

Supplementary Appendix 2

This appendix has been provided by the authors to give readers additional information about their work.

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Protocol

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

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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 glyceimic 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 glyceimic 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.

Table 1.2: Glucose Lowering Trials and CVD in People with Diabetes

Study	Yrs	HbA1c (Intense)	HbA1c (Control)	Therapy	Outcome	Relative Risk Reduction (RRR) (CVD)	RRR (micro)
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%
VACS DM (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)
VACSMD ^(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 glycaemic 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 glycaemic 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 glycaemic 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 glycaemic 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 (Abaira 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/m²) 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 glycosylated Hb 13%), continuous subcutaneous insulin for a 3 week period achieved a normal glycosylated 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.

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

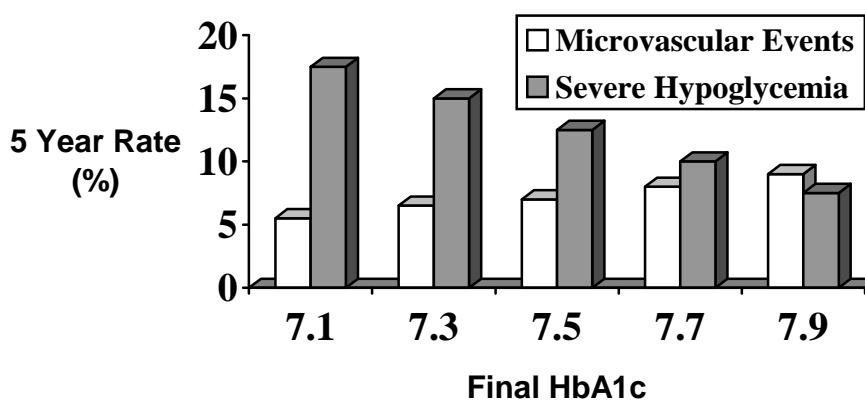
- a) The baseline (pre-randomization) HbA1c will be 8.5% (which it was in the Vanguard).
- b) The annual absolute risk of severe hypoglycemia will be greater than 2.5% per 1% fall in HbA1c from baseline. Thus this estimate represents the minimum risk.
- c) The microvascular benefits for ACCORD standard 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.

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 (Abaira 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.

Population	Trial	N	LDL-Cholesterol (mg/dl)			Agent
			Eligibility	Mean On Placebo	Mean On Statin	
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.

Population	Trial	N	Event Rate		Event Definition
			Placebo	Statin	
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.

Table 1.8: Event Rates in Diabetic Patients in Statin Trials					
	Trial	# Diabetic Patients	Event Rate		Event Definition
			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 rhabdomyolysis. 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:

<u>Phase</u>	<u># of Months in Phase</u>	<u>Calendar Time</u>	<u>Trial Activities</u>
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, ≤ 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 ≤ 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 ≥ 140 mm Hg or DBP ≥ 95 mm Hg.
 - Current cigarette smoking
 - Body mass index > 32 kg/m²

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/m²
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 glyemic 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 inclusive 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	<u>In mg/dL</u> the LDL-C Must Be Between (inclusive):	<u>In mmol/L</u> 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
Ezetimibe (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 funduscopy) 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 Intensive Glycemia + Intensive Blood Pressure Groups

Evaluations	Schedule in Months																																	
	Scrn ^r	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	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 ⁷							M				M				M		M		M		M			M										
HbA1c (POC) ⁴		X		X	X	X	X	prn	X	prn	X	prn	X	prn	X	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	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	
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 ⁵				X															X														X	
MIND: MRI				C ^λ																													C ^{λλ}	
Serum Storage		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 2.2A:

- 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):
- not currently on antihypertensive therapy
 - but who had a SBP \geq 130 mm Hg on the first clinic visit
 - 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:
- Monitoring K⁺ and Creatinine after starting and/or significantly changing ACEI, ARB and thiazides
 - 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 after 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 must also be made between all 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 Intensive Glycemia + Standard Blood Pressure Groups

Evaluations	Schedule in Months																																
	Scr [†]	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 [†]	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 [‡]			(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	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 ^ε				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 after 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 must also be made between all 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 Intensive Glycemia Group + Lipid Trial

Evaluations	Schedule in Months																															
	Scrn ^r	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 ⁷			(none)																													
HbA1c (POC) ^A		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	
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								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 ^ε				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 after 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 must also be made between all 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)

Scr_n=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 Standard Glycemia + Intensive Blood Pressure Groups

Evaluations	Schedule in Months																															
	Scr ⁿ	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							X	
BP Mileposts ⁷							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	
ECG	L	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	
MIND:Cognitive ^ε				X															X									X				
MIND: MRI				C ^λ																								C ^{λλ}				
Serum Storage		C													C														C		C	
EDTAPlasma Storage		C																														
Urine Storage		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 after 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.

Scr_n=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 Standard Glycemia + Standard Blood Pressure Groups

Evaluations	Schedule in Months																																
	Scr [†]	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								X		
Weight	X	X		X [†]			X				X				X		X		X		X		X								X		
BP Mileposts ⁷			(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								X	
Diet,Phys Actv*		X												X												X		X					
HRQL*		X												X												X		X					
Costs*		X				X				X				X		X		X		X		X		X									
Eye Substudy		C ^o																											C				
Visual Acuity		X																			X				X							X	
MIND:Cognitive ⁵				X																								X					
MIND: MRI				C ^Δ																								C ^{ΔΔ}					
Serum Storage		C												C							C								C			C	
EDTAPlasma 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):
- not currently on antihypertensive therapy
 - but who had a SBP \geq 130 mm Hg on the first clinic visit
 - 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:
- Monitoring K⁺ and Creatinine after starting and/or significantly changing ACEI, ARB and thiazides
 - 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 after 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 Standard Glycemia Group + Lipid Trial

Evaluations	Schedule in Months																															
	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 ⁷			(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	
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								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 ⁵				X																X									X			
MIND: MRI				C ^λ																									C ^{λλ}			
Serum Storage		C													C														C		C	
EDTA Plasma Storage		C																														
Urine Storage		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 after 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)

Scr_n=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 a measure of subclinical cardiovascular disease, and persons with low ABI may be 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

Drug Dispensing

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).

Group	HbA1c Targets	“Action Required” Threshold	
		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 (1 st 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; ^aless 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).

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 ≥ 1.4 mg/dl for women or ≥ 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%)

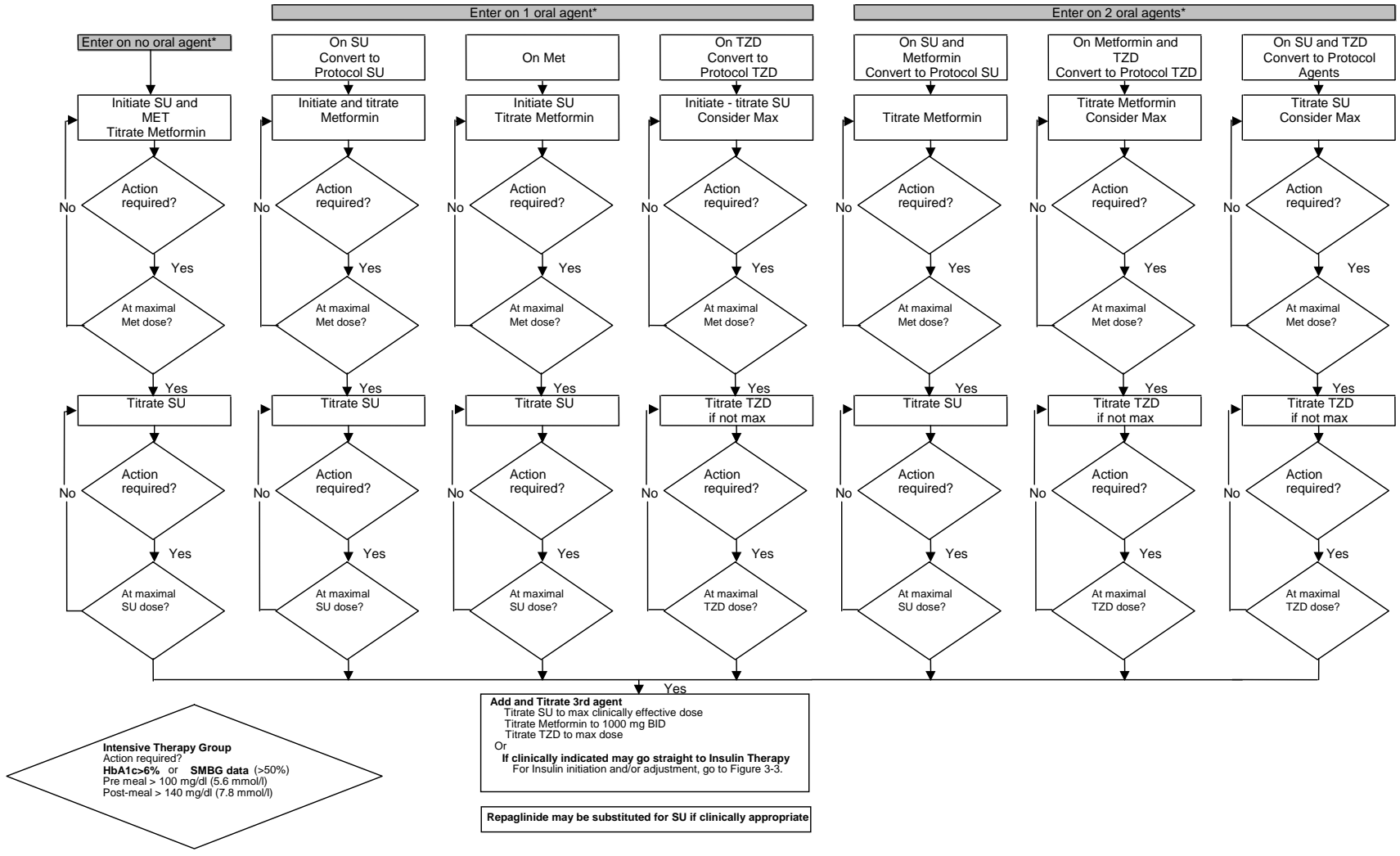


Figure 3.2:
Treatment Group Algorithm for Standard Glycemia Therapy Group (Goal: HbA1c 7% to 7.9%)

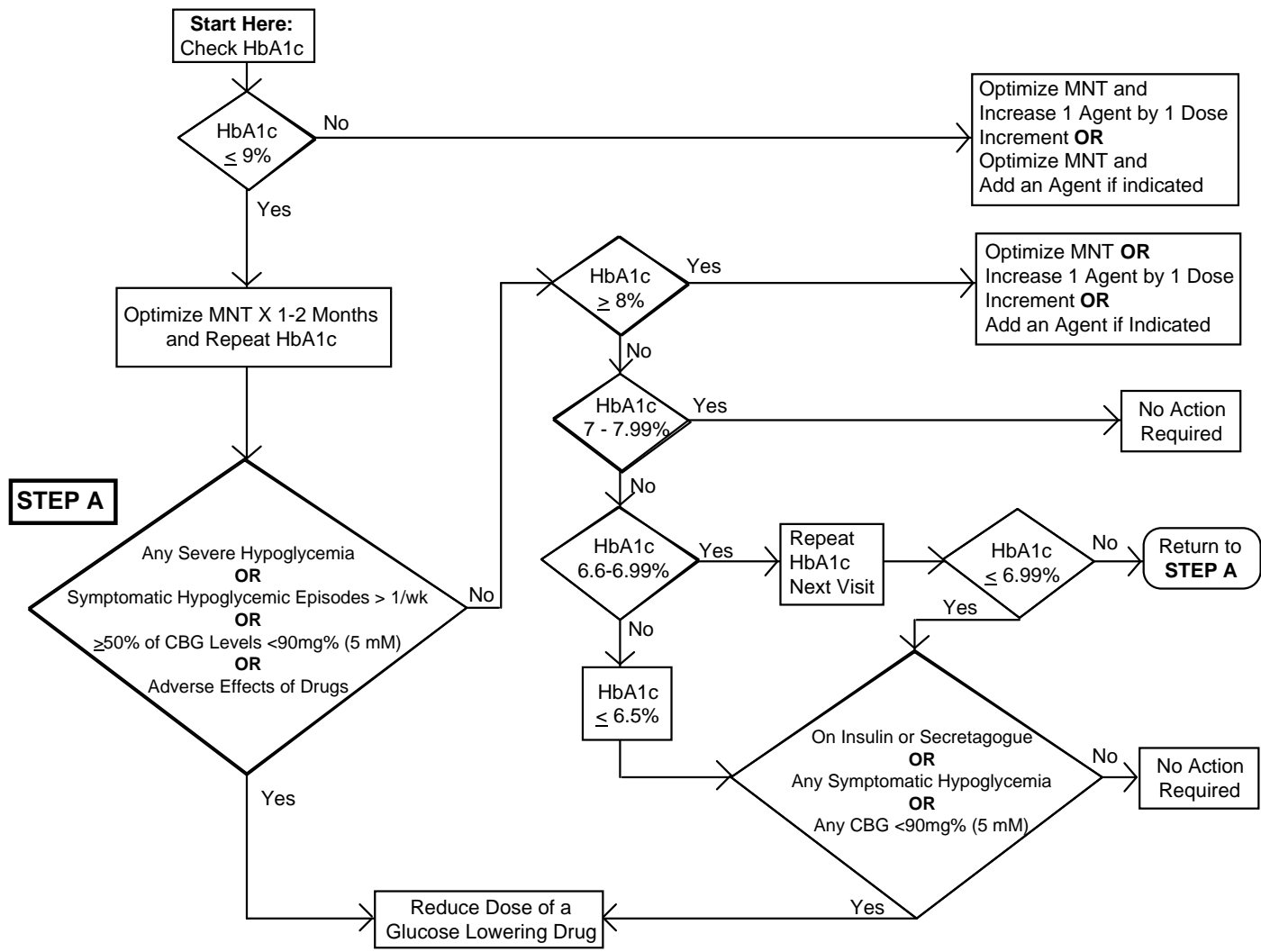
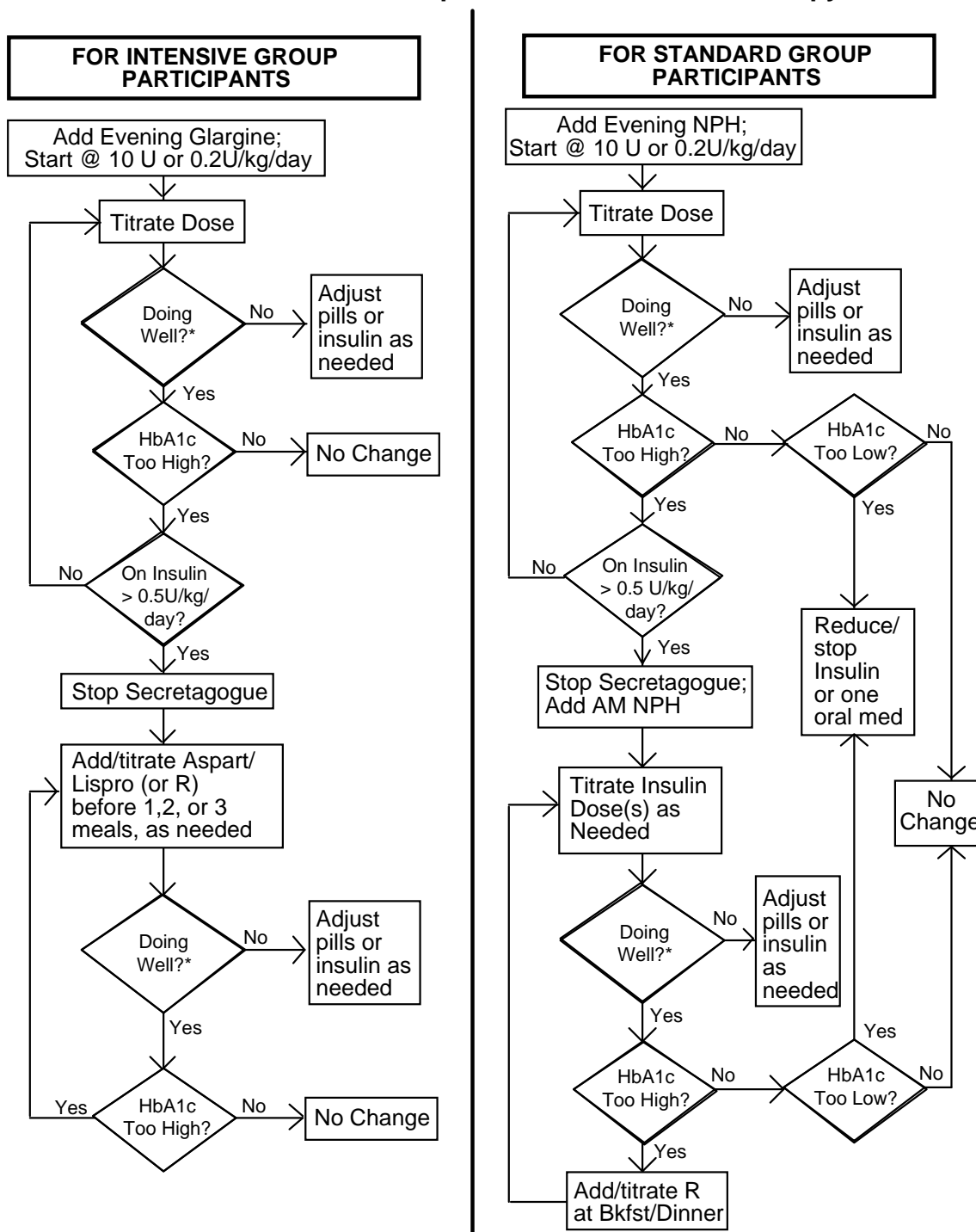


Figure 3.3:
Use of Insulin for Participants On Maximal Oral Therapy



*Doing well: no severe hypoglycemic or adverse event or 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 ≥ 50 ml/min/1.73m² 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/1.73m² 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/1.73m² 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/1.73m², 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 (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

