 'lower dosage'.

If the estimated GFR falls below 30 mL/min/1.73^2 at any time, a confirmatory blood draw will be required within 2 weeks. If the estimated GFR remains below 30mL/min/1.73^2, the masked study medication will be permanently discontinued, regardless of fenofibrate or placebo assignment.

To monitor renal function during follow-up, all lipid participants will be required to have an additional tube of blood drawn for creatinine at the routine blood draw every 4 months, which will be analyzed centrally.

Because ACCORD will now be employing an estimate of GFR to identify significant renal impairment (<30 mL/min/1.73^2), the section in the protocol indicating that the masked medication will be permanently discontinued if a serum creatinine greater than 2.5 mg/dl (221 umol/l) on two consecutive measurements is now removed and replaced with the GFR value of 30 mL/min/1.73^2.

As Currently Stated in the November 21, 2003 Protocol:

Currently, all participants in the lipid arm randomized to fenofibrate are placed on 160 mg of the agent, with no provision for the down-titration for any reason. The current protocol mandates that the masked medication (fenofibrate or placebo) be permanently discontinued if the serum creatinine measures greater than 2.5 mg/dl (221 umol/l) on two consecutive measurements four months apart.

Reason for Changes to the Protocol

This amendment mandates that the dose of the masked medication (either fenofibrate/placebo) be down-titrated if there is evidence of moderate renal impairment (estimated MDRD-GFR 30 to <50 mL/min/1.73m^2). This is in line with the fenofibrate package insert that recommends reduction of the dose of fenofibrate from 160 mg tablet per day to 54 mg tablet per day in patients with renal impairment (defined in the package insert as creatinine clearance <50 mL/min) to avoid accumulation of metabolites.

The use of an estimated GFR (rather than simply using a serum creatinine value) was selected to better reflect the changes in renal function. The well validated modified/abbreviated MDRD-GFR equation will be used in ACCORD to estimate GFR.   This estimation procedure and the levels for dose change/discontinuation were recommended to ACCORD by kidney experts at the National Institute of Diabetes and Digestive and Kidney Diseases. Additionally, the MDRD equation is being used more frequently in clinical practice as a feasible way of estimating renal functioning, accounting for differences in creatinine by age, gender and race. It is also used by the National Kidney Foundation in their guidelines on chronic renal disease.

These changes are now incorporated into Section 3.3.b of the August 31, 2004 Protocol.

Major Change Made to August 31, 2004 Version of ACCORD
("Action to Control Cardiovascular Risk in Diabetes") Protocol
(April 8, 2005)

This document describes the new amendment (Amendment 31) approved by the ACCORD Steering Committee since the adoption of the August 31, 2004 version of the ACCORD Protocol.

AMENDMENT 31:
Among participants in the Lipid Trial, the daily dose of open-labeled simvastatin will be increased from 20 to 40 mg for participants categorized as "secondary prevention." Using Protocol Section 2.1.a.6 as a guide, secondary prevention includes a history (before or after randomization) of any of the following:

- **myocardial infarction (MI)**
- **stroke**
- **coronary revascularization (e.g., coronary artery bypass graft surgery, stent placement, percutaneous transluminal coronary angioplasty, or laser atherectomy)**
- **carotid or peripheral revascularization (e.g., carotid endarterectomy, lower extremity atherosclerotic disease atherectomy, repair of abdominal aorta aneurysm, femoral or popliteal bypass)**
- **angina with ischemic changes (resting ECG), ECG changes on a graded exercise test (GXT), or positive cardiac imaging study**

<u>As Currently Stated in the August 31, 2004 Protocol</u>

The current protocol increases the daily dose of simvastatin from 20 to 40 mg only in those participants whose LDL-C is greater than 100 mg/dl on two consecutive follow-up visits.

<u>Rationale for Change in Protocol</u>

This amendment expands the use of the higher dose of simvastatin to secondary prevention participants, for whom evidence is emerging that a higher dose of a statin is beneficial.

Specifically, this change was made in response to the recently presented findings from the *Treating to New Targets Trial* (TNT). TNT compared the effects of maximal dose of atorvastatin (80 mg/day) with low dose atorvastatin (10 mg/day) on cardiovascular events in 10,001 high risk, secondary prevention participants.

After a median of 4.9 years of follow-up, the high dose group had a 22% reduction in cardiovascular events (P<0.001).

Major Change to May 11, 2005 Version of ACCORD
("Action to Control Cardiovascular Risk in Diabetes") **Protocol**
January 5, 2009

This document describes the new amendment (Amendment 32) approved by the ACCORD Steering Committee since adoption of the May 11, 2005 version of the ACCORD Protocol.

AMENDMENT 32:

As described in Section 1.6 of the May 11, 2005 ACCORD Protocol, participants in the ACCORD Trial will have their final follow-up and treatment ("close-out") visits during the period March 1, 2009 through June 30, 2009.

This amendment establishes a post-trial, non-treatment, observation-only period during which participants who give consent will continue to be followed by phone by ACCORD clinic staff every six months from the anniversary of their close-out visit until December 31, 2010. On these calls, information will be collected on the occurrence of medical events, including myocardial infarction, strokes, other diabetes related events, and death.

From May 11, 2005 Protocol

The May 11, 2005 Protocol does not provide for the collection of clinical event data after the close-out visit.

Rationale for Change in Protocol

It was reported on June 12, 2008 in the *New England Journal of Medicine* (N Engl J Med 2008;358:2545-59) that the use of intensive glycemic therapy to target normal glycated hemoglobin levels during the trial increased mortality and did not significantly reduce major cardiovascular events. Because of the increase in mortality, the glycemia ACCORD trial was stopped on February 6, 2008. The blood pressure and lipid trials of this factorial study are continuing.

The information collected on the follow-up phone calls between the close-out visit and December 31, 2010 will determine whether differences seen during the trial in mortality and cardiovascular events persist or change over time.