

ACCORDION:

The ACCORD Follow-On Study

Protocol

(March 18, 2011–**Version G**)

CONFIDENTIAL

ACCORDION PROTOCOL
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Abstract

ACCORDION (the ACCORD Follow-up Study) is a prospective, observational follow-up study of at least 8000 participants who were treated and followed in the *Action to Control Cardiovascular Risk in Diabetes* (ACCORD) Trial. Treatment in ACCORD ended in 2009 and ACCORDION is designed to further elucidate and clarify the long-term effects of the ACCORD treatment strategies and provide additional data on the long-term relationships among various cardiovascular and diabetic risk factors.

ACCORD was a randomized cardiovascular clinical trial in 10,251 with type 2 diabetes who were treated and followed for an average of approximately 5 years from 2001 through mid-2009. The original goal of ACCORD was to test three complementary treatment strategies to provide more options for reducing the high rates of major cardiovascular disease (CVD) events observed in people with diabetes. Specifically, the trial was designed to test the effects on major CVD events of intensive glycemia control, of intensive blood pressure control, and of treatment with fenofibrate in the context of good LDL-C control. At the end of the ACCORD, all three ACCORD trials showed only at most 10% nonstatistically significant relative reductions in major cardiovascular events attributed to the intensive glycemia, blood pressure and lipid therapies. Also, there was a statistically significant increase in mortality in the intensive glycemia treatment group. These unexpected results provide the basic rationale for continued follow-up of these participants.

ACCORD participants who agree to participate in ACCORDION will continue to be followed through clinic and phone visits for an average of 3.5 years in the period 2011 through 2014. This will provide the ACCORDION participants with approximately 10 years of post-randomization follow-up. Participants will be seen in 72 clinics across the United States and Canada.

Like the original trial, the primary ACCORDION outcome will be the first occurrence of a major cardiovascular event. Secondary outcomes will include all cause mortality, other ACCORD macrovascular secondary outcomes, and disease-free survival time. Lab and ECG measurements will also be taken periodically during the study. The primary ACCORDION hypotheses are:

- (1) Does a therapeutic strategy that initially targeted an A1C of < 6.0% for a mean of 3.5 years reduce the long-term mean 10 year risk of major CVD events after 6.5 additional years of follow-up compared to a strategy that initially targeted an A1C of between 7 and 7.9%?
- (2) Does a therapeutic strategy that initially used a fibrate to raise HDL-C/lower triglyceride levels and a statin for treatment of LDL-C for a mean of almost 5 years reduce the long-term mean 10 year risk of major CVD events after 5

additional years of follow-up compared to a strategy that only used a statin for treatment of LDL-C?

- (3) Does a therapeutic strategy that initially targeted a systolic blood pressure (SBP) of < 120 mm Hg for a mean of almost 5 years reduce the long-term mean 10 year risk of major CVD events after 5 additional years of follow-up compared to a strategy that targeted a SBP of < 140 mm Hg?

ACCORDION is a prospective observational follow-up study that will provide the scientific community with a large, rich, evolving database that may be examined to address many questions. For example, eye and cognitive hypotheses will be addressed within two substudies embedded within ACCORDION, the ACCORDION-MIND Follow-up Study and the ACCORDION Eye Follow-up Study. Finally, the established ACCORDION clinics, overall organization, and study population will also provide a platform for future ancillary studies that could be conducted at lower cost.

Chapter 1

Introduction and Overview

1.1 General 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 continues to be 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. More than a decade ago, scientists on three panels convened or sponsored by the National Institutes of Health 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. In response to the recommendations from these panels, the *Action to Control Cardiovascular Risk in Diabetes* (ACCORD) trial was funded in 1999. Treatment and follow-up continued until 2009.

The long-term, prospective, observational study described in this protocol is called ACCORDION (the ACCORD Follow-On Study). Through in-clinic and phone visits, ACCORDION will continue to follow at least 8000 former ACCORD participants in 72 former ACCORD clinical sites across the United States and Canada for clinical events

and other health-related information. By the scheduled end of the study, these participants would have accrued 5 or more years of post-trial follow-up.

The general objective for this observational follow-up to the ACCORD trial is to collect additional data on these participants to clarify trends and relationships reported by ACCORD and to use this rich resource for additional analyses and ancillary studies. Specific hypotheses are described below in Protocol Section 1.3. Beyond these specific hypotheses, ACCORDION will provide the scientific community (including both ACCORDION and non-ACCORDION investigators) with a large, rich, evolving database that may be examined to address many other questions. The established ACCORDION clinics, overall organization, and study population will also provide a platform for future ancillary studies that could be conducted at lower cost simply because the participants were already being followed.

To understand the rationale for ACCORDION, a brief description of the original ACCORD trial is necessary.

1.2 General ACCORD Description

Details regarding the original ACCORD trial design, conduct, results and trial organization are presented in Chapter 2. Briefly, ACCORD was a randomized, multicenter, double 2 X 2 factorially designed trial in 10,251 patients with type 2 diabetes mellitus who were at high risk of a cardiovascular event (Goff 2007; ACCORD 2007). It was designed to test the effects on major cardiovascular disease (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 10,251 participants were in an overarching glycemia trial. In addition, one 2 X 2 trial addressed the lipid question in 5,518 participants and the other 2 X 2 trial addressed the blood pressure question in 4,733 participants. The ACCORD primary outcome was the first occurrence of a major CVD event (specifically, a nonfatal myocardial infarction, nonfatal stroke, or death from a cardiovascular cause).

Randomizations began on January 11, 2001 and ended on October 29, 2005. In January 2008, the overarching glycemia trial was stopped early after a mean 3.5 years of treatment and follow-up because of a 22% higher mortality rate in the intensive group ($P=0.04$) (ACCORD 2008). Intensive glycemia treatment also did not significantly reduce the primary outcome among these participants. Intensive glycemia participants

were then transitioned to the standard goal for the duration of the project, with treatment and follow-up in the lipid and blood pressure trials continuing until June 30, 2009. In 2010 it was reported that after 4.7 years of follow-up there were no significant reductions in the primary outcome attributed to good lipid and intensive blood pressure control in the lipid and blood pressure trials, respectively (ACCORD 2010a; ACCORD 2010b). There were also no statistically significant differences in all cause mortality in either trial.

The results from this set of three inter-related trials were unexpected. The ACCORD Steering Committee discussed and agreed that additional follow-up of former trial participants would be scientifically important to clarify trends and relationships. Supporting this notion were the richness of the trial population, the close and strong participant-clinic relationships that had developed during the long-term trial, and the documented success of the conduct of the trial and its organization.

It is expected that at least 8000 of the original 10,251 randomized ACCORD participants will be available for follow-up under ACCORDION. (Details provided in Protocol Chapter 3.)

1.3 Prespecified ACCORDION Hypotheses

1.3.a Primary ACCORDION Hypotheses

The primary outcome for ACCORDION will be the same as the primary outcome for the ACCORD trial, specifically the first occurrence of a major CVD event. This is defined and described in Chapter 4. The ACCORDION secondary outcomes include an expanded macrovascular outcome; major coronary artery disease events; nonfatal myocardial infarction; total stroke: nonfatal stroke; total mortality; cardiovascular mortality; congestive heart failure; and cardiovascular disease free survival. These are also described in Protocol Chapter 4.

The primary ACCORDION hypotheses are:

- (1) Does a therapeutic strategy that initially targeted an A1C of < 6.0% for a mean of 3.5 years reduce the long-term mean 10 year risk of major CVD events after 6.5 additional years of follow-up compared to a strategy that initially targeted an A1C of between 7 and 7.9%?
- (2) Does a therapeutic strategy that initially used a fibrate to raise HDL-C/lower triglyceride levels and a statin for treatment of LDL-C for a mean of almost 5 years reduce the long-term mean 10 year risk of major CVD events after 5

additional years of follow-up compared to a strategy that only used a statin for treatment of LDL-C?

- (3) Does a therapeutic strategy that initially targeted a systolic blood pressure (SBP) of < 120 mm Hg for a mean of almost 5 years reduce the long-term mean 10 year risk of major CVD events after 5 additional years of follow-up compared to a strategy that targeted a SBP of < 140 mm Hg?

The background and rationale for these hypotheses are in Chapter 2.

1.3.b ACCORDION MIND and Eye Substudies

Embedded within ACCORDION are two substudies, the ACCORDION-MIND Follow-up Study and the ACCORDION Eye Follow-up Study.

MIND ('Memory in Diabetes') was a substudy within the original ACCORD trial (Williamson 2007). The general aim for this new substudy is to further delineate how intensive therapy for diabetes affects brain function. Details regarding the MIND substudy are in Protocol Chapter 5. The data from this follow-up will more closely examine rates of decline in cognitive function, and using funding from another source for additional MRIs, use data from this MIND follow-up to more closely examine whether and how observed changes in brain structure ultimately impacts ongoing declines in cognitive function.

Specifically, the primary hypothesis for the ACCORDION-MIND cognitive outcomes is that, as a result of a "legacy effect" from intensive therapy, the rate of decline in cognitive function (as measured by the Digit Symbol Substitution Test (DSST)) will be lower in the group randomized to intensive glycemic control compared to the group randomized to standard glycemic control. The primary hypothesis for the MRI outcomes is that the rate of decline in total brain volume (TBV) will be lower in the group randomized to intensive glycemic control compared to the group randomized to standard glycemic control.

ACCORD Eye was also a substudy within the original trial (Chew 2007; Chew 2010). The general aim for this new ACCORDION Eye substudy is to better delineate the relationship between diabetic retinopathy and cardiovascular disease, and the relationship between their responses to control of glycemia and other risk factors.

Details regarding the Eye substudy, including other specific aims, are in Protocol Chapter 6.

The specific aims for the ACCORDION-Eye substudy include: (1) evaluate the long term effects of intensive glycemic control, dyslipidemia management with fenofibrate and simvastatin, and intensive blood pressure control on diabetic retinopathy progression at 8 years post-randomization; and (2) evaluate whether there is a similar “memory imprint” seen in the diabetic retinopathy progression in the DCCT/EDIC trial of persons with type 1 diabetes also in this study of participants with type 2 diabetes.

1.4 Other Questions May be Posed

In addition to the primary hypotheses presented above for the primary outcome (Section 1.3.a), also of interest are mirror hypotheses for each of the pre-specified secondary outcomes (described in Chapter 4), but especially for the total mortality and cardiovascular mortality outcomes where intensive glycemia therapy was associated with harm during the main trial. The intent is to explore these hypotheses for each of the pre-specified secondary outcomes, although the results may be reported in detail only for the primary outcome and for total and cardiovascular mortality.

The combined ACCORD/ACCORDION databases can and will also be used to address many other important medical and public health questions by ACCORDION and non-ACCORDION investigators. This is a rich evolving database of at least 8000 people with diabetes and at high risk of cardiovascular events who will be followed for up to 10 years post-randomization and from whom much information has been and will continue to be collected. This includes information on diabetes, cardiovascular disease events, lipids, glucose levels, blood pressure, medication use, eye disease, health-related quality of life, data related to health care costs, MRI data, cognitive functioning, etc. There are many natural history and associations that may be posed and explored, including questions not necessarily related to diabetes and/or heart disease.

1.5 Potential for Ancillary Studies

There may be questions that ACCORDION cannot currently or adequately address because the appropriate data are not being collected. Because ACCORDION has an established population that will be followed over time in clinics that have close relationships with the participants, this is a fertile environment that provides exceptional opportunities for investigators, either within or outside of ACCORDION (see Section

11.4), to conduct ancillary studies at lower cost. Protocol Chapter 11 describes the processes that will be followed in soliciting, reviewing, and monitoring ACCORDION Ancillary Studies

1.6 Operational Overview

The 10,251 randomized ACCORD participants were treated and followed through spring 2009. Between September 1, 2009 and December 31, 2010, approximately 8000 surviving and consenting participants have been followed by phone and/or record surveillance for clinical events. By the time ACCORDION follow-up begins in May 2011, these participants would have already accrued at least 1.5 years of post-trial follow-up. Through three in-clinic visits and four phone calls during ACCORDION, more detailed event and medical follow-up information will be collected over an additional 3.5 years of observational follow-up, providing 5 years of post-trial follow-up information.

Organizationally, the original ACCORD trial units will continue in ACCORDION. These include the Coordinating Center, 7 Clinical Center Networks, 72 ACCORD clinical sites, the Central Laboratory and ECG Reading Center. These units and their responsibilities are described in Protocol Chapter 14.

Chapter 2

Background and Rationale

2.1 The ACCORD Trial

Clinical trials completed through the late 1990's suggested that cardiovascular disease (CVD) risk might be reduced in patients with diabetes. However, there was a critical gap in knowledge regarding the relative CVD benefits of intensively targeting for a normal glucose, blood pressure and lipid status (Goff 2007). As a consequence, a number of large trials began, including the NIH-sponsored *Action to Control Cardiovascular Risk in Diabetes* (ACCORD) trial.

ACCORDION will be the observational follow-up of participants who were recruited, treated, and followed in the ACCORD Trial. A description of ACCORD and its study population and findings provides a foundation for understanding ACCORDION scientifically and organizationally. Additional details may be found on the ACCORD website (www.accordtrial.org) and by reviewing the original ACCORD protocol and published papers (also found on the ACCORD website).

2.2 ACCORD Design and Timeline

The overall goal of the ACCORD trial was to test three complementary medical treatment strategies for type 2 diabetes to enhance the options for reducing the very high rate of major CVD morbidity and mortality in this disease (ACCORD 2007; Gerstein 2007; Cushman 2007; Ginsberg 2007; Kingry 2007; Bonds 2007; Sullivan 2007). It was an NHLBI-sponsored, randomized, multicenter, double 2 X 2 factorial design in 10,251 patients with type 2 diabetes mellitus and was 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). The three specific primary ACCORD hypotheses were: 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 glyceemic 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 glyceemic 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 was the first occurrence of a major cardiovascular disease event, specifically nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Total mortality was one of several prespecified secondary outcomes. Deaths, myocardial infarctions, and strokes were adjudicated by a central committee, which was masked to treatment allocation and used predefined criteria.

ACCORD was conducted in 77 clinical centers aggregated within 7 networks across the United States and Canada. Volunteers with type 2 diabetes mellitus (T2DM) who had an A1C level > 7.5% and were either 40-79 years old with previous CVD events, or who were age 55-79 years with either anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least 2 additional risk factors for CVD (dyslipidemia, hypertension, current smoking or obesity) were recruited (ACCORD 2007). Key exclusion criteria included frequent or recent serious hypoglycemic events, unwillingness to do home glucose monitoring or inject insulin, a body mass index > 45 kg/m², serum creatinine > 1.5 mg/dl (133 umol/l), or other serious illnesses.

All 10,251 participants were randomly allocated to a comprehensive intensive glycemia therapeutic strategy to lower A1C levels to below 6.0%, or to a standard glycemia strategy targeting A1C levels between 7.0 and 7.9% (Gerstein 2007). Under the double 2 X 2 factorial design, 4733 of these participants were randomized to intensive or standard blood pressure (BP) lowering strategies (systolic BP target < 120 or < 140 mmHg respectively) (Cushman 2007), and the other 5518 participants were randomized to masked fenofibrate or placebo on a background of good LDL-C control with simvastatin (Ginsberg 2007).

Participants were given educational and behavioral counseling regarding diabetes care and other CVD risk factors and lifestyle issues (issues such as smoking, weight loss, physical activity and use of cardiac medications). Participants were provided with glucose-lowering medications from an ACCORD formulary and glucose monitoring supplies. Also from the formulary, participants in the blood pressure portion of ACCORD were provided with blood pressure-lowering medications and participants in the lipid portion were provided with simvastatin and the masked medication (either fenofibrate or placebo). Therapeutic regimens were individualized at the discretion of the ACCORD investigators and participants based on the participant's treatment assignment and response to therapy. The occurrence of any adverse effects of therapy was carefully

audited both locally and centrally to ensure participant safety. Participants were seen every two to four months, depending upon treatment group assignment.

The investigators first met in October 1999 to begin trial planning. The first participant was randomized on January 11, 2001 and the last was randomized on October 29, 2005. Participants were followed until spring 2009 with the last clinic visit occurring on June 30, 2009. As a measure of follow-up success on June 30th, final vital status was obtained on 96% of the participants; there was incomplete follow-up on that date for 395 people (although their vital status was known at earlier points of time for analyses purposes).

2.3 ACCORD Results

2.3.a ACCORD Glycemia Trial Results

Background: Since late 2001, interim results were reviewed approximately every 6 months by an independent 10-member Data Safety and Monitoring Board (DSMB) appointed by the NHLBI. After reviewing mortality trends for several months (and as part of a preplanned safety analysis), the DSMB concluded on January 8, 2008 that the harm associated with the greater rate of total mortality in the intensive versus the standard glycemia group outweighed any potential benefits and recommended that the intensive glycemia treatment be discontinued for safety reasons. This recommendation was accepted by the NHLBI. ACCORD participants were informed of this decision on February 5, 2008 (17 months ahead of the scheduled termination of the glycemia trial) and subsequently switched to the standard glycemia approach. The public was informed by a press release on February 6, 2008 and the results published in the *New England Journal of Medicine* in June 2008 (ACCORD 2008). The lipid and blood pressure trials continued until the scheduled end of treatment and follow-up in spring 2009.

Glycemia Trial Results: A total of 10,251 men and women (38%) of mean age 62.2 years, and median A1C 8.1% were randomly assigned to either the intensive or the standard glycemia intervention group. Key baseline characteristics were distributed equally between randomized glycemia groups. The mean duration of follow-up at the time the DSMB recommended stopping the intensive glycemia intervention was 3.5 years (median =3.4 years). The two therapeutic strategies rapidly achieved different A1C levels. Within 4 months of randomization the median A1C had fallen from the baseline median of 8.1% to 6.7% in the intensive group and 7.5% (interquartile range [IQR]=7.0-8.2) in the standard group; stable median levels of 6.4% and 7.5%

respectively, were achieved at 1 year and maintained throughout the follow-up period (i.e., the goal to achieve a delta of at least 1% between the groups was achieved). Compared with standard group participants, intensive group participants experienced more hypoglycemia, weight gain, and fluid retention. Based upon adjudication of causes of death, 1 death in each group was attributed to hypoglycemia. Participants in both groups used similar amounts of CVD protective interventions and experienced similar changes in nonglycemic variables associated with CVD events.

During the intervention period 723 experienced the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or CVD death and 460 people died. There were fewer occurrences of the composite primary outcome in the intensive group with primary outcome rates beginning to separate after 3 years. This trend was not significant (6.86% versus 7.23%, HR 0.90, P=0.16) and comprised a lower rate of nonfatal myocardial infarctions in the intensive group (3.63% versus 4.59%, HR 0.76, P=0.004), a higher rate of CVD mortality (2.63% versus 1.83%, HR 1.35, P=0.02), and no significant difference in nonfatal stroke (1.31% versus 1.19%, HR 1.06, P=0.74). All-cause mortality was higher in the intensive than the standard group (5.01% versus 3.96%, HR 1.22, P=0.04). Mortality rates in the 2 treatment groups began to separate within one to two years and the differences persisted throughout the follow-up period.

The investigators concluded that compared to a strategy targeting A1C levels of 7-7.9%, using current therapies to target normal A1C levels increased mortality and did not significantly reduce major CVD events during 3.5 years in people with T2DM with high A1C levels and previous CVD or additional CVD risk factors.

2.3.b ACCORD Lipid Trial Results

Unlike the ACCORD Glycemia trial that ended 17 months ahead of schedule because of the higher mortality rate observed in the intensive treatment group, the ACCORD Lipid and Blood Pressure trials continued until their scheduled termination in spring 2009. The last participant clinic visit was on June 30, 2009. 5,518 men and women were enrolled into ACCORD Lipid (ACCORD 2010a). They were randomized to receive placebo + simvastatin (referred to as “placebo”) (n=2,753) or fenofibrate + simvastatin (referred to as “fenofibrate”) (n=2,765). Baseline characteristics were similar between the two groups. Thirty-seven percent had a history of a CVD event, the mean LDL-C was 100.6 mg/dl (2.60 mmol/L), mean HDL-C was 38.1mg/dl (0.99 mmol/L), median triglyceride was 162 mg/dl (1.83 mmol/L), and about 60% of the participants were on a statin prior to enrollment. The mean duration of follow-up was 4.7 years for the primary outcome (95% of the potential follow-up) and 5.0 years for total mortality. Adherence to

masked study medication was high: 77.3% of fenofibrate and 81.3% of placebo participants were on their assigned medication at the final study visit. At the end of the trial, 86% were still adherent to a LDL-C lowering background therapy. Fasting plasma lipids were similar between the two groups at baseline. LDL-C levels fell over the course of the study, as statin therapy was intensified, and were approximately 80 mg/dl in both groups at study end. By study end, HDL-C had increased by 8.4% in the fenofibrate group and 6.0% in the placebo group. At study end, median plasma TG was reduced by 22.2 % in the fenofibrate group and 8.7% in the placebo group.

The annual primary outcome rate was 2.2% among fenofibrate participants vs 2.4% among placebo participants, (Hazard Ratio (HR) = 0.92, $p=0.32$ after adjustment for monitoring) (ACCORD 2010a). Hazard ratios for secondary endpoints, including the individual components of the primary outcome ranged from 0.82 to 1.17 (all $P>0.10$). Annual total mortality rates were 1.47% in the fenofibrate group and 1.61% in the placebo group (HR 0.91, adjusted $p=0.33$). At the 0.05 level, only gender showed evidence of an interaction by treatment group: the primary outcome was 17.6% lower for men in the fenofibrate group, but was 37.8% higher for women in the fenofibrate group (interaction $P=0.0106$). There was also evidence suggestive of heterogeneity when participants with both TG in the highest tertile (≥ 204 mg/dl) and HDL-C in the lowest tertile (≤ 34 mg/dl) were compared to all other participants (interaction $p=0.057$). In this high TG/low HDL-C subgroup, fenofibrate was associated with a 31% lower primary outcome rate compared to placebo, while there was no benefit of fenofibrate in all other participants.

The investigators concluded that the combination of fenofibrate and simvastatin did not reduce the rates of fatal cardiovascular events, non-fatal myocardial infarction, or non-fatal stroke compared to simvastatin alone. The results of ACCORD Lipid did not support the routine use of combination therapy with fenofibrate and simvastatin to reduce CVD in high-risk patients with T2DM.

2.3.c ACCORD Blood Pressure Trial Results

Like the Lipid trial, the ACCORD Blood Pressure trial continued until its scheduled termination in spring 2009 (ACCORD 2010b). The last participant clinic visit was on June 30, 2009. Participants had a mean age of 62.2 years, mean SBP and DBP of 139.2 mm Hg and 76.0 mm Hg; 48% were women and 34% had CVD at baseline. Key baseline characteristics were similar in the two randomized groups. At the end of the trial (June 2009), vital status was known for 95.1% of randomized participants. The mean duration of follow-up for mortality was 5.0 years or 98.4% of the potential person-

years of follow-up that would have been obtained if all surviving participants had been followed until the end of the trial. For the primary outcome, the mean duration of follow-up was 4.7 years: 95% of the potential follow-up. The two therapeutic strategies rapidly achieved different SBP levels. After the first year of therapy, average BP across all 4 month protocol visits common to the two groups was 119.3/64.4 mm Hg in the intensive group and 133.5/70.5 mm Hg in the standard group, resulting in an average difference in SBP between treatment groups of 14.2 mm Hg (greater than the 10 mm Hg goal difference).

The primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes occurred in 445 participants. The rate was 1.87%/year in the intensive group and 2.09%/year in the standard group with no significant difference between groups (hazard ratio 0.88, $p=0.2$) (ACCORD 2010b). There were 294 deaths from any cause and 118 CVD deaths. There were more deaths in the intensive (150 total, 60 CVD) than standard group (144 total, 58 CVD). Neither trend was significant (total mortality, HR=1.07, $p=0.55$; CVD mortality HR=1.06, $p=0.74$). Among other secondary outcomes, only total stroke (HR=0.59, $p=0.01$) and non-fatal stroke (HR=0.63, $p=0.03$) attained nominal significance.

The investigators concluded that the observed trial results provided no conclusive evidence that targeting normal systolic pressure compared with a standard goal reduced a composite of major cardiovascular events in high-risk patients with type 2 diabetes.

2.4 Examples of Other Post-Trial Observational Follow-up Studies

The post-trial observational follow-up of ACCORD participants is similar in concept to earlier observational studies that followed participants after the completion of treatment in a clinical trial, two examples of which are described here. First, the Coronary Drug Project (CDP) was a clinical trial of five lipid lowering agents, including niacin, conducted between 1966 and 1974 in 8341 men with a documented MI followed for an average of 6.2 years (CDP 1975). The primary outcome was all cause mortality. Whereas niacin therapy showed a modest 26% benefit in reducing the incidence of recurrent MI ($p=0.002$) compared to placebo, there was no difference in all cause mortality (3.9% reduction, $p=0.50$). However, in an observational/nontreatment follow-up study of the former CDP participants with a mean follow-up of 15 years, mortality in the niacin group was 11% lower than in the placebo group ($p<0.001$) (Canner 1986). The investigators postulated that the time lag in development of a beneficial trend in mortality might be explained in part to the earlier decrease in nonfatal MI. Regardless of

any mechanistic explanation, however, is the clear observation of a treatment group difference that manifested itself nearly 9 years after the end of trial treatment.

Another example would be the more recent Epidemiology of Diabetes Interventions and Complications (EDIC) study, which was an observational follow-up to the Diabetes Control and Complications Trial (DCCT 1993). DCCT was a trial comparing intensive versus conventional glucose therapy among 1441 patients with type 1 diabetes who were treated/monitored between 1983 and 1993. After a mean of 6.5 years, DCCT reported that therapy aimed at maintaining A1C levels as close to normal as feasible reduced the risks for the development and progression of early microvascular and neurologic complications. The subsequent EDIC observational study reported in 2005 that after a mean 17 years of follow-up, intensive treatment reduced the risk of any CVD event by 42% ($P=0.02$) and the risk of nonfatal MI, stroke, or CVD death (and outcome like ACCORD's primary) by 57% ($P=0.02$) (EDIC 1999a; EDIC 1999b; DCCT/EDIC 2005).

2.4.a Lessons from Other Post-Trial Observational Follow-up Studies: Is it Possible to Observe a Post-Trial Treatment Group Difference Following a Negative or Neutral Trial?

Many long-term observational follow-up studies of trials are from trials that demonstrated a definite effect. In the case of ACCORD, however, the primary hypotheses were not confirmed and a null or harmful effect of the interventions was observed. The question could be posed whether continued follow-up of the participants would be warranted. But there are also examples of trials in which important outcomes were not confirmed during the trial itself, but were confirmed during the subsequent observational follow-up. For example, treatment group differences in cardiovascular events in EDIC (DCCT 1995) and myocardial infarction and all-cause mortality (UKPDS 1998) in UKPDS were not noted during the randomized glycemia clinical trial phase, but were found during the subsequent observational follow-up periods of each study (DCCT/EDIC 2005; Holman 2008). Moreover, during ACCORD, the risks of non-fatal myocardial infarction (ACCORD 2008) as well as macroalbuminuria and three line loss of visual acuity (Ismail-Beigi 2010) were significantly decreased by intensive glycemic treatment during the trial and remained so after the transition of the intensive group to standard treatment. Thus the start of a legacy effect or metabolic memory from intensive glycemic treatment can already be seen in ACCORD and it is of scientific and clinical interest to learn whether this effect will continue for a number of years in ACCORDION.

Also of note, the hazard ratios of the primary outcome for the intensive/standard glycemic treatment comparison was 0.90, (95% CI 0.78 - 1.09, $p = 0.13$) until the transition point and was 0.91 (95% CI 0.81 – 1.03, $p=0.1$) for the whole 5 years of the trial (ACCORD 2011). This trend toward benefit warrants further observation to determine whether an ultimately statistically significant benefit eventually emerges. While the increased mortality in the intensive group warns against using the exact intensive treatment regimen as practiced in ACCORD in a high cardiovascular risk ACCORD type population, it would not diminish the scientific validity of supportive evidence that lowering glucose levels diminishes overall cardiovascular disease (CVD) complications during ACCORDION. Since the cause of the increased mortality with intensive treatment is still unknown, whether increased mortality continues as a legacy effect in ACCORDION, and the characteristics of those who subsequently might die, may inform us as to what that cause is.

2.4.b Lessons from Other Post-Trial Observational Follow-up Studies: ACCORDION and the Relevance of Other Long-term Observational Follow-up Studies in Relation to the Respective Duration of the Intervention and Observational Phases of those Studies

The DCCT cohort had been diagnosed with diabetes for 5.5 years on average, mean age 28 and no CVD at baseline (DCCT 1993). EDIC was preceded by a mean DCCT intervention period of 6.5 years; a beneficial effect on retinopathy and nephropathy was discovered after four years of observation (DCCT/EDIC 2000), on carotid-intimal thickness after six years (EDIC 1999a; DCCT/EDIC 2003), on coronary calcium at eight years (Cleary 2006), and on CVD events after 11 years (DCCT/EDIC 2005).

At randomization, ACCORD participants had been diagnosed with diabetes for 10 years on average, mean age was 62, and one-third had CVD events while two-thirds had subclinical disease or at least 2 CVD risk factors at baseline (ACCORD 2008). The intensive intervention phase in ACCORD was 3.7 years but glycemic separation between the intensive and standard groups continued, albeit to a lesser degree, until the end of the trial for a total of five years (Ismail-Beigi 2010). Initial observational follow-up in ACCORDION (including the 1.5 yr post-ACCORD period) is planned for five years.

THE UKPDS cohort of newly diagnosed patients with diabetes had an average age 53 years and 7.5% had CVD at baseline (UKPDS 1998). UKPDS had an intervention phase of 11 years, and a legacy effect on CVD was apparent after a ten year observational phase, similar to EDIC (Holman 2008).

2.4.c Lessons Other Post-Trial Observational Follow-up Studies: the biologic rationale for a time lag in treatment effect and how this could affect ACCORDION Outcomes

Atherosclerosis is a slow process and its effects take many years to eventuate in recognizable clinical events. Evidence of a time lag in glycemic treatment effects on CVD events is provided by the DCCT-EDIC study. From a starting average duration of type 1 diabetics of 5.5 years, intensive was compared to standard glycemic treatment in a clinical trial lasting 6.5 years (the DCCT phase) (DCCT 1993). Observational follow-up has been carried on for 16 years in the EDIC phase. Early in EDIC (duration 14 years) when few CVD events had occurred, the beginning of atherosclerosis was revealed by an increase only in males in internal carotid intimal – medial thickness (CIMT) compared to normal participants (EDIC 1999a). Six years later (duration 20 years) combined CIMT was now greater in the whole diabetic cohort than in age and gender matched controls (DCCT/EDIC 2003). Moreover, in the interval period of observation, although HbA1c levels were similar in the two original treatment groups, there was significantly less progression of CIMT-defined atherosclerosis in those who had been treated intensively compared to those treated in standard fashion during the DCCT (DCCT/EDIC 2003). Finally, it took 4-5 more years (duration 24 years), before a significant decrease in CVD events from intensive glycemic treatment became demonstrable (DCCT/EDIC 2005).

While this example is from type 1 diabetic participants experiencing an intervention earlier in their disease than the ACCORD type 2 participants, it illustrates vividly that there can be a time lag between a glycemic intervention and an ultimate effect on clinical CVD events, even though the lag period glycemic levels are similar. During this time lag, reflecting the previous glycemic differential of the intervention period, a differential biologic process is presumably occurring that culminates in a clinical event difference. This lag time is likely to be less in the ACCORD cohort whose duration of diabetes was ten years at baseline and who almost certainly had some atherosclerosis at baseline, given their high prevalence of hypertension and dyslipidemia and given that one-third had already suffered a CVD event. During the entire five year period of ACCORD, HbA1c levels were lower in the intensive than the standard group. It is plausible that a beneficial legacy glycemic effect on CVD events may become evident in ACCORDION.

2.4.d Lessons from Other Post-Trial Observational Follow-up Studies: Biologic Rationale for a Larger Effect Size after Long-term Follow-up Than the One Observed During ACCORD Intervention

During the EDIC observational phase, the absolute reductions in risk of complications brought by intensive treatment during the DCCT actually increased as more events accrued (DCCT/EDIC 2000). There are currently at least two major possible biological bases for this metabolic memory phenomenon. EDIC demonstrated in an ancillary study that levels of advanced glycation end products (AGE's) (resulting from hyperglycemia) measured in skin collagen near the end of the DCCT predicted the future incidence of retinopathy and nephropathy during the first ten years of EDIC (Genuth 2005). Collagen molecules have a half life of 15 years (Verzija 2000), so molecules glycated during the DCCT intervention could well have caused altered basement membranes and thickened intima in many tissues (e.g. kidney, blood vessels) many years later. Moreover, atherosclerotic plaques modified by AGE's in their collagen may become more vulnerable to rupture. AGE's also interact with specific receptors (RAGE's) resulting in activation of NFκB leading to increased synthesis of inflammatory factors (Aronson 2002; Alexiou 2010). Inflammation is now accepted as an important contributor to atherosclerosis (Hansson 2009). The levels of AGE-modified collagen near the end of the DCCT were lower in intensive than standard treatment participants (Monnier 1999), so a reduction in AGE-altered collagen or other long-lived proteins is one mechanism that could account for a long term increasing benefit from intensive treatment.

A second mechanism currently being investigated by the EDIC study involves an epigenetic effect. Exposure to elevated glucose concentrations – in vitro and in vivo – has been shown to induce epigenetic changes in chromatin via methylation and acetylation of histones (Miao 2007; Miao 2008). These changes can result in activation or deactivation of various genes, even after return to a normal glucose environment (Miao 2007; Roy 1990; Ceriello 2008). If such epigenetic changes persist in cells long term, they too could explain a continuing or even an increasing differential biological effect of treatment during ACCORD on later CVD events during ACCORDION (Ceriello 2009).

2.5 Summary and Rationale for ACCORDION

It was unexpected that all three ACCORD trials would show as point estimates only at most 10% nonstatistically significant relative reductions in major cardiovascular events attributed to the intensive glycemia, blood pressure and lipid therapies. As perplexing was the statistically significant increase in mortality in the intensive glycemia treatment

group. Obvious questions flow from observations like these, as they do at the end of most clinical trials (as exemplified above). For example, would there be a legacy effect in any of these trials? Might a statistically significant beneficial (or harmful) effect on major CVD or renal events manifest itself years after the termination of treatment? With the addition of a few extra years of follow-up, would the mortality differential in the glycemia trial get larger or smaller, or possibly even disappear? What would happen to the excellent A1C, blood pressure, and lipid differentials that were observed in ACCORD a few years after the cessation of treatment?

These obvious questions, and the success of other post-trial observational studies with additional follow-up time made available to possibly clarify trends, provide the rationale for the continued and more detailed post-trial follow-up of the ACCORD participants. ACCORDION also presents the investigators with an excellent opportunity, through ACCORDION-MIND, to further delineate how intensive therapy for diabetes affects brain function, and through ACCORDION Eye, to further evaluate the effect of treatment on diabetic retinopathy.

Chapter 3

Methods and Study Design

3.1 Overview

ACCORDION is a simple, prospective observational follow-up study of participants who had originally participated in ACCORD (*Action to Control Cardiovascular Risk in Diabetes*), a randomized clinical trial of people with type 2 diabetes mellitus who were at high risk of a cardiovascular event. ACCORDION participants will be followed for major clinical events (including nonfatal myocardial infarctions and strokes), deaths, and other key measures of health. The major ACCORDION-specific primary and secondary outcomes are defined in Protocol Chapter 4, as are other events of interest. Since the end of ACCORD in spring 2009 (at which time participants had had an average of 4.7 years of follow-up), consenting participants have been followed by phone or medical surveillance for events for an additional 1.5 years. Under ACCORDION, at least 8000 surviving consenting former-ACCORD participants will be followed more closely for 3.5 more years, including having 3 clinic visits, 4 additional telephone contacts, plus laboratory and ECG measurements obtained twice during the study. The ACCORDION timeline and visit schedule are presented below in Section 3.5. Details regarding the original ACCORD trial design are presented in Protocol Chapter 2.

Because ACCORDION is not a clinical trial but rather an observational study, clinic personnel will not administer medical care for diabetes or any other disorder as part of this study. Medical care will continue to be provided by the participant's local primary care provider (PCP).

3.2 Number of Participants Expected in ACCORDION

Randomizations for ACCORD began on January 11, 2001 and treatment and follow-up ended on June 30, 2009. In all, 10,251 participants were recruited for the trial. When ACCORD treatment and follow-up ended in 2009, there were 9138 known surviving participants. Of these, 8530 (93%) gave consent and have been monitored over the subsequent 1.5 years by phone or medical record surveillance to ascertain the occurrence of medical events, including myocardial infarction, strokes, and death. Through December 2010, ACCORD clinics have successfully maintained contact with approximately 8000 surviving participants (94% of those who gave consent at the end of the trial). Under ACCORDION, all surviving ACCORD participants will be contacted again in late spring 2011 for consent to be followed more closely for 3.5 additional years

(through late-2014) in this observational study, providing the investigators with 5 years of post-trial follow-up information.

Although there were 77 clinics operating during most of ACCORD, one clinic ceased operation a year before the scheduled end of the trial and four clinics have subsequently merged with other clinics. Thus, the targeted and expected goal for ACCORDION recruitment is at least 8000 participants from 72 participating clinical sites across the United States and Canada.

3.3 Eligibility Criteria for ACCORD / ACCORDION

ACCORDION participants were all treated and followed in the ACCORD trial and thus needed to fulfill the original ACCORD entry criteria, which are presented in detail in Appendix A. Briefly and overall for the overarching Glycemia Trial, the participants were men or women consenting volunteers who had type 2 diabetes mellitus and a glycated hemoglobin level of 7.5% or more and who either were between the ages of 40 and 79 and had cardiovascular disease or were between the ages of 55 and 79 years and had anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, and at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current smoker, or obesity). Key exclusion criteria included frequent or recent hypoglycemic events, unwillingness to do home glucose monitoring or inject insulin, a body-mass index greater than 45 kg/m², serum creatinine more than 1.5 mg per deciliter (133 micro-mol/L), or other serious illness. ACCORD participants in the Lipid Trial were also required to have an LDL-cholesterol between 60 and 180 mg/dl (1.55 to 4.65 mmol/L), an HDL-cholesterol below 55 mg/dl (1.42 mmol/L) for women and blacks or below 50 mg/dl (1.29 mmol/L) for other groups, and a triglyceride below 750 mg/dl (8.5 mmol/L) if they were not receiving lipid therapy or below 400 mg/dl (4.5 mmol/L) if they were receiving lipid therapy. ACCORD participants in the Blood Pressure Trial were required to have a systolic blood pressure between 130 and 180 mmHg, taking three or fewer medications, and have the equivalent of a 24-hour protein excretion rate of less than 1.0 grams.

The original entry criteria for ACCORD are presented in Appendix A. There are no additional criteria for ACCORDION. To be eligible for ACCORDION, a person must have been a participant in ACCORD and be willing to sign an informed consent. The only exclusion is to have not participated in ACCORD.

3.4 Characteristics of Participants at End of ACCORD

Table 3.1 presents the characteristics of the ACCORD participants at their last recorded follow-up clinic visit, by trial. Because it is expected that most of these participants will consent to ACCORDION, these characteristics will likely closely describe the ACCORDION population.

Table 3.1: Participant Characteristics* at Last Follow-Up Visit, By ACCORD Trial
(Restricted to those final visits occurring during the period February 2008 through June 2009)

Participant Characteristics	Glycemia Trial (N=8912)	Lipid Trial (N=4793)	Blood Pressure Trial (N=4119)
Age, yrs	67.2 +/- 6.8	67.2 +/- 6.8	67.2 +/- 6.9
% female	38.3%	47.0%	30.8%
% minority	36.8%	33.8%	40.3%
Weight, kg	94.7 +/- 20.5	93.4 +/- 20.4	95.8 +/- 20.5
Body mass index, kg/m ²	32.8 +/- 6.1	32.8 +/- 6.2	32.8 +/- 6.0
Waist circumference, cm	108.4 +/- 15.2	107.4 +/- 15.2	109.3 +/- 15.1
Systolic blood pressure, mm/Hg	128.9 +/- 16.9	127.5 +/- 16.7	130.0 +/- 17.1
Diastolic blood pressure, mm/Hg	68.0 +/- 10.3	67.6 +/- 10.3	68.4 +/- 10.3
HbA1C, percent	7.6 +/- 1.2	7.6 +/- 1.2	7.6 +/- 1.2
Fasting serum glucose, mg/dl	149.2 +/- 55.6	148.4 +/- 55.0	149.9 +/- 56.1
Mean +/- SD LDL-C, mg/dl	87.9 +/- 33.4	96.4 +/- 38.3	80.7 +/- 26.5
HDL-C Women, mg/dl	49.2 +/- 13.6	52.5 +/- 14.6	45.0 +/- 10.8
HDL-C Men, mg/dl	40.5 +/- 10.8	42.9 +/- 12.8	38.9 +/- 8.9
Total cholesterol, mg/dl	163.6 +/- 42.2	176.5 +/- 45.7	152.5 +/- 35.3
Triglycerides, mg/dl	163.2 +/- 120.0	168.7 +/- 127.2	158.4 +/- 113.3
Potassium, mEq/L	4.4 +/- 0.4	4.3 +/- 0.5	4.4 +/- 0.4
Serum creatinine, mg/dl	1.1 +/- 0.4	1.0 +/- 0.4	1.1 +/- 0.4

* Plus-minus values are means +/- standard deviation. Data accessed on February 14, 2011.

Abbreviations: HbA1c=hemoglobin A1C; LDL-C=low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol

3.5 ACCORDION Timeline and Visit Schedules

Table 3.2 presents the overall timeline for ACCORDION. The first four months of the study (January 2011 through April 2011) will involve finalizing the ACCORDION

Protocol, developing a Manual of Procedures, establishing subcontracts, obtaining all necessary IRB and other regulatory approvals, and conducting training.

Table 3.2: ACCORDION TIMELINE

Calendar	ACCORDION FUNDING STARTS				ACCORDION FOLLOW-UP VISITS (through October 2014)----->								
Year	Jan-11	Feb-11	Mar-11	Apr-11	May-11	Jun-11	Jul-11	Aug-11	Sep-11	Oct-11	Nov-11	Dec-11	
2011	Protocol/MOP/Forms Development, Subcontract Approvals, IRB Approvals, Training, etc				<----- 24 Month Post-Trial Follow-up Visits -----> (50% Phone, 50% Clinic)								
Year	Jan-12	Feb-12	Mar-12	Apr-12	May-12	Jun-12	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12	Dec-12	
2012	-- 30 Month Post-Trial Follow-up Visits ----> (50% Phone, 50% Clinic)				<----- 36 Month Post-Trial Follow-up Visits -----> (75% Phone, 25% Clinic)								
Year	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	
2013	-- 42 Month Post-Trial Follow-up Visits ----> (50% Phone, 50% Clinic)				<----- 48 Month Post-Trial Follow-up Visits -----> (75% Phone, 25% Clinic)								
Year	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	
2014	-- 54 Month Post-Trial Follow-up Visits ----> (50% Phone, 50% Clinic)				<----- 60 Month Post-Trial Follow-up Visits -----> (50% Phone, 50% Clinic)								Analysis, Paper Writing, Presentations, Final Database Creation, etc
Year	Jan-15	Feb-15	Mar-15	Apr-15									
2015	Analysis, Paper Writing, Presentations, Final Database Creation, etc				= period with participant visits								

The first ACCORDION follow-up visits (the 24 month post-trial follow-up visits) will begin on May 1, 2011; follow-up will end (with the 60 month post-trial follow-up visits) on October 31, 2014. The schedule in Table 3.2, with participant contact occurring every 6 months (either by phone or in clinic), was carefully selected to simplify participant scheduling and balance in-clinic workload. For example, the May 1st start date was selected because ACCORDION funding would not be available until January 1st and because of the need to spend the appropriate amount of time in study preparation. Recognizing that the ACCORD participants had their trial close-out visits in a 4 month period from March 1 through June 30, 2009, the dual constraints of wanting to have contact visits every 6 months with the first visit occurring on May 1st, led to stretching the “24 month” visits over a 6 month period from May 1 through October 31, 2011. That is, some of the “24 month” visits will occur slightly beyond 2 years since the close-out, but would be within a reasonable visit window. Importantly, this slight “resetting” of the study clock permits simple future participant scheduling. Note: the post-trial times noted

here (e.g., “24 month”) are for scheduling purposes only. Analyses such as survival analyses will always use the real, exact calendar date and time from randomization in the trial.

The final six month period of the ACCORDION contract, from November 1, 2014 through April 30, 2015, will be devoted to clinic close-out, study analyses, paper preparation, presentations, and final database preparation and documentation. Although the timeline identifies study analyses as being a major feature of this period, it is planned that study analyses would occur throughout the entire ACCORDION time period. In contrast to ACCORD, which like many other clinical trials had no publications presenting follow-up results as long as participants were being treated, the ACCORDION investigators are no longer under this typical trial constraint and plan on publishing findings when appropriate.

Features of the Proposed Timeline: When devising the participant timeline, a number of specific features were identified by the investigators as critical, including (1) the participants should be contacted every 6 months for 3.5 years, for a total of 7 contacts; (2) 3 of these contacts would be in-clinic and 4 would be by phone; and (3) the 3 clinic visits would occur ‘at the beginning’ (at either the 24 or 30 month visits), ‘at the end’ (at either the 54 or 60 month visits), and ‘in the middle’ (at either the 36, 42 or 48 month visits). The rationale for this last criterion is that it is desirable to spread clinic visits across calendar time as much as possible so that in every calendar month clinics have approximately the same number of clinic visits and same workload. The alternative, which was unacceptable, would be to have a bolus of clinic visits at post-trial months 24, 42, and 60, and only phone visits for a year at a time in-between. This inefficiency would lead to erratic clinic staffing and funding patterns.

During those 12 month periods of time in which half the contacts are in-clinic and half are by-phone (e.g., from May 2011 through April 2012), the Coordinating Center (CoC) will inform the clinics which participants should have a clinic visit and who should have a phone contact. Specifically, in each of these months in which participants are scheduled for a contact, the CoC will randomly assign who should be contacted by phone and who should come into the clinic. This random assignment will protect against any selection bias that might arise and it would also help guarantee that the workload is evenly distributed across time.

Finally, it is noted that the ACCORDION in-clinic visits occur every 15 months on average. This is a compromise between having annual visits and having visits every 18 months. Annual visits, while usually the more desirable alternative, are too expensive for ACCORDION. Having less frequent visits would mean that ACCORDION resources could be better used on the remaining visits. Also, having the visits more frequently than every 18 months would potentially enhance retention and would permit a better and timelier collection of post-trial data, including event reports.

3.6 Recruitment of Former ACCORD Participants for ACCORDION

All ACCORD participants who were known to be alive at the end of the trial in 2009 will be invited to continue follow-up in the ACCORDION study. Because ACCORD follow-up ended in December 2010, new informed consents will be administered before data are collected. (See Protocol Chapter 10).

As described in Section 3.2 above, the clinical sites have maintained contact with over 8000 former ACCORD participants through December 2010. Although there has only been a minimum loss to follow-up between the end of the trial in spring 2009 and December 2010, re-enrollment for the ACCORDION will not be taken for granted. In addition to the 8000 participants with whom the clinical sites had contact through 2010, there were approximately 600 participants still known alive at the end of the trial who did not consent to be followed for the subsequent 1.5 years (Section 3.2). These participants may also be contacted for possible participation in ACCORDION.

3.7 Monitoring Participant Recruitment

As throughout ACCORD, real-time reports accessed via the internet will be provided by the Coordinating Center for ACCORDION reflecting data entry of the participants' enrollment and visits at the clinical sites. Examples of real-time reports on recruitment activities include number of clinics actively recruiting and percent at target (overall and to date). The 72 clinical sites and 7 Clinical Center Networks (CCNs) will have access to live data indicating exactly where their clinics stand in relation to their recruitment goals and the other clinical centers, as well as projections of activity needed to meet their goals. Regular communication between the CCNs and clinics ensure that the participants are enrolled as soon as possible and as delays are observed, prompt action to catch up is taken. This will also be a prime role of the Operations/Retention Subcommittee to monitor, discuss and recognize any problems that arise and act quickly to resolve. Committee members will have expanded access to information

across all clinical sites for the purpose of monitoring recruitment and retention performances for the study as a whole.

3.8 Phone and Clinic Visits

3.8.a Participant Orientation

At the end of ACCORD, several processes were put in place to ensure contact with ACCORD participants for ACCORDION. At the final ACCORD in-clinic visit, clinical site staff conveyed to each participant some basic information about the potential follow-on study and informed them that the clinical site staff will call them once the study is available. This procedure did not represent a consenting process to participate in the study, nor did it obligate them to participate. The staff also continued to mention ACCORDION and the anticipated start-up of May 2011 during the 18 month extension phone visit.

After local IRB approval, participants may be contacted and scheduled for their ACCORDION visits.

3.8.b Information Collected During Visits

Consented participants will be contacted every 6 months for 3.5 years, for a total of 7 contacts. Three of the contacts will be in-clinic visits, and 4 of the contacts will be by phone. (See Table 3.2, above.) At these contacts, sites will collect information regarding events, including the primary and secondary study outcomes, other hospitalizations, hypoglycemia, medication usage, and information regarding health habits. In-clinic visits will also include a physical examination, and at the first and last visits, include collection of urine and blood samples for analysis, a standardized ECG recording, and health-related quality of life data. Also, at the last visit a visual acuity examination will be conducted.

3.8.c Contact Information

At the first contact, and throughout the study as necessary, clinic personnel will update each participant's contact information, including at least one person who may know the participant's whereabouts in the event that the clinic is unable to reach the participant.

3.8.d Medical History and Events

Medical history will continue to be updated and collected at in clinic and phone contacts primarily for event ascertainment. Information will be collected on the occurrence of medical events, including myocardial infarctions, strokes revascularization procedures, hypoglycemia and other diabetes related events, dialysis, hospitalizations, and death. Concomitant medication therapy will be collected on all current therapies, with emphasis on antihypertensive, glycemetic and lipid-lowering therapies.

3.8.e Physical Examination Measures

The following procedures and measures will be performed at ACCORDION clinic visits. Full details and instructions will be included in the Manual of Procedures (MOP) and reviewed thoroughly during training for all study staff.

- Anthropometric Measures: Anthropometric measures to be collected will include participant weight, height, and waist circumference.
- Blood Pressure (BP) and Pulse: BP and pulse are measured three times at each clinic visit. The readings for ACCORDION are the averages of the first, second and third systolic and diastolic BP's and pulses.
- Neuropathy Examination (Foot Exam): This is a specialized foot examination, adopted from the Michigan Neuropathy Screening Instrument, and will be used to identify the presence and/or development of diabetic peripheral neuropathy.
- Laboratory Data: At the first and last of the three in-clinic visits, blood will be drawn and urine samples obtained, processed and shipped for the central measurement of A1C, total cholesterol, HDL-c, triglycerides, serum creatinine, ALT, urine creatinine, and urine microalbuminuria.
- Electrocardiography (ECG) Data: A standard 12-lead ECG will be obtained for ACCORDION participants at the first and last of the three in-clinic visits and the measurements sent electronically to the ECG Reading Center. Along with the information regarding Q-waves, ST depression, ST elevation, and T-waves, ascertainment of the occurrence of a silent (unrecognized) MI will be identified.
- Visual Acuity Measurement: A history of each participant's eye disease will be gathered at each in-clinic visit; visual acuity measurements will only be obtained at the last visit. If a participant complains of visual symptoms to clinic staff, he/she will be referred back to his/her ophthalmologist for evaluation and treatment if necessary.

Chapter 4

Study Outcomes

4.1 Outcomes

This chapter describes the components of the ACCORDION pre-specified primary and secondary clinical outcomes. The events used in primary analyses will be those reported by the participants and clinics, not events classified by the ACCORDION Morbidity and Mortality (M&M) Subcommittee. In contrast to ACCORD, for which 100% of the reported deaths, nonfatal myocardial infarctions, and nonfatal strokes were reviewed and classified by the Morbidity and Mortality (M&M) Subcommittee (and used in the papers describing the ACCORD main results [ACCORD 2008; ACCORD 2010a; ACCORD 2010b]), the ACCORDION M&M will only classify a 10% sample of the events for the purpose of quality control. The justification for this and a description of the data collection are given below in Sections 4.7 and 4.6.

4.2 Primary (Macrovascular) Outcome

The primary endpoint for ACCORDION is the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The definitions to be used by the clinics and the M&M subcommittee are presented below. Specifically, cardiovascular deaths are defined in Section 4.3.a, myocardial infarctions are defined in Section 4.3.b, and strokes are defined in Section 4.3.c. These definitions are exactly the same as those used in ACCORD.

4.3.a Cardiovascular Death

- 4.3.a.1 Unexpected death: Unexpected death presumed to be due to ischemic cardiovascular disease, occurring within 24 hours of the onset of symptoms without confirmation of cardiovascular disease, and without clinical or post mortem evidence of other etiology.
- 4.3.a.2 Fatal Myocardial infarction (MI): death within 7 days of the onset of documented MI (see 4.3.b).
- 4.3.a.3 Congestive heart failure (CHF): death due to clinical, radiological or postmortem evidence of CHF without clinical or postmortem evidence of an acute ischemic event (cardiogenic shock to be included).
- 4.3.a.4 Death after invasive cardiovascular interventions: death associated with the intervention, i.e., within 30 days of cardiovascular surgery, or within 7 days of

- cardiac catheterization, arrhythmia ablation, angioplasty, atherectomy, stent deployment, or other invasive coronary or peripheral vascular intervention.
- 4.3.a.5 Documented arrhythmia: death due to bradyarrhythmias or tachyarrhythmias not associated with an acute cardiac ischemic event.
 - 4.3.a.6 Death following non-cardiovascular surgery: death due to cardiovascular causes as defined in 4.3.a.1-4.3.a.5, 4.3.a.7-4.3.a.8 within 30 days of surgery.
 - 4.3.a.7 Stroke: death due to stroke occurring within 7 days of the signs and symptoms of a stroke (see 4.3.c).
 - 4.3.a.8 Other cardiovascular diseases: death due to other vascular diseases including pulmonary emboli and abdominal aortic aneurysm rupture.
 - 4.3.a.9 Presumed cardiovascular death: Suspicion of cardiovascular death with supporting clinical evidence that may not fulfill criteria otherwise stated. Example: Patient admitted with typical chest pain of 3 hours duration and treated as an MI, but without ECG and enzymatic documentation to meet usual criteria.

4.3.b Myocardial Infarction

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

- 4.3.b.1 Q-wave MI: Diagnosis based on the occurrence of a compatible clinical syndrome with prolonged ischemic symptoms, associated with the development of new significant Q waves (defined in the ECG Reading Center Manual of Procedures). Diagnostic elevation of cardiac enzymes will include: increase in CK-MB mass to a level > twice the upper limit of normal, and/or and increase in Troponin T or I to a level that indicates myonecrosis in the laboratory performing the study.
- 4.3.b.2 Non Q-wave MI: Diagnosis based on the occurrence of a compatible clinical syndrome with prolonged ischemic symptoms, associated with elevation of serum enzymes, as for Q-wave MI. Only in the case that both Troponin and CK-MB mass measurements are not available, would the elevation of total CK to \geq twice the upper limit of normal qualify for diagnosis.

- 4.3.b.3 Silent (unrecognized) MI: development of new significant Q waves without other evidence of myocardial infarction (the date of event will be assigned halfway between the date of discovery and last normal ECG).
- 4.3.b.4 Probable non Q-wave MI: Diagnosis based on the occurrence of a compatible clinical syndrome with prolonged ischemic symptoms, without documentation of cardiac enzyme elevation, but associated with the development of new and persistent significant ST-T changes (>24 hr in duration). (Changes are defined in the ECG Reading Center Manual of Procedures).
- 4.3.b.5 MI after cardiovascular invasive interventions Diagnosis based upon the occurrence of CK-MB (or Troponin) elevations to a level increased 3-5 times normal for the laboratory performing the studies, occurring within 7 days of cardiac catheterization, arrhythmia ablation, angioplasty, atherectomy, stent deployment or other invasive coronary, carotid or peripheral vascular intervention.
- 4.3.b.6 MI after coronary bypass graft surgery: Diagnosis based upon the occurrence of CK-MB (or Troponin) elevations to a level increased \geq 5-10 times normal for the laboratory performing the studies, occurring within 30 days of cardiac surgery.
- 4.3.b.7 MI after non-cardiovascular surgery: MI (as defined above, occurring within 30 days of non-cardiovascular surgery).

4.3.c Stroke

- 4.3.c.1 Definite ischemic stroke: CT or MRI scan within 14 days of onset of a focal neurological deficit lasting more than 24 hours with evidence of brain infarction (mottled cerebral pattern or decreased density in a compatible location), no intraparenchymal hemorrhage by CT/MRI, no significant blood in the subarachnoid space by CT/MRI or by lumbar puncture, or autopsy confirmation. A nonvascular etiology must be absent.
- 4.3.c.2 Definite primary intracerebral hemorrhage: Focal neurological deficit lasting more than 24 hours. Confirmation of intraparenchymal hemorrhage in a compatible location with CT/MRI scan within 14 days of the deficit onset, or at autopsy, or by lumbar puncture.
- 4.3.c.3 Subarachnoid hemorrhage: Sudden onset of a headache, neck stiffness, loss of consciousness. There may be a focal neurological deficit, but neck stiffness is more prominent. Blood in the subarachnoid space by CT/MRI or lumbar puncture or intraventricular by CT/MRI.

- 4.3.c.4 Stroke of unknown type etiology: Definite stroke of unknown etiology when CT, MRI, or autopsy are not done. Information is inadequate to diagnose ischemic (infarction), intracerebral hemorrhage, or subarachnoid hemorrhage.
- 4.3.c.5 Non-fatal stroke after cardiovascular invasive interventions: stroke (as defined in 5.1.c.1-5.1.c.4) associated to the intervention within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterization, arrhythmia ablation, angioplasty, atherectomy, stent deployment or other invasive coronary or peripheral vascular interventions.
- 4.3.c.6 Non-fatal stroke post non-cardiovascular surgery: stroke (as defined in 5.1.c.1-5.1.c.4) occurring within 30 days of non-cardiovascular surgery.

4.4 Pre-specified Secondary Outcomes

The secondary endpoints for ACCORDION are as follow.

- An expanded macrovascular outcome, specifically the combination of the primary endpoint plus any revascularization plus hospitalization for congestive heart failure
- Major coronary heart disease event, specifically fatal events (defined in Section 4.3.a.1 through 4.3.a.6 and 4.3.a.8 through 4.3.a.9), nonfatal myocardial infarction (defined in Section 4.3.b), and unstable angina (defined in Section 4.5).
- Nonfatal myocardial infarction (defined in Section 4.3.b)
- Total stroke, specifically fatal strokes (defined in Section 4.3.a.7) and nonfatal strokes (defined in Section 4.3.c).
- Nonfatal stroke (defined in Section 4.3.c)
- Total mortality
- Cardiovascular mortality
- Congestive heart failure death (defined in Section 5.1.a.3) or hospitalization for congestive heart failure (with documented clinical and radiological evidence)
- Cardiovascular disease free survival (defined as the primary composite outcome plus total mortality).

Embedded within ACCORDION are two substudies, the ACCORDION-MIND Follow-up Study and the ACCORDION Eye Follow-up Study. The substudy-specific outcomes for these are described in detail in Chapters 5 and 6, respectively.

4.5 Other ACCORD Outcomes

The combined ACCORD/ACCORDION database will be a rich source of data for many analyses examining long-term treatment effects, disease trends, epidemiologic associations, etc. For these analyses, other outcomes that will be collected in ACCORDION include changes in health and medication use, hypoglycemia, A1C levels, blood pressure levels, other chemistry values (including measures of safety, such as creatinine, ALT, micro- and macroalbuminuria), health-related quality of life measures, data related to health care costs, and the incidence/recurrence of cardiovascular revascularization procedures, unstable angina, cancer, nephropathy, neuropathy, and miscellaneous eye complications.

Unstable angina, which is part of the ACCORDION secondary outcome “Major Coronary Heart Disease Event” is defined as new onset exertional angina, accelerated or rest angina, or both, and at least 1 of the following (Downs 1998):

- at least 1-mm ST segment deviation and reversible defect on stress perfusion study, **or**
- angiographic findings of at least 90% epicardial coronary artery or at least 50% stenosis in the left main coronary artery, **or**
- at least 1-mm ST segment deviation with pain on ECG stress testing and/or rest ECG and evidence of at least 50% stenosis in a major epicardial coronary artery.

4.6 Identification, Documentation, and Reporting of Study Outcomes in ACCORDION

The ACCORDION event ascertainment procedures will be the same as in the original ACCORD trial, with the exception that participants would be queried regarding events less frequently in ACCORDION because the participants will be contacted less frequently. In ACCORD, event ascertainment was performed at 4 month visits common to all treatment groups and was based on participant self-report in response to a series of questions concerning hospitalization, emergency room visits and out of hospital procedures occurring since the last clinic visit. In ACCORDION, this same information will be collected in the same manner (whether by phone or in-clinic), but on a 6 month

contact cycle. Ascertainment for silent (unrecognized) MI will be based on 12-lead ECG readings obtained at the beginning of ACCORDION and at the end. For participants lost to follow-up or refusing further contact, ascertainment of vital status will be supplemented with a National Death Index (NDI) search of deaths, as was done in ACCORD.

The clinical sites and Clinical Center Networks (CCNs) will have the responsibility of assuring the accurate and prompt identification, reporting, and documentation of study outcomes. The clinical sites will query each participant at every in-clinic and phone contact for event ascertainment. Upon discovery of a reportable outcome, the sites will collect all relevant and requested data (e.g. hospital records, death certificates, etc.) necessary to adjudicate the event. The clinical site PI will be responsible for reviewing the collected information and records on the event to confirm it meets the study definitions for reporting. If so, the outcome information will be collated and submitted to the Coordinating Center.

The CCN personnel will add an additional layer of event verification by also reviewing a subset of the reported events during quality control site visits to confirm proper event identification and reporting and collection of the required supporting documentation for the event.

4.7 ACCORDION Adjudication Processes (in Sample of Events)

ACCORD utilized a centralized adjudication process for all deaths, and hospitalizations for myocardial infarction and strokes. However, using data analyzed for the ACCORD Glycemia, Blood Pressure and Lipid Trials (ACCORD 2010a; ACCORD 2010b; ACCORD 2011), a comparison of events as reported by the clinical sites with events generated by adjudication indicates that the ACCORD investigators would have come to the same conclusions regarding the effects of glycemia, blood pressure, and fenofibrate treatment on the primary outcome without adjudication. Although the number of events and the rates (events per year) are higher using the simple clinical reports, the hazard ratio (HR) estimates (and the 95% confidence intervals) and the p-value for the treatment effect on the primary outcome (first occurrence of a major cardiovascular event) are extremely close, as shown below in Table 4.1. This observation has been noted in other trials and with other outcomes (Einhorn 2007; Granger 2008; Pogue 2009).

Table 4.1: Treatment Group Differences in the ACCORD Primary Outcome (First Occurrence of a Major Cardiovascular Event). Comparison of the Event as Classified by the Morbidity and Mortality Subcommittee vs the Event as Reported by Clinic. Mean Follow-up of 4.7 Years (through the original planned end of treatment and follow-up for all three trials). Number of Events (Event Rate/Year).

A) For the Glycemia Trial				
Event Classified by:	Intensive Glycemia Group	Standard Glycemia Group	Hazard Ratio (95% CI)	P
M&M Subcommittee	503 (2.1)	543 (2.3)	0.91 (0.81-1.03)	0.12
Clinical Sites	552 (2.3)	588 (2.4)	0.92 (0.82-1.03)	0.15

B) For the Blood Pressure Trial				
Event Classified by:	Intensive Blood Pressure Group	Standard Blood Pressure Group	Hazard Ratio (95% CI)	P
M&M Subcommittee	208 (1.9)	237 (2.1)	0.88 (0.73-1.06)	0.20
Clinical Sites	225 (2.0)	254 (2.2)	0.90 (0.75-1.07)	0.23

C) For the Lipid Trial				
Event Classified by:	Fenofibrate Group	Placebo Group	HR (95% CI)	P
M&M Subcommittee	291 (2.2)	310 (2.4)	0.92 (0.79-1.08)	0.32
Clinical Sites	321 (2.5)	340 (2.6)	0.93 (0.80-1.08)	0.36

Because there is no obvious benefit with adjudicating 100% of the reported events, and because adjudication is a resource (time and funding) intensive activity, ACCORDION will at least initially adjudicate a 10% sample of events for quality assurance. If sensitivity analyses, to be conducted annually, suggest that information is lost in not adjudicating more events, this 10% sample will be increased, up to 100% again, if necessary.

Regardless of whether an event is adjudicated, the relevant information regarding each reported event will still be collected centrally, as done in ACCORD. Specifically, upon

identification of a potential outcome, clinical site staff will obtain all relevant medical records (if the outcome was a hospitalization) or details regarding the case (if the case was an out-of-hospital death). At the Coordinating Center, if the case is randomly selected for adjudication, it will be assigned by the Project Manager to two reviewers who will complete their adjudications independently. Two criteria will be followed when assigning a case to a reviewer. First, the reviewers must be in different Clinical Center Networks, and second, the reviewer cannot be affiliated with a clinical site within the Clinical Center Network of the clinical site submitting the case. Reviewers will consist of physicians (general internists, cardiologists, and endocrinologists) associated with the study and serving on the Morbidity and Mortality committee. Stroke cases will also be independently reviewed by an experienced stroke adjudicator in addition to the two primary reviewers. Cases in which the original reviewers agree on the primary outcome (myocardial infarction, stroke, or cause of death) will be considered closed. If there were disagreement between the two (or three in the case of stroke) primary reviewers, the case will be presented to the entire Morbidity and Mortality subcommittee and consensus obtained on the outcome.

Chapter 5

ACCORDION-MIND (Memory in Diabetes) Follow-up Substudy

5.1 Study Overview

The primary aim of this follow-up study is to further delineate how diabetes affects the brain. The aging of the cohort, longer follow-up and an additional measure of cognitive function and a third MRI will allow us to study the longitudinal effects of diabetes-related factors on the brain, and to investigate how these factors, in combination with older age, interact leading to worse outcomes. Due to the expected age-related increase in rates of nursing home placement and dementia, the major clinical endpoints that result from pathologic changes in brain structure and function will be able to be investigated. Also, how adverse brain changes affect the course of diabetes will be studied, as will factors that may propagate, or mitigate, the development of cerebral pathology. This follow-up study will be conducted in a sub-sample of 2800 people who participated in the National Heart Lung and Blood Institute (NHLBI) randomized factorial clinical trial Action to Control Cardiovascular Risk in Diabetes (ACCORD) follow-up study – ACCORDION.

5.2 Background

Type 2 diabetes and cognitive impairment are two of the most common chronic conditions found in persons 60 years and older. Approximately 18%-20% of older persons suffer from diabetes (Harris 1998). And, in the general population, the prevalence of cognitive impairment, measured with the simple Mini-Mental State Exam, increases steadily from 5% at 65 years to 15% percent at 80 years of age (Launer 1993). Many persons with cognitive impairment go on to develop dementia, which doubles in incidence and prevalence every additional five years of age (Lobo 2000). Studies suggest diabetes is one risk factor for cognitive impairment and dementia. For example, several clinical studies have shown impaired neuropsychologic functioning in patients with diabetes (Strachan 1997; Coker 2003). In epidemiologic samples, diabetes has been associated with a higher prevalence of global cognitive impairment (Kalmijn 1995) and a higher incidence of cognitive decline (Gregg 2000). In the Cardiovascular Health Study (CHS), diabetes and high levels of glucose were significantly associated with a seven-year decline in cognitive function (Haan 1999). Population-based studies have also shown that diabetes is a risk factor for Alzheimer's disease (AD) (Ott 1999; Leibson 1997) and vascular dementia (VaD) (Curb 1999), the two most common forms of dementia. Further, the brains of people with diabetes are at risk for adverse sequela following repeated hypoglycemic events (Langan 1991; Perros 1997).

5.3 History of the ACCORD-MIND Substudy

The Memory in Diabetes (MIND) substudy of ACCORD aimed to compare the effect of these interventions on cognitive function and structural brain changes in a subset of 2977 randomized people, 632 of whom underwent MRI. Briefly, the basic study design included measures of cognitive function with a short battery of tests, and acquisition of Magnetic Resonance Images to evaluate brain structure. The cognitive tests were administered at baseline, 20 and 40 months after randomization; MRI was acquired at baseline and 40 months. On February 6, 2008 the intensive glycemia intervention was stopped due to safety concerns (ACCORD 2008). Those still active in the intervention were transitioned into the standard intervention and the blood pressure and lipid trial continued as planned. The interventions and clinic visits were completed in June 2009.

Recruitment into MIND was excellent; the sub-sample of MIND cognitive and MRI participants are representative of all trial participants and one-third of the sample included Black non-Hispanic, Hispanic or other minorities. Therefore the results can be generalized to the whole trial cohort. The MIND substudy also had excellent retention, with 92% of persons participating in all three cognitive exams (baseline, 20 month and 40 month). At baseline, 632 MRIs (98% goal) were acquired, as were 525 repeat MRIs at 40 months (88%). Of those who did not receive a second MRI, many developed exclusions precluding their participation.

5.4 Rationale

Although the data suggest a vulnerability of the brain to diabetic changes, little is known about the trajectory of brain changes in older diabetics and, within a cohort of diabetics, what factors modulate the risk for brain changes. We have started to identify such factors. For instance, based on the MIND baseline measures, we found variation in cognitive function was significantly associated with baseline glycemic control and duration of diabetes. Specifically, we found, corrected for age, a 1% increase in A1C was associated with a 1.75 points lower Digit Symbol Substitution Test score ($p < 0.0001$) and -0.20 points lower score in the Memory test (Rey Auditory Verbal Learning Test; $p < 0.05$) (Cukierman-Yaffee 2009). In a preliminary analysis of 614 baseline MRIs, we find decreasing total brain volume is significantly associated with increasing duration of diabetes; this more strongly reflects a significant decrease in normal gray matter, but normal white matter decreases as well.

Obtaining an additional measure of brain function and structure will bring many benefits to aging and to diabetes related research – MIND has a unique and large, well

described sample of older diabetics, who are entering the age period of risk for conversion to dementia or for nursing home placement, outcomes that have major social and financial costs. It is the largest multi-racial cohort of persons with diabetes whose cognitive trajectories and brain changes have been prospectively well characterized.

5.4.a Study Hypothesis and Aims

As previously stated, the aim of the ACCORDION-MIND is to further delineate how diabetes affects the brain. The primary hypothesis for the cognitive outcomes is that, as a result of a “legacy effect” from intensive therapy, **the rate of decline in cognitive function (as measured by the Digit Symbol Substitution Test (DSST)) will be lower in the group randomized to intensive glycemic control compared to the group randomized to standard glycemic control.**

The primary hypothesis for the MRI outcomes is that **the rate of decline in total brain volume (TBV) will be lower in the group randomized to intensive glycemic control compared to the group randomized to standard glycemic control.**

For both the DSST and TBV, we will also address the sub-hypothesis that the rate of decline will be lower in the group randomized to intensive blood pressure control compared to the group randomized to standard blood pressure control. The possibility of an interaction between the blood pressure and glycemia interventions will also be investigated.

Additional secondary hypotheses that will be addressed include:

- Changes observed in the brain (total brain volume) between baseline and 40-months will be related to the post 40-month rate of decline in cognitive function, as measured by the DSST.
- The effect of intensive glycemia (or intensive blood pressure) therapy on cognitive function will differ by subgroups defined by the following baseline factors: prior cardiovascular disease, gender, duration of diabetes, age, DSST score and clinical center network.
- The occurrence of hypoglycemic episodes during the initial 40 months of follow-up in ACCORD-MIND will be related to a more rapid rate of cognitive decline between month 40 and the ACCORDION cognitive follow-up.

- Changes in Body Mass Index (BMI) between baseline and 40 months will be related to changes in cognitive function to 40 months and post 40 months, as measured by the DSST.
- The total quantity of insulin administered between baseline and 40 months will be related to the changes in cognitive function to 40 months and post 40 months, as measured by the DSST.
- The effect of the glycemia and blood pressure interventions on secondary outcomes including total gray/white matter and abnormal gray/white matter at the additional visit.
- The interaction between blood pressure and glycemia interventions on the secondary MRI outcomes at the additional visit.
- The overall trajectory of change in brain structure within/between glycemia/blood pressure groups.
- Risk factors (including fasting levels of glucose, A1C levels or prior hypoglycemia events) associated with temporal changes in brain structure.
- Changes in brain structure and the subsequent risk of other diabetes comorbidities (retinopathy, nephropathy and neuropathy), important aging-related outcomes such as institutionalization (nursing home or assisted living placement), or death.

In addition, we will compare the post 40-month trajectories in three groups: those on at least 40 months of standard glycemic therapy; those on at least 40 months of intensive glycemic therapy; and those who were randomized to the intensive group but were transitioned into the standard group prior to receiving a full 40-months of intensive therapy as a result of the decision to stop the intensive intervention.

5.4.b Study Design

ACCORDION-MIND adds one additional measure of cognitive function at approximately 80 months from baseline, and a third MRI on the ACCORD-MIND MRI sub-sample.

A. Study Population

Participants for the ACCORDION-MIND follow-up will be the same participants recruited as part of the preceding ACCORD-MIND. The mean age of the participants at baseline was 62 years. Given the anticipated start date of May 2011 for ACCORDION, the mean age will be 69 years, with 38% over age 70. Sample projections by age are shown in the

table below. We also estimated the number of participants per 5 year age groups, who are projected to have MMSE<24, an indicator of suspected dementia.

Table 5.1. Sample Projections by Age of ACCORDION-MIND Participants

Age Distribution					% MMSE<24	
Age (years)	Baseline		ACCORDION MIND		MIND Cog Fx FUP	
	N	%	N	%	N	%
< 60	1083	36.4	41	1.6	2	8.3
60 – 64	964	32.4	721	28.2	42	11.0
65 – 69	517	17.4	828	32.4	61	11.2
70 – 74	283	9.5	516	20.2	39	15.9
75 +	130	4.4	452	17.7	48	19.4

B. Enrollment of Participants

1. Cognitive Function Component

The same six networks that participated in the preceding ACCORD-MIND substudy will participate in the MIND Cognition Follow-up (Northeast Network – Columbia University; Southeast Network – Wake Forest University School of Medicine; Minnesota Network – University of Minnesota; Western Network – University of Washington; Canadian Network – McMaster Medical Centre; and the Ohio Network – Case Western Reserve University). Participants who previously participated in the ACCORD-MIND substudy will undergo another round of cognitive testing after being consented as part of ACCORDION.

2. MRI Component

Four of the ACCORD-MIND networks will participate in the ACCORD MIND MRI FUP Study (Northeast Network – Columbia University; Southeast Network – Wake Forest University School of Medicine; Minnesota Network – University of Minnesota; and the Ohio Network – Case Western Reserve University). Each network will have one MRI center. Participants who previously received a MRI in the ACCORD-MIND substudy will be asked to consent for the third, ACCORDION MRI. Participants who agree to the third MRI will be screened for new contraindications for MRI both in the clinic and just prior to MRI scanning using a standard MRI screening instrument.

5.5 Power Considerations

5.5.a Primary Cognitive Hypothesis

The test of the primary hypothesis on the DSST will be carried out using repeated measures, analysis of covariance. Based on DSST outcome data collected in ACCORD, we have estimated that the adjusted, standard deviation of the DSST outcome obtained during ACCORDION will be approximately 7.89. This estimate was obtained adjusting for factors used to stratify randomization (prior history of cardiovascular disease, clinical center network, allocation to blood pressure or lipid trial, randomization to the intensive BP group, randomization to the fibrate lipid group, baseline DSST measurement and elapsed time since randomization). Assuming a 2-sided 0.05 significance level and 1175 participants per glycemia intervention group, ACCORDION-MIND will have 90 (80)% power to detect a difference of 1.06 (0.91) in the mean DSST scores during ACCORDION-MIND.

5.5.b Primary MRI Hypothesis

At the month 40 MRI visit, we obtained 503 (230 intensive and 273 standard glycemia) usable MRIs out of 614 with readable baseline scans. The range of follow-up times for the additional MRI visit will be between 66 and 104 months, with a median length of post-randomization follow-up of approximately 83 months. If we project an additional 20% missing scans during this average additional 43 months of follow-up (similar to what was observed in the initial 40-months) we will have measurements on approximately 200 participants per glycemia group during ACCORDION-MIND (possibly slightly fewer in the intensive glycemia group). In Table 5.2 below, we detail the projected power for the test of equal average total brain volume between glycemia groups for this additional ACCORDION-MIND measurement.

This calculation assumes a 2-sided 0.05 significance level and an adjusted SD=15.0, as estimated from the 40-month ACCORD-MIND MRI data and adjusted for baseline total brain volume and skull size. Note that ACCORD-MIND observed a mean difference of 4.6 at 40 months between glycemia arms. Thus, ACCORDION-MIND will have greater than 79% power to detect around a 9% reduction in the 40 month difference between the glycemia follow-up means (mean difference = 4.2), even if up to 20% of those who had 40-month MRIs do not provide a measurement during ACCORDION-MIND (200 participant per group). If the 20% loss is specific to each group, resulting in approximately 186 intensive MRIs during ACCORDION, the power will be at least 80% to detect a difference of at least 4.4.

**Table 5.2: Power Based on Specified Sample Size
Per Glycemia Group**

Diff Between Means At Follow-Up	225	212	200	187	175
4.6	90	88	86	84	81
4.4	87	85	83	80	78
4.2	84	82	79	77	74
4	80	78	75	72	70
3.8	76	73	71	68	65

5.6 Training of Neuropsychologic (NP) Technicians & Quality Assurance of NP Data

After a central refresher training of the CCN coordinating leadership, a one-day training and certification session on the ACCORDION-MIND cognitive battery will be provided at each of the network sites by the Coordinating Center (CoC). The latter will be held in conjunction with each network's overall ACCORDION training. Training includes a presentation on each test in the cognitive battery, detailed instruction on the administration and scoring of each test, discussion of challenges to data fidelity, and practice test administrations with feedback. Depending on the level of technician experience, it may be possible to award certification at training if the observed administration is deemed acceptable. If additional practice is warranted, technicians will submit an audiotape of their best practice administration for review and certification at the Coordinating Center. Certification in this way assures that each NP technician demonstrates adequate skills to accurately and consistently administer the cognitive battery.

In addition to training and certification of NP technicians, quality assurance (QA) of the NP data will be monitored at the CC at Wake Forest by random review of 10% of the NP test administrations with feedback to the technician, the ACCORDION-MIND network coordinator, and the ACCORDION-MIND PI. Participants will be asked to provide consent for audio taping of NP test administrations to allow for ongoing review of the NP technician skills. QA will be conducted on administrations of the NP battery conducted in both English and Spanish.

During the course of the study if additional certification is needed for new staff members, trained and certified technicians will train the new technician. The new technicians will be certified by central review in the same manner described above. To prevent significant decay in testing skills, the ACCORDION MIND Coordinating Center will recertify all technicians annually.

5.7 Ascertainment of Response Variables

5.7.a Assessment of Cognitive Function

To address the study questions outlined above, we plan to administer the same in-person cognition assessment protocol implemented in the preceding ACCORD-MIND substudy (Williamson 2007) as well as several additional questionnaires. The cognitive tests noted below in Table 5.3 have been previously described (Williamson 2007) and include: the Digit Symbol Substitution Test of processing speed, the Rey Auditory Verbal Learning Test of memory, the Stroop test of executive function, the Mini-Mental State Exam (MMSE) of global cognitive function, and the Patient's Health Questionnaire measuring depression symptomology. If an in-person interview is not possible, we will administer the Telephone Interview for Cognitive Status (TICS), a telephone based test similar to the MMSE. If the participant can no longer participate in a telephone interview, the Functional Activities Questionnaire (FAQ) will be administered to a proxy. The FAQ is a 10-item informant-based measure of functional abilities (Pfeffer 1982). Informants (i.e. family members, caregivers) rate the participant's performance of 10 complex, higher order activities that typically decline with onset of dementia. Clinic personnel or the CCN coordinator will administer the questionnaire, via telephone, to a designated family member or caregiver. To identify those with *suspected* dementia, administration of the FAQ will be triggered if a participant has a drop in the DSST score (-2 standard deviations) from the last DSST score, or does poorly on the TICS

In addition to the battery noted in Table 5.3, three additional areas described below will be ascertained on all ACCORDION participants, even those not in the MIND substudy.

1. *Use of anti-dementia medications.* At each clinic visit, the use of FDA approved anti-dementia prescription drugs will be ascertained.
2. *Self management of diabetes management.* At each clinic visit, participants will be questioned regarding the level of assistance needed in order to manage their diabetes.
3. *Categorization of assistance in performing daily activities.* At each clinic visit and on the phone visits, changes in the living situations of participants will be monitored and the incidence of nursing home and assisted living admissions will be captured.

Table 5.3. The Battery and Administration

<u>Domain</u>	<u>Time (min)</u>	<u>English</u>	<u>Spanish</u>	<u>Outcome Score</u>
Global Mental Status	5	MMSE	MMSE (Spanish Version)	Total Score
Memory I	7	Rey Auditory Verbal Learning Test	Spanish-English Verbal Learning Test	Total Immediate Recall
Mental Speed	2	Digit Symbol Substitution Test (DSST)	Symbol-Digit	Number of correct entries
Executive Function	7	Stroop Test	Stroop Test (Spanish Version)	Interference Score
Depression	3	PHQ	PHQ	Total Score
Memory II	4	Rey Auditory Verbal Learning Test-Delayed Recall	Spanish-English Verbal Learning Test	Delayed Recall Score

5.7.b Measurement Changes in Brain Anatomy through MRI

The participant will be briefly screened at the clinic, and again at the MRI facility, for exclusions that make the participant ineligible for the MRI. The MRI scan protocol is described below in Table 4. It is anticipated that the participant will spend 20 minutes in the scanner, and an additional 20 minutes will be needed to explain the procedure to the participant, set the participant up in the scanner, and take the participant out upon completion. The technician has constant verbal contact with the participant so if a problem arises during the scan, the protocol can be stopped and the participant removed.

Table 5.4. MRI Scan Protocol and Length

Step #	Time Consuming Factors	Time (min)
1.	Participant preparation	9:00
2.	Participant setup and positioning	2:50
3.	Three plane localizer	0:14
4.	Sagittal T1-W mid slice image	1:03
5.	Axial FSE PD/T2 W (fast spin echo, proton density- and T2 weighted)	5:20
6.	Axial FLAIR T2 W (fluid attenuated inversion recovery)	6:24
7.	Axial 3D FSPGR (3-D fast spoiled gradient echo, T1 weighted)	10:16
8.	Remove participant from scanner	3:00
TOTAL		38:12

- **Axial, coronal and sagittal GRE (gradient echo) scout views:** acts as a localizer; important for longitudinal studies.
- **Sagittal T1-W mid slice image:** AC/PC location.
- **Axial 3D FSPGR T1W:** gives segmentation of gray and white matter, volume assessment of the brain and its components, and voxel based morphometry.
- **Axial FSE PD/T2 W:** used to detect pathology.
- **Axial FLAIR T2 W:** gives better visualization of white matter hyperintensities that border the CSF spaces.

5.8 Quality Control

5.8.a Cognitive Testing

The quality control plans for the cognitive portion of this substudy are described in Section 5.7 above.

5.8.b MRI

The central ACCORDION-MIND quality control MRI Reading Center will be located at the University of Pennsylvania School Of Medicine, Department of Radiology and will be under the direction of R. Nick Bryan, MD, PhD. All ACCORDION-MIND MRI Field Centers (FC) will be American College of Radiology (ACR) MR QC accredited sites. MRI QC will be based on the ACR MRI Quality Control Program that is fully detailed in the MR Quality Control Manual and can be reviewed at their website: <http://www.acr.org/dyna/?doc=frames/main-sitemap.html>. This program is based on weekly analysis of scans of the ACR/NEMA QC phantom that costs approximately \$750. Specific tests include: magnetic field homogeneity evaluation, slice position accuracy, slice thickness accuracy, radio-frequency coil checks, including signal-to-noise ratio and image intensity uniformity, interslice RF interference and MRI phase stability. Each MR FC will send monthly to the ACCORDION-MIND MRI QC Center digital images of their phantom QC data for in-house review. Each FC will be responsible for keeping their ACCORDION scanners within the ACR performance specifications. The ACCORDION-MRI QC Center will monitor FC compliance. It is anticipated that compliance with this phantom based QC program will result in MRI data quality adequate for subsequent quantitative analysis.

In addition to the phantom based QC, there is a contingency QC program for major equipment change. Machine and software changes in the interval between ACCORD-MIND and ACCORDION will be checked and the quality of the scans compared to the

last previously acquired MRI scans. Whenever a major equipment change (such as installation of a new scanner) is made at a FC scanner, not only will ACR QC phantom evaluation be made shortly before and after equipment modifications but, in addition, a test scan will be performed on one normal subject with the ACCORDION MRI protocol before and after modification. These additional QC studies must be performed and reviewed by the ACCORDION-MIND MRI QC Center before any further ACCORDION studies are performed. On the basis of the phantom and human studies, every effort will be made by the QC and FC to duplicate scanner performance before equipment modification. This data may also be used by any subsequent image analysis program to correct for equipment change affects.

5.9 Analysis Plans

Cognitive Function – The primary glycemia hypothesis in ACCORDION-MIND will be tested within the framework of repeated measures, analysis of covariance with a covariance structure that accounts for the differential length of follow-up between repeatedly measured outcomes (a mixed effects approach). Maximum likelihood (ML) will be used to obtain tests for fixed effects in the presence of a selected covariance structure, whereas restricted maximum likelihood (REML) will be used to evaluate covariance structure parameters for a selected group of fixed effects. Since estimation will be done using maximum likelihood techniques, the planned analyses will account for the possibility that missing outcomes are dependent upon either observed covariates or previously observed outcomes.

Our model addressing the primary hypothesis will be parameterized to allow us to focus on a set of parameters specific to the ACCORDION period of follow-up. We will include all outcome measurements in the analysis, since this approach helps to adjust for missing outcomes being dependent on previously observed outcomes (MAR). Our model will include the glycemia effect, the baseline DSST measurement, and factors used to stratify randomization (prior history of cardiovascular disease, clinical center network, allocation to blood pressure or lipid trial, randomization to the intensive BP group, and randomization to the fibrate lipid group). We will also include variables that represent a time factor (20-month, 40-month or ACCORDION visit) and the interaction between this factor and the glycemia effect. A contrast will be used to estimate (and test) the overall difference in cognitive function between groups during ACCORDION follow-up. Other secondary analyses will explore whether the glycemia effect during ACCORDION follow-up is dependent on both: (1) the length of time from randomization to when the intensive glycemia intervention was discontinued (February 5, 2008) and (2) the time from discontinuation to the ACCORDION visit.

The blood pressure effect will be tested using a similar model within that subgroup of participants. The possible interaction between the blood pressure and glycemia interventions will be tested by adding this term into the above model. Secondary analyses within the blood pressure trial will explore whether the blood pressure effect during ACCORDION follow-up is dependent on both: (1) the length of time from randomization to the exit visit when blood pressure treatment was turned over to community physicians, and 2) the time from the exit visit to the ACCORDION visit.

The association between changes observed in the brain (total brain volume) between baseline and 40-months and the post 40-month rate of decline in cognitive function, as measured by the DSST, will be investigated using regression techniques, adjusting for the length of post 40-month follow-up and intervention assignment. The effect of intensive glycemia (blood pressure) therapy on cognitive function within subgroups will be investigated by entering terms representing the subgroup and the interaction between the subgroup effect and the intervention effect into the models addressing the primary hypothesis. The effect of hypoglycemic episodes during the initial 40 months of follow-up in ACCORD-MIND on cognitive decline between month 40 and the ACCORDION cognitive follow-up will be investigated using regression techniques, adjusting for the length of post 40-month follow-up and intervention assignment. Similar techniques will be used to investigate the relationship between changes in body mass/total insulin exposure and the change in cognition to 40 months and post-40 months.

MRI Outcomes – Analyses addressing intervention comparisons of TBV will be carried out using the exact same mixed effects models as those described above for the DSST outcome. The main difference between analyses is that for TBV we will have measurements from the 40-month visit and the ACCORDION MRI follow-up, whereas for DSST a 20-month visit was also available.

The effect of the interventions on secondary outcomes will be investigated using similar statistical approaches. We will investigate the overall trajectory of change in brain structure within glycemia/blood pressure groups by using the baseline value of each primary/secondary outcome as an additional dependent variable, thus providing three repeated measurements to fit random effect slopes using mixed effects models. An investigation of risk factors associated with increased, as well as reduced risk for adverse changes in brain structure will be carried out by looking at the interactions between such risk factors and the overall slope relating the outcome to follow-up time.

The impact of changes in fasting glucose, A1C and hypoglycemia events can also be examined in these models by using time dependent covariates. Changes in brain structure and the subsequent risk of other diabetes comorbidities (retinopathy, nephropathy and neuropathy), important aging-related outcomes such as institutionalization (nursing home or assisted living placement), or death will be investigated using proportional hazards regression models permitting us to relate time-dependent covariates representing changes in brain structure to time until each event.

Chapter 6

ACCORDION Eye Substudy

6.1. Introduction and Background

6.1.a. Diabetic Retinopathy

Diabetic retinopathy (DR) is an important complication of type 2 diabetes mellitus, which contributes both to individual patient morbidity and to the health care burden on society. The burden is the result of both the cost of treatment of DR when it advances to threaten vision, as well as to the loss of productivity of individuals so affected. Clinically significant macular edema and proliferative retinopathy are major causes of vision loss, even to the point of legal blindness. DR resulting from type 2 diabetes is currently responsible for more than half of all photocoagulation procedures performed in patients with diabetes.

Many patients in the older type 2 diabetes population studied in ACCORD have both DR and cardiovascular disease (CVD) and DR has been suggested to be a risk factor for CVD. For these reasons it is important to better delineate the relationship between DR and CVD and the relationship between their responses to control of glycemia and other risk factors.

6.1.b. ACCORD and the ACCORD Eye Study

A subset of 2856 ACCORD participants was evaluated for the effects of the glycemia, blood pressure, and lipid interventions on the progression of diabetic retinopathy at 4 years. Among these participants, intensive glycemic therapy significantly reduced the risk of progression of diabetic retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) Severity Scale for Persons at four years (7.3% vs. 10.4% with standard therapy, $P=0.0025$). The ACCORD Eye study results also showed a beneficial effect of fenofibrate therapy on diabetic retinopathy progression at four years in participants with type 2 diabetes who were also receiving simvastatin (6.5% vs. 10.2% with placebo, $P=0.0056$). A statistically significant effect of intensive vs. standard blood pressure control on the progression of diabetic retinopathy was not demonstrated at 4 years (10.4% vs. 8.8%, $P=0.29$). The **primary microvascular** outcome measurement in the ACCORD Trial was diabetic retinopathy as measured by fundus photography performed in the ACCORD Eye Study. It is important to evaluate the primary outcome measure of the follow-up study of ACCORDION in a similar manner.

6.2. Aims of ACCORDION Eye Study

1. Evaluate the long term effects of intensive glycemic control, dyslipidemia management with fenofibrate and simvastatin, and intensive blood pressure control on diabetic retinopathy progression at 8 years. The original aims of ACCORD were:
 - a. Will lowering A1C to a goal < 6.0% reduce the development and progression of DR compared to maintaining A1C in the range of 7.0-7.9% with an expected median of approximately 7.5%?
 - b. In type 2 diabetic patients whose low density lipoprotein cholesterol levels have been reduced appropriately by statin therapy, will the addition of fibrate therapy, to reduce triglyceride levels and raise high density lipoprotein cholesterol levels, decrease the risk of DR?
 - c. Will targeting systolic blood pressure to 120 mm Hg or less reduce the development and progression of DR compared to maintaining systolic blood pressure at less than 140 mm Hg?
2. Is there a similar “memory imprint” seen in the diabetic retinopathy progression in the DCCT/EDIC trial of persons with type 1 diabetes also in this study of patients with type 2 diabetes? Following the cessation of the clinical trial of intensive glycemic control in DCCT/EDIC, the glycosylated hemoglobin A1C differences narrowed and were essentially eliminated but even 10 years later, the progression rates of diabetic retinopathy continued be reduced in those who had been randomized previously to intensive glycemic control for a median period of 6.5 years. Could this phenomenon also occur in type 2 diabetes?
3. Would the beneficial effects of fenofibrate continue with follow-up?
4. With longer follow-up, could the effects of intensive blood pressure control be reversed to show a beneficial effect? Or could the effects continue with no effect or perhaps towards a harmful effect?
5. With longer follow-up, the associations between cardiovascular disease and diabetic retinopathy can continue to be evaluated.
6. The correlation of diabetic retinopathy with changes in the MIND study will continue to be examined.
7. There are limited information regarding long term rates of diabetic retinopathy progression in this new era of tighter glycemic and blood pressure control. These rates would be invaluable for the design of future studies of diabetic retinopathy. This is quite apparent as the rates from the Wisconsin Epidemiologic Study of

Diabetic Retinopathy (WESDR) were used to calculate the sample size. These rates grossly over-estimated the current rates found in ACCORD.

8. The association of the presence or the progression of diabetic retinopathy with cardiovascular disease will also be examined. This will be conducted with the baseline and year 4 visits but the additional visit will increase the power of this analysis.

6.3. Eye Study Design

The ACCORD Eye Study consisted of 2 eye exams with fundus photography of 7 stereoscopic fields, at baseline and year 4 of follow-up. ACCORDION Eye adds one additional visit at 8 years post-randomization.

All ACCORD participants who had a baseline eye exam (with or without eye exam at year 4) will be invited to participate. It is anticipated that with the given death rates, etc. 2,700 ACCORD participants will be examined.

The clinical coordinator of each clinical site will obtain the informed consent for the eye exam and fundus photographs and schedule the patient with the ophthalmologist's office. The clinical coordinator will enter the appointment information on a web-based form residing at the coordinating center. The fundus photographs will be uploaded to the website for the central Fundus Reading Center at the University of Wisconsin. The Reading Center will automatically upload to the Coordinating Center a confirmation of receipt of photographs and eye exam information. The Coordinating Center will monitor for missed visits and will report these to the clinical coordinator who will contact those patients to facilitate the visit to the ophthalmologist. The Coordinating Center will provide lists to the CCNs of patients with completed examinations so that the CCNs can pay the ophthalmologists quarterly.

6.4. Analysis Plan

6.4.a. Primary Outcome

The primary outcome variable of the ACCORD Eye study was the combined outcome of progression of diabetic retinopathy of at least 3 stages on the ETDRS scale, photocoagulation, or vitrectomy. For ACCORDION Eye only the progression of diabetic retinopathy of at least three stages on the ETDRS scale will be used as the primary outcome. Analysis will be according to the intention-to-treat principle and only participants with data at both baseline and 8 years will be used in the primary analysis.

6.4.b. Analysis Exclusion

Participants who do not have the potential to reach the endpoint of 3 steps progression of the ETDRS retinopathy scale will be excluded from the analysis of retinopathy progression.

6.4.c. Secondary Outcomes

Secondary outcome variables include loss of visual acuity (moderate: more than three lines; legal blindness: 20/160 or worse; severe vision loss: 5/200), cataract extraction, and development or progression of macular edema.

6.4.d. Statistical Analysis for Primary Hypotheses

For the primary hypotheses listed in Section 6.2, separate models will be used to test the primary hypothesis associated with each intervention. The main comparisons of the original randomized intervention groups with respect to the incidence of DR progression will be based on logistic regression incorporating adjustment for important design factors specified below. This will be the primary analysis. The primary analysis will focus on the marginal effects in the factorial design of randomization to glycemia control, lipid use, and blood pressure control treatment groups. Estimates of DR incidence will be obtained for the intervention and control groups for each hypothesis and confidence intervals for these rates will be calculated. An unadjusted analysis will also be performed.

1. Glycemic Hypothesis: The glycemic hypothesis will be tested in all randomized participants who participate in the DR portion of the trial. The model to be fit will contain separate indicator variables that identify participants: (a) in the BP trial, (b) in the BP trial AND randomized to the BP(+) intervention, (c) in the lipid trial, (d) in the lipid trial AND randomized to fibrate(+), and (e) randomized to intense glycemic control. In addition to these variables, indicator variables will be included that identify: (f) secondary prevention participants, and (g) Clinical Center Networks. The reasoning for including term (f) is that secondary prevention participants should have higher event rates than primary prevention participants. Likewise, term (g) will be included because the clinical networks contain very different types of participants that may have different event rates. For example, the VA clinics will primarily consist of men. The main comparison in this model will be based on the chi-square statistic from a likelihood ratio test obtained from logistic regression models with/without term (e).

2. Lipid Hypothesis: The lipid hypothesis will be tested in all randomized DR participants who participate in the lipid arm of the trial. The model to be fit will contain terms (d), (e), (f) and (g). This hypothesis will be tested using a likelihood ratio test for models with/without term (d).

3. Blood Pressure Hypothesis: The blood pressure hypothesis will be tested in all randomized DR participants who participate in the blood pressure arm of the trial. The model to be fit will contain terms (b), (e), (f) and (g). This hypothesis will be tested using a likelihood ratio test for models with/without term (b).

6.4.e. Subgroup Hypotheses

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

6.4.f. Sensitivity Analyses

It is recognized that there will be participants who are examined at baseline will be lost to follow-up or will die before their follow-up exams are conducted. To examine the effect of this missing data in the analysis, the same multiple imputation approach used in the ACCORD Eye main results paper will be used in ACCORDION (Chew 2010).

6.5. Logistical Considerations

Consent procedures for the ACCORDION Eye Study are described in Chapter 10. At the time of consent, the participant should be scheduled for their eye exam and fundus photography visit. The eye exam should occur 8 years after randomization. There will be only one eye exam per participant.

Patients may also have cataracts but it is rare that the severity of the cataract would preclude fundus photography. A red reflex photograph will be taken prior to the fundus photography to document the state of the lens. In addition, the ophthalmologist will assess the status of the cataract in the data collected at the eye exam.

Each clinical center will identify a study ophthalmologist or group of ophthalmologists to conduct the study eye exams. Some clinics may need the help of the Reading Center to identify study ophthalmologist(s). The photographers will be certified by the Reading Center to ensure that the photographic protocol will be standardized.

As previously stated, the role of the clinical coordinator is to explain the eye exam to the patient, obtain informed consent, and schedule the ophthalmology visit. During the scheduling of the visit, the clinical coordinator will provide the participant's study ID number to the ophthalmologist's office and hand the participant an appointment card that will also contain the study id. The clinical coordinator will use the ACCORDION website to enter data about the scheduled appointment including the study ID and date of visit.

The Reading Center will use the participant list to prepare study packets which will be sent directly to the ophthalmologists. The completed forms and fundus photographs will be uploaded by the ophthalmologist's office to the Reading Center. Upon receipt of data the Reading Center, an automated procedure will download the data to the Coordinating Center. The data include the study ID, date of visit, and the information required to pay the ophthalmologist (address to whom the check should be sent). The Reading Center will enter the photograph grading in a data base that resides at their institution. These data will be transmitted regularly to the Coordinating Center.

The Coordinating Center will also generate reports to notify the Reading Center and clinical centers of missing visits and to notify the Clinical Center Networks (CCNs) of the number of patients examined and the participating ophthalmologists' names and addresses. Based on these data, the CCNs will pay the ophthalmologists quarterly.

When the eye exam reveals abnormalities that may require more vigilant monitoring or treatment, the study ophthalmologist should inform the patient. Treatment may be offered and communication with the patient's ophthalmologist is encouraged. Care will not be provided by the study.

6.6. Eye Examination Procedures

6.6.a. Introduction

The procedures for carrying out the eye examinations required in the substudy are described in this section. Required ocular examinations include visual acuity measurement, intraocular pressure measurement, and ophthalmoscopic examination. The procedures to be used in the clinical centers for taking fundus photographs and transmitting them to the reading center will be described in the Manual of Procedures.

6.6.b. Visual Acuity Measurement

A staff member in the examining ophthalmologist's office should conduct the visual acuity measurement with the method customarily used in that office using the patient's glasses, if available.

6.6.c. Pupil Dilation and Fundus Photography

Photographs should be taken through a maximally dilated pupil. It is recommended that 2 sets each of 2.5% Neo-syneprine and 1% Mydracyl be instilled 2-5 minutes apart. Photographs should be taken prior to any planned contact lens examination, which may distort the tear film and impair the quality of photographs.

6.6.d. Ophthalmoscopic Examination

The ophthalmologist may use his or her usual examining technique, which should include direct ophthalmoscopy or slit-lamp biomicroscopy with precorneal or contact lens in order to provide adequate magnification for detection of microaneurysms.

The following items should be recorded:

- Lens assessment
- Retinopathy severity level;
- Presence or absence of scars of panretinal photocoagulation (or local photocoagulation, presumably for new vessels);
- Presence or absence of scars of focal or grid photocoagulation for macular edema;
- Presence or absence of macular edema (retinal thickening, with or without lipid deposits, within one disc diameter of the center of the macula), and, if present, whether or not the center of the macula is involved;
- If visual acuity is worse than 20/40 (with pinhole, if used), primary and contributing causes of the decreased acuity.

6.6.e. Risks and Hazards associated with Eye Study Examination

The procedures used in this study are standard examination techniques that are used in a comprehensive eye exam. The risks include rare corneal abrasions resulting from tonometry, a method of measuring intraocular pressure and rare angle closure

glaucoma secondary to dilation. These adverse effects are treated readily in the ophthalmologist's office. The light from the fundus photography may cause temporary discomfort for the patient.

6.6.f. Benefits to the Patients

An eye exam for patients with diabetes should be considered an essential part of medical care. Diabetic retinopathy requiring treatment, such as laser photocoagulation for diabetic macular edema or proliferative diabetic retinopathy may be identified on such study visits. The ophthalmologist participating in the study will make recommendations to the patients. For those patients who have had laser photocoagulation prior to their second eye exam, they will still be asked to participate in the second eye exam.

Chapter 7

Participant Retention and Adherence Efforts

7.1. Background and Rationale

Beyond the initial goal of successfully re-recruiting former ACCORD participants for ACCORDION, obvious subsequent goals for ACCORDION are to retain the participants during the course of the study and have them maintain good adherence to the protocol. Whereas this is not a clinical trial, the retention and adherence issues in this observational study will be similar to those addressed during ACCORD.

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

As part of the training for ACCORDION, investigators and clinic site coordinators will receive refresher instructions on retention and adherence issues.

7.2 Determining Adherence Potential

Having the knowledge, understanding, and previous experience with the ACCORD participants for many years both in the trial and during the post-trial extension period with the same clinic staff will be advantageous and should result in a similarly high level of adherence as seen in ACCORD. Participants know and trust the staff to continue to be forthright in providing printed and updated information, treating them with respect, and true partners in the study. The adherence of the research participants to the highly complex protocol of ACCORD was extraordinary over the 5 years of the study with less than 4% loss to follow-up. A lesson learned again in ACCORD was that success can be achieved in multiple ways including empowering the participant as well as giving them a role in their own protocol adherence. Since ACCORDION is an observational study, the prime focus will be on visit retention to acquire the most data possible from these participants. Important considerations with the ACCORDION population will be the aging of the population, difficulty in transportation, and/or moving in with relatives or into assisted living facilities as changes occur in their lives. Careful planning and

individualized flexibility in scheduling in-clinic visits will be important in each clinic to encourage continued participation.

7.3 Monitoring Retention and Adherence

The excellent retention and adherence experience in ACCORD was due in part to the development and use of dynamic retention and adherence web reports. ACCORDION will follow the same approach, using the earlier ACCORD reports as models. These reports enable a user to click on a static link that starts a real-time report processed by SAS and returned as output in the user's web browser. These reports access live data and run within seconds. Examples of real-time reports used during ACCORD on recruitment activities include number of clinics actively recruiting, percent at target (overall, to date, and by demographic subgroups such as women and race/ethnic group). Real time ACCORDION reports for retention and adherence will include number of participants consented and completing the various follow-up visits for each site, both CCN, and study- wide. CCN staff and clinical sites will have access to live data showing exactly where their clinic stands in relation to their re-recruitment or adherence goals and the other clinical centers, as well as projections of activity needed to meet their goals. The prime role of the Operations/Retention Subcommittee (described in Protocol Section 14.3) will be to monitor, discuss and recognize any problems that arise and act quickly to resolve them.

The consistent relationship of the CCN staff with the clinical staffs developed throughout ACCORD will continue in ACCORDION so that the regular communication and problem-solving will carry on. The group of very experienced CCN coordinators who have remained nearly intact from the beginning of ACCORD is well positioned to assist clinic personnel in carrying out the tasks of ACCORDION. Of particular utility is the procedure for insuring complete follow-up. During ACCORD, all participants who wanted to dropout or withdraw at an individual clinic center had to have the case reviewed after presentation by the local clinic coordinator to the respective CCN coordinator. The procedure required involvement of the clinical center PI and specific designation of either partial or complete withdrawal. Those who were designated as only partial withdrawals were contacted at the end of the trial for mortality and primary endpoint confirmation. The CCN coordinators had a large impact on this very high follow-up percentage and will continue to work with the clinics in ACCORDION.

Throughout ACCORDION, the Coordinating Center will provide the Steering Committee, its subcommittees, and the Program Office with timely reports on re-recruitment, retention, adherence and quality control. During the planning phase of the study, an

initial roster and timeline for monitoring reports will be developed. As the goals of each type of report are identified, the analysis issues related to the relevant data will be identified and alternatives will be considered. Once these reports are identified, the programming behind the report generation will begin. Draft reports will be circulated to committee members for input and approval prior to final programming.

7.4 Procedures for Maintaining/Improving Retention and Adherence

The details for an overall retention and adherence program will be provided in the Manual of Procedures. The ACCORD overall adherence program was implemented at the time that recruitment was started. At the beginning of ACCORDION, a refresher course with renewed focus on ACCORDION issues will be included in training meetings for the Clinical Center Network (CCN) and Clinical Site staffs, with periodic updates throughout the study.

The Operations/Retention Subcommittee will meet by conference call on a quarterly basis during ACCORDION for the purpose of monitoring retention and adherence performance. The Subcommittee will review data provided by the Coordinating Center that will be directed at assessing adherence at the site, CCN, or overall study level. Adherence at the individual Clinical Site level will be reviewed by the respective CCNs. Guidance to the individual CCNs will be provided as needed.

7.5 Components of an Overall Retention and Adherence Program

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

- *Pay attention to signs and symptoms of potential poor adherence.* Codifications of red flags for potential poor adherence have been used previously in observational studies and clinical trials. These may help Clinical Site staff identify potential non-adherers at any time during study conduct.
- *Use an adherence team approach, if possible.* More than one individual sees participants in a clinic. All interactive information can be useful in the maintenance of good adherence. This may not always be possible in ACCORDION due to less clinic staff.
- *Use a constant caretaker model, if possible.* Participant interaction with the same staff person consistently is thought to be useful. Use when possible. Transitions to other staff may be necessary. Make the transitions as smooth as possible.
- *Use established retention and adherence techniques.* There are a host of techniques that have been used previously in observational studies and trial, such as the use of occasion

cards, appointment reminders, intervening phone calls, etc. These will be systematically reviewed for staff use.

- *Use the behavioral counseling approach.* Interviewing and counseling techniques have been shown to aid staff in sustaining long term adherence performance. These include identification of barriers to adherence and individualized problem solving.
- *Have an intervention program for poor adherer to study visits/procedures.* Poor adherers and drop-outs are recoverable to productive study participation, as shown in other studies. Instruction to staff will be provided for the approach to these challenging participants.
- *Have a maintenance plan for all participants.* Sustaining long-term adherence in studies such as ACCORDION is a challenging task to begin with, and will be a key issue in this study as well.

Chapter 8

Data Management and Training

8.1 Overview

Data will be entered by approved/certified ACCORDION personnel onto a secure ACCORDION website using any available PC or laptop connected to the internet. All Clinical Center Networks and Clinical Sites will have a password protected area on the ACCORDION Home page through which data can be entered. Web reports that summarize the frequency of recruitment, withdrawals, loss to follow-up, inactivity, and missed visits can also be accessed via the password protected area. Access will be restricted based on membership in specific networks, clinical sites or study committees.

8.2 Allocation to Follow-up Schedule

Per the ACCORDION timeline (presented in Protocol Section 3.5), consented participants will be contacted every 6 months for 3.5 years, for a total of 7 contacts. In each of the months in which participants are scheduled for a contact, the Coordinating Center will randomly select which participants will be contacted by phone and which will come into the clinic. This random process for visit type (phone or in-clinic) will protect against selection bias that might arise and will also guarantee that the workload is evenly distributed within clinics across time.

8.3 Participant Monitoring

The Coordinating Center will generate reports to summarize the frequency of recruitment, withdrawals, loss to follow-up, participant inactivity, and missed visits. In addition to the routine monitoring reports sent to the Steering Committee, results can be reviewed by clinic and CCN staff in real time via the ACCORDION website, as soon as data entry is complete. The Coordinating Center will also provide automated emails informing Clinical Sites and Network PIs and Coordinators whenever specific events requiring action have occurred. This process will also be adapted for any notification that is necessary.

8.4 Web-based Data Entry

Data Entry screens are developed in HTML, with a Cold Fusion to SQL (Structured Query Language, a relational database management system) backend. The design of

the web-based data entry screens mirror the paper forms and thereby enhance ease and accuracy of data entry and minimize data entry errors.

As participant visits are completed, paper forms are filled out and checked for accuracy. Data are entered by approved/certified ACCORDION clinical staff into any available computer via the web-based browser application. During data entry, key variables are checked for accuracy with the assignment of ranges. Where data are entered outside of preset ranges, entry is denied pending the review for accuracy. Override capabilities exist; however, these responses are flagged for review upon receipt by the Coordinating Center. The Project Manager will reconcile any data entry responses that continue to be questionable.

8.5 Data Editing

The ACCORDION Coordinating Center will be responsible for data editing, which will include checks for missing data and crosschecks for inconsistencies. The Coordinating Center will produce data query requests that will be distributed directly to the appropriate Clinical Site. Clinical Site staff will be responsible for responding to the data queries in a timely manner.

A routine system of data edit reports will be generated to help ensure that all data are entered in a prompt and complete manner. These reports will include both the assessment for each Clinical Site of the time between data collection and entry, including the number of queries unresolved for more than 30 days, and the generation of reports by the Coordinating Center of missing items. All of the reports will be provided to the appropriate Clinical Center Network and their respective Clinical Sites.

8.6 Central Training

Central training will consist of a “train the trainer” model. CCN representatives will be trained in-person by the Coordinating Center and the CCN Representatives will subsequently be responsible for meeting with their sites later in the month to review the ACCORDION protocol and train on implementation of the study. This would include enrollment of the ACCORD participants, data collection procedures such as ECG, lab, BP measurements as well as review of case report forms, data entry, web reports, and stressing the importance of event collection, quality of data, retention of participants, and adherence to all protocol instructions. The content used to train the clinical staff will be the same for all networks. The methods and location of the training will be influenced by such factors as the training needs and geographic distribution of the clinics and

available financial and operational (e.g. web-based and/or off-site training venues, etc.) resources necessary to provide effective training. Following the initial training, the CCN and Coordinating Center personnel will continue as resources for the clinical staff to meet their on-going learning and training needs.

As part of their commitment to the ACCORDION Study, all key personnel at each ACCORDION Site and the ACCORDION Coordinating Center underwent education in the protection of human research participants. ACCORDION Clinical Sites with new staff need to send proof of such education to the Coordinating Center at the beginning of the study and at any time a new staff member begins working on ACCORDION. (This activity will be monitored by the Coordinating Center. Additionally, other non-key personnel may be trained to fulfill local site requirements.

Chapter 9

Statistical Considerations

9.1 Overview

As detailed in Chapter 1, the primary objective of ACCORDION is to examine the effect of the three ACCORD interventions on major cardiovascular events over 10 years of follow-up. Secondary objectives include examination of intervention effects on several pre-specified secondary outcomes, and also the comparison of treatment effects between periods of active intervention and post-trial follow-up. Many other outcomes and measurements, such as HbA1c, lipid profiles, blood pressure, health related quality of life, and results of assays performed on blood and urine specimens will also be analyzed.

The analysis plans for these primary and secondary ACCORDION objectives are described below. Definitions for the primary and secondary outcomes are presented in detail in Chapter 4, and statistical considerations specific to the objectives of the ACCORD-MIND and ACCORD EYE Substudies are described in Chapters 5 and 6, respectively.

9.2 Analysis Plans for Primary Outcome

Primary comparisons of intervention groups will be performed according to the intention-to-treat principle. All randomized participants in these analyses will be grouped according to their intervention assignment at randomization, regardless of adherence. The primary analysis will apply Cox proportional hazards regression (Kaplan 1958; Peto 1977; Cox 1972; Cox 1984; Lachin 2000) to randomized participants to compare the time from randomization to the first occurrence of the primary CVD composite endpoint between the randomized groups for the three interventions. Follow-up time will be censored at the last date of event ascertainment. The p-value from the primary analysis will be based on the chi-square statistic from a likelihood ratio test obtained from proportional hazards models with and without the term for intervention arm. This likelihood ratio test will constitute the primary test of statistical significance for the primary analysis. Kaplan-Meier plots will be used to graphically describe the distribution of the time until the initial primary outcome by intervention group. These analyses will be performed at three distinct time points during ACCORDION, after the completion of the first, second and third clinic examination cycles.

Primary Hypotheses -- The three primary study hypotheses of ACCORDION each will be tested based on a two-tailed significance level of 0.05. As was done for the ACCORD analyses, the Cox model used to test the glycemia effect on the primary outcome will contain a term representing glycemia group allocation plus terms accounting for factors used to stratify randomization: a) additional assignment to the blood pressure or lipid trial; b) randomization to the intensive BP intervention within the blood pressure trial; c) randomization to fibrate within the lipid trial; d) the 7 clinical center networks; and e) participants with prior evidence of CVD versus those with no prior CVD. The proportional hazards assumption will be examined through inspection of log-log plots and martingale residuals. During ACCORD follow-up, there was no evidence for a violation of the proportional hazards assumption within this model. As was done for ACCORD analyses, separate proportional hazards regression analyses will be used to test the main effects of the blood pressure and lipid interventions within these subgroups of participants. These models will contain a factor representing the glycemia group, factors (d) and (e) and either (b) or (c), depending on whether the blood pressure or lipid trial is being analyzed.

Secondary Hypotheses -- As a secondary analysis, a test of whether the hazard ratios are the same during post-randomization periods is of interest. For example, for the glycemia trial, there are three distinct periods of interest: 1) during the initial 3.7 years of active intensive therapy treatment, 2) during the subsequent 1.3 years when all participants were treated with standard therapy, and 3) during the ACCORDION follow-up period where participants were treated by community physicians. For the blood pressure and lipid studies, there are two primary periods of interest: 1) during the initial periods of active treatment prior to close-out in the spring of 2009, and 2) during the ACCORDION passive follow-up. Analyses investigating whether the hazard ratios are similar during these follow-up periods will be performed using Cox models with time-dependent covariates representing the phase of follow-up. These models allow a direct test of whether the hazard ratios comparing treatment groups are the same in the early periods of follow-up versus the later periods. Interactions between treatment groups will also be explored in additional secondary analyses, both across all periods of follow-up and within specific periods as defined above.

Subgroup Analyses -- The consistency of intervention effects will also be examined across several subgroup variables pre-specified in the ACCORD protocol and primary results papers (ACCORD 2008; ACCORD 2010a; ACCORD 2010b). For all three interventions, these subgroup variables include age (<65 vs. \geq 65), gender (male vs. female), race/ethnicity (white vs. non-white), CVD history (positive vs. negative) and baseline HbA1c level (\leq 8% vs. >8%). Additional subgroup variables considered for the blood pressure intervention include glycemia group (intensive vs. standard), baseline

SBP (tertiles), baseline DBP (tertiles) and anti-hypertensive medication use at screening (0 or 1 medication vs. 2 or 3 medications). Additional subgroup variables considered for the lipid intervention include glycemia group (intensive vs. standard), baseline LDL cholesterol level (tertiles), baseline HDL cholesterol level (tertiles), baseline triglyceride level (tertiles) and a combined dyslipidemia variable representing the participants in the lowest tertile of HDL and the highest tertile of triglycerides. For each subgroup variable, an indicator variable representing the subgroup will be added to the proportional hazards models described above along with a term representing the subgroup by treatment interaction. Results will also be described using forest plots.

9.3 Analysis Plans for Pre-specified Secondary Outcomes

The primary and secondary hypotheses described above for the primary outcome are also of interest for each of the pre-specified secondary outcomes, but especially for the total mortality and cardiovascular mortality outcomes where intensive glycemia therapy was associated with harm during the main trial. The intent is to explore these hypotheses for each of the pre-specified secondary outcomes, although the results may be reported in detail only for the primary outcome and for total and cardiovascular mortality.

Each pre-specified secondary outcome will be analyzed using a proportional hazards model as described above for the primary analysis. These will be reported with 95% confidence intervals and nominal p-values without an adjustment for multiple comparisons, since the intent is to articulate a pattern of effects closely related to the primary outcome, rather than to provide additional tests of efficacy.

9.4 Analysis Plans for Other Outcomes

ACCORDION will produce a rich, evolving database of about 8000 people with diabetes and at high risk of cardiovascular events, suitable for addressing a variety of epidemiologic questions concerning the etiology, progression, treatment and control of diseases including, but not limited to, diabetes, hypertension, dyslipidemia and CVD. Although the variety of potential topics and outcomes precludes description of specific analyses plans general considerations for discrete and continuous secondary outcomes are provided below.

During data collection, ACCORDION data will undergo extensive data checks and cleaning within the framework of the web-based data entry system. Analysts will also examine the distributions of individual variables and evaluate the need for transformations to approximate normality. Summary statistics will be calculated,

including means, standard deviations, quartiles, and ranges for continuous variables, and counts and percentage for categorical variables. Outliers and influential points will be identified and addressed by using transformations, alternative analytic methods, or exclusion.

Repeatedly Measured Continuous Outcomes -- Initially, the longitudinal data for continuous outcomes (e.g., HbA1c, SBP, LDL-C, weight, etc.) will be displayed graphically with individual trajectories. The graphical displays will help to highlight aggregate patterns of potential scientific interest and identify unusual values. The inter-relationships among these repeated measures will also be explored by characterizing their correlation structure. Intervention effects on repeated, follow-up outcomes (including assessments from both ACCORD and ACCORDION) will be estimated using mixed effects analysis of covariance models. An estimate of the effect size at follow-up visits will be obtained by using a contrast to estimate the difference between mean levels of the outcome for intervention groups at each time point. The analyses will contain factors used to stratify randomization, the baseline measure of the outcome, and the intervention group assignment. Because measurements are being obtained at unequally spaced intervals in ACCORDION, it may be necessary to represent follow-up “visit” with a continuous time-since-randomization variable. Further analyses will explore for linearity in the trends of response over time

Mixed-effects models allow for both time-varying changes in covariates and departures from linearity in the relationship between the outcome and time. Mixed effects models are flexible enough to permit random rates of progression, consistent with a perspective that different participants progress through time at different rates. Use of random intercepts and/or slopes provides a source of autocorrelation between repeated measures. The choice of methods for accounting for serial correlation will depend on the plausibility of the model and the number of outcomes relative to the number of subjects. For example, with many subjects and few repeated measurements, an unstructured covariance matrix can often provide for the most efficient estimation of model parameters. Maximum likelihood (ML) will be used to obtain tests for fixed effects in the presence of a selected covariance structure, whereas restricted maximum likelihood (REML) will be used to evaluate covariance structure parameters for a selected group of fixed effects.

To identify factors that provide information as to the probability of missing responses, the first step will be to compare the baseline characteristics of people who do and do not have follow-up measures. Since estimation will be done using maximum likelihood techniques, the planned analyses will account for the possibility that missing outcomes are dependent upon either observed covariates or previously observed outcomes

(Espeland 1999). Sensitivity of results to missing outcomes that may be dependent on unobserved outcomes will be investigated through the use of either pattern-mixture models (Miller 2001; Little 1996), or multiple imputation techniques (Rubin 1987).

Repeatedly Measured Discrete Outcomes – Some repeated outcomes obtained during ACCORDION will be discrete in nature (e.g. left ventricular hypertrophy, peripheral neuropathy, retinopathy, etc.) the associations among all pairs of a discrete outcome will be calculated at different visits using odds ratios. This can help us to understand the correlation structure for the discrete outcome, and patterns in prevalence over time. To assess the long-term effects of the interventions on discrete outcomes, marginal models for repeatedly measured discrete outcomes will be used. These types of models will be fit using generalized estimating equations (GEE) that account for the dependency between repeated measures. GEE techniques provide a mechanism for estimating model parameters and their standard errors from longitudinal data having continuous and discrete responses and potentially missing observations. An advantage of this technique is that the assumptions required are weaker than those of maximum likelihood techniques; one need not specify the distribution of the dependent variable, just the relationships between the marginal mean and variance, and between the marginal mean and covariates. Odds ratios for the association between discrete outcomes and intervention will be estimated. The analyses will adjust for factors used to stratify randomization, the baseline measure of the outcome, and the intervention group assignment. SAS GENMOD procedure (SAS Institute, Cary, NC) will be used for analysis. For participants lost to follow-up, it is planned to use all available information until the time of death or loss to follow-up. If loss to follow-up is related to either observed covariates or observed outcome measures, then the results will be somewhat biased. This bias can be reduced by including in the model those factors that predict the probability of loss to follow-up. Logistic regression will be used to identify such factors and weighted transitional GEE models will be used to explore the sensitivity of estimates to missing observations.

9.5 Sample Size and Power

In Table 9.1 below are presented the number of ACCORD events and annualized event rates for the primary outcome (based on clinical reports) and for total mortality for each of the three interventions. Also presented are the projected number of ACCORDION participants and the projected number of ACCORDION events assuming the ACCORD event rates continue to hold over the post-trial follow-up period.

Note that for total mortality the projections include all ACCORDION participants, while for the primary outcome only that subset without a prior ACCORD event is included.

The sum of ACCORD events and projected ACCORDION events determines the expected number of events available for assessing treatment differences over the full 10 year follow-up period, and is approximately 88% (primary outcome) to 90% (total mortality) larger than the number of events available from ACCORD. The final two columns of the table show the minimum reduction in event rates detectable with 80% and 90% power assuming a two sided significance level of 5% (Schoenfeld 1983). For example, ACCORDION is expected to have 80% power to detect a reduction in the primary outcome event rate for participants randomized to the intensive glycemia treatment group relative to participants randomized to the standard glycemia group that is as large or larger than 11.4% over the full 10 year follow-up period, and to have 90% power to detect reductions in primary outcome event rates as large or larger than 13.1%. These power estimates may be considered to be conservative, since there are a number of reasons to believe that event rates will increase during the post-trial follow-up period (e.g., increased age of the cohort, reduced adherence without access to study medications, decreased frequency of clinic visits, etc.).

Table 9.1 Projected Number of Events and Power

Outcome / Original Intervention Trial	ACCORD (clinical reports)			ACCORDION (projected)		Detectable Reduction In Event Rates (%)	
	Participants (N)	Events (N)	Rate (%/yr)	Participants (N)	Events (N)	80% Power	90% Power
Primary Outcome							
Glycemia	10251	1140	2.36	7500	1001	11.4	13.1
Blood Pressure	4773	479	2.16	3460	425	17.0	19.4
Lipids	5478	661	2.53	4040	576	14.8	16.8
Total Mortality							
Glycemia	10251	718	1.40	7998	649	14.0	16.1
Blood Pressure	4773	294	1.24	3687	266	21.1	24.0
Lipids	5478	424	1.54	4311	383	17.9	20.4

Chapter 10

Human Subjects Protection and Confidentiality

Participant rights and the confidentiality of participant data are essential components of ACCORDION. Each participating investigator has primary responsibility for the rights and welfare of the individual participants under his/her care. Clinical sites must have approval from their local IRB before any study procedures, including any participant contact for research purposes, can begin.

10.1 Informed Consent

The ACCORDION Steering Committee has developed model informed consent documents for use at all local sites. Sites will be able to make minor modifications to the documents as required for local IRB approval. Once IRB approval is obtained locally, participants will be contacted by their former ACCORD clinical sites to discuss potential participation in ACCORDION. Before making the decision to participate, each potential participant will be given an IRB-approved informed consent document to review. Consent will be obtained by the PI or his/her designee at each site. Before signing the consent, all participants will be given the opportunity to read the entire document and have their questions answered. Written informed consent must be obtained before any study procedures may be performed.

The model consent documents will include a main document for the overarching ACCORDION observational study (Appendix B) and three addenda, two for MIND and one for the Eye Substudy (attached as Appendices C, D and E). Local IRBs have the authority to change these formats, if required. The formats in the models were adopted to minimize the burden to participants and to allow for flexibility among sites. For example, not all sites are participating in all substudies. The addenda format allows sites to only use the consent document(s) applicable to their participation.

10.2 Diminished Mental Capacity

There are no plans to recruit special classes of participants such as institutionalized individuals. However, it is possible that a participant who has developed diminished mental capacity will be asked to participate. It is also possible that a person with full mental faculties at the beginning of ACCORDION experiences a decrease in mental capacity during the trial.

Participants with diminished mental capacity (e.g., due to Alzheimer's, dementia, or other cause), are eligible to participate in ACCORDION but only with the written consent of their Legally Authorized Representative (LAR). LAR designations vary by state, and each local site should follow procedures in accordance with state and local laws and policies.

If diminished mental capacity is noted at the time of initial consent, the participant's LAR should be involved in the consent process and must provide written authorization for the participant to begin being followed in ACCORDION. If a participant has questionable diminished mental capacity, and/or at the discretion of the local investigator, a site should perform a standardized test, such as the Mini-Mental State Exam (MMSE), to determine if an LAR is needed.

Likewise, at any follow-up visit, if a participant appears to have diminished in mental capacity, the local principal investigator should perform a standardized test to determine mental capacity. If the participant shows signs of diminished mental capacity, an LAR should re-consent for the participant to continue on in ACCORDION.

In either case, the local site should follow all applicable regulations, state laws, and institutional or other local policies, including the use of specific standardized tests for determining mental capacity.

10.3 Risks/Benefits/Subject Compensation

Risks to Subjects: The ACCORDION study meets the requirements for minimal risk as described in 45 CFR 46.102(i), which states: *“Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or test.”*

The two identifiable risks of participating in ACCORDION are risks from the clinical blood draws and breach of confidentiality. Risks due to the blood draws include mild pain, minor bruising at the puncture site, infection, and, rarely, fainting. These will be minimized by using standard blood draw techniques and universal precautions during each draw, ensuring that the area is properly cleansed prior to needle stick.

Risks involving confidentiality will be minimized to the fullest extent possible. (Please see Section 11.4 for details regarding protecting confidentiality.) Risks inherent to participation in the ACCORDION Sub-Studies are discussed below.

Because ACCORDION is an observation-only study with no intervention, serious adverse events (SAEs) due to study participation are not expected. Information will be collected on the occurrence of hospitalizations, however it is expected that any hospitalizations will be related to underlying disease and not to participation in ACCORDION.

Risks Involved with the EYE Substudy: The procedures used in this substudy are standard examination techniques that are used in a comprehensive clinical eye exam. The risks include rare corneal abrasions resulting from tonometry, and readily treated in the ophthalmologist's office. The light from the fundus photography may cause temporary discomfort for the patient.

Risks Involved with the MIND Substudy: Procedures in the MIND substudy are generally accepted parts of routine care. There are no additional risks to subjects participating in the MIND substudy, although those in the MRI portion of the MIND study may experience discomfort or claustrophobia during the MRI. Measures are in place to prevent and/or alleviate these risks.

Potential Benefits: Regular medical care is essential in the treatment of diabetes. While participants are expected to seek out medical care from their own providers, there is a possible benefit that clinic visits for the ACCORDION study could detect problems before they would otherwise be identified. Laboratory reports, eye exams, and dementia assessments may provide diagnoses, and allow recommended treatments to begin, earlier than would be expected with regular medical care.

In addition to potential individual benefits, there may be benefit to others in the future as the information collected regarding heart attacks, strokes, and deaths may help further the medical understanding of the treatment of diabetes.

Subject Compensation: Subjects will not be compensated for their participation in ACCORDION. If their budgets allow, some sites may elect to provide reimbursement

for parking or other costs, however such action is not required and must be approved by the local IRB.

10.4 Confidentiality and Personal Health Information (PHI)

The confidentiality of all participant information will be protected at all study levels. Paper records and computer files must be appropriately safeguarded from unauthorized access.

Paper records for study participants, including signed originals of all consent forms, will be stored at the clinical sites. Copies of study records for cardiovascular outcomes, including necessary medical records, will be sent to and stored at the Coordinating Center. All study related records will be stored in locked filing cabinets and/or filing rooms within secure office space. Only study personnel who have completed ACCORDION training in data handling will have access to study forms.

Participant identifiers (name, medical record number, etc) will not be used on any ACCORDION forms or labels, only assigned code numbers will be used. Access to linking information will be only at the local site level and will be properly secured in a locked file cabinet or password-protected and encrypted computer with limited access.

A minimum amount of Personal Health Information (PHI) will be electronically transmitted to the Coordinating Center to ensure the success of the study. Such information includes names, addresses, phone numbers, and the name(s) of other individual(s) who may be contacted to assist in locating participants. This information will be encrypted (see section 11.4) and only used at the Coordinating Center level in the event of natural or other major disaster affecting a clinical site. When sending medical records for the adjudication of outcome events, sites will be instructed to black out all non-vital Personal Health Information (PHI), such as participant names, addresses, medical record numbers and billing information.

Sites are expected to explain the confidential nature of the data collected, processed, and stored as part of this study to all new personnel. Responsibility for securing confidentiality at the local site, including the training of new personnel, lies with the Principal Investigator at each site.

10.5 Data Access Security

Access to Data: Access to the data in the ACCORDION database will be controlled by a system of user identification names and passwords. Each ACCORDION staff member must complete the ACCORDION data handling training program before being given an ID and password to use the data system. The privileges allowed to each ID will be individually specified, allowing for a needs-based access to data. (For instance, local site personnel are only allowed access to data from their own participants; not data from other sites.) All passwords stored within the system will be encrypted using Secure Socket Layer (SSL) encryption.

All electronic participant data sent to and stored at the Coordinating Center is also encrypted using SSL encryption. In addition, all such databases are protected by passwords that must be supplied before the data can be accessed. Passwords are released only to Coordinating Center staff with a need to use the particular file, and are changed on a regular schedule.

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

Chapter 11

Ancillary Studies

11.1 Introduction

Observational follow-up studies such as ACCORDION provide ready platforms for expanded scientific discovery through ancillary studies. Combined with the ACCORD trial database, ACCORDION will provide a rich, evolving collection of data from 8000 or more people with diabetes who are at high risk of cardiovascular events. Whereas Chapter 2 of this protocol describes the specific study questions ACCORDION will address (questions that flowed naturally from the experiences in ACCORD), there are many more questions that may be posed, including questions not necessarily related to diabetes and/or heart disease. However, there may be questions that ACCORDION cannot currently or adequately address because the appropriate data are not being collected. Because this study has a population that will be followed over time in clinics that have close established relationships with the participants, this is a fertile environment that will provide exceptional opportunities for investigators, either within or outside of ACCORDION, to conduct additional projects at lower cost.

An ancillary study is defined as an investigation with objectives that are not pre-specified in the ACCORDION protocol but uses ACCORDION participants, samples, or data collected by ACCORDION (and/or using data or samples collected during the ACCORD). In most cases, an ancillary study will involve acquisition of additional data that are not compiled as part of the standard ACCORD data set. An ancillary study may or may not use all participants or be conducted in all clinical sites.

ACCORDION and non-ACCORDION investigators will be actively encouraged to propose and conduct ancillary studies. Such studies enhance the value and productivity of ACCORDION and, for ACCORDION investigators, help ensure the continued interest of the diverse group of investigators who are critical to the continued success of the study.

11.2 Ancillary Study Proposal Review Process

To protect the integrity of ACCORDION, all ancillary studies must be reviewed and approved by ACCORDION before access to data, samples, or participants is permitted. New ancillary study proposals will be sent to the ACCORDION Ancillary Study (AS)

Subcommittee. Ancillary study application forms and instructions can be obtained by accessing the *Ancillary Studies* link on the public side of the ACCORDION website. When the application is complete, the study proposal will be sent by the Coordinating Center to the AS Subcommittee for review and preparation of a recommendation to the Steering Committee. Preliminary approval/disapproval will be made by the Steering Committee, with a final recommendation for approval/disapproval (based upon participant burden and not scientific merit) made by the Observational Study Monitoring Board to the NHLBI Director.

For ancillary study proposals from investigators who are not part of ACCORDION, it would be advisable, although not required, to have an ACCORDION investigator included in the proposal because of their knowledge of and experience with ACCORD/ACCORDION. If Coordinating Center resources are to be used, arrangements must be made with the Coordinating Center Principal Investigator. In general, costs associated with ancillary study data management at the Coordinating Center must be budgeted into each ancillary study.

All proposed ancillary studies must be submitted to the Ancillary Study Subcommittee in time for review, circulation to appropriate committees, and to obtain clearance prior to submission to a funding agency. As a beneficiary of a collaborative study, each investigator must realize that other investigators must be given an opportunity to participate in proposed studies and to offer a critique of the proposal. Such collaboration will often strengthen the ancillary study. Studies submitted for approval less than 60 days prior to a funding application deadline may not receive timely approval.

During the review process, highest priority will be given to studies which:

- do not interfere with the main ACCORDION objectives,
- have the highest scientific merit,
- produce the least burden on ACCORDION participants,
- have objectives closest to those of ACCORDION,
- require the unique characteristics of the ACCORDION cohort, and
- provide opportunities for more junior investigators to serve as the Principal Investigator of a project.

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

11.3 Applying for an Ancillary Study

Investigators (ACCORD- and non-ACCORD alike) will find ancillary study application forms and instructions by accessing the Ancillary Studies link on the public side of the ACCORDION website. This link will also provide some basic information about ACCORD and ACCORDION to help the investigator develop his/her proposal.

Specifically the site will contain at least the following:

- The ACCORD Protocol
- The ACCORDION Protocol
- Copies of the ACCORD and ACCORDION Clinical Data Entry Forms
- A Data Dictionary for the Forms
- A Matrix describing the Timing and Scope of Visits and Procedures
- A Description of the Number and Type of Stored Samples (Blood, urine, etc)
- A Copy of the Ancillary Study Application Form
- A Form to Request a Budget from the Coordinating Center
- A Description of the Level of Consent for Use of Genetic Material
- The Results of a Genetics Pilot Study Describing the Number and Viability of ACCORD Stored Materials
- Simple sample size estimates for various participant subgroups.

The Coordinating Center will assist outside investigators develop their ancillary study proposals, helping them navigate through the web reports described above. Information regarding how to contact the appropriate Coordinating Center personnel will also be on this website.

11.4 Promoting Collaboration with Non-ACCORDION Investigators

The ACCORDION investigators will actively promote the use of this study by any researcher. The ACCORDION investigators understand that a collaborative approach to research is advantageous to ACCORDION- and non-ACCORDION investigators alike. Although not required, non-ACCORD investigators who include ACCORD Investigators

in their research are able to take advantage of their considerable knowledge of the ACCORD participants and data as well as knowledge of research and analytic methodologies appropriate for the data.

To promote the submission of ancillary studies, the ACCORDION website will note in a prominent place on its homepage that ACCORDION welcomes the submission of potential ancillary studies and substudies. The investigators will also have an ACCORDION Contact Slide as the last slide of all future ACCORD and ACCORDION presentations. This slide will invite people to contact ACCORD (with the contact information presented) if they have ideas for ancillary studies (or manuscripts), and would remain up on the screen during the usual Question/Answer periods. Whereas these are passive endeavors, they still should generate some interest and are first step.

Regarding the more active promotion of ACCORDION as a study receptive of ancillary study ideas, ACCORDION will encourage its investigators to give ACCORDION presentations at non-ACCORDION institutions and encourage these outside investigators to consider working with the ACCORD/ACCORDION group. This strategy has worked well in other NHLBI observational studies such as the Multi-Ethnic Study of Atherosclerosis (MESA).

ACCORDION will also participate (as do other NHLBI observational studies) in national observational study workshops, such as the one MESA participated in at Northwestern in 2010. That workshop resulted in the recruitment of a large number of investigators outside of MESA.

Chapter 12

Publication Policies

12.1 Data Analysis and Release of Results

The Coordinating Center will be responsible for the collection, storage, analysis, and release of all ACCORDION collaborative study data. Analyses from the main database will be performed by the Coordinating Center. In the case of ancillary studies, the Coordinating Center will review the data analyses of manuscripts using the ACCORD database. Distributed data analysis may be necessary if proposed analyses require special expertise that does not exist at the Coordinating Center, or if a particular analysis cannot be completed by the Coordinating Center within a reasonable time period. In both these situations, verification of final distributed analyses will be performed at the Coordinating Center. (See Protocol Chapter 13 for a detailed description of the ACCORDION Data Sharing Plan.)

12.2 Manuscript Proposal Process

The review process of an ACCORDION manuscript begins with the submission of a manuscript proposal. Instructions on the format of publications can be obtained by accessing the ACCORDION website. The completed manuscript proposal will be submitted to the ACCORDION Publications and Presentations (P&P) Subcommittee for review and approval. Approved proposals will then go to the Steering Committee for possible additional nominations of co-authors allowing investigators from every CCN and study unit have the opportunity to participate on papers. The P&P Subcommittee may change the composition of a Writing Group that has failed to produce the required manuscript according to the schedule originally agreed upon by the Group and the P&P Subcommittee.

A limited number of ACCORDION manuscripts, such as major design papers and the papers describing long-term treatment effects on the major endpoints, will be authored by the ACCORDION Study Group with reference to all investigators in an appendix. The ACCORDION Coordinating Center, with input from the Steering Committee, will determine priorities for scheduling a start date for manuscripts authored by the ACCORDION Study group.

The Writing Group Chairperson is responsible for all phases of manuscript preparation, from conception through publication. Members of the Writing Group are responsible for

performance of tasks assigned by the Chairperson within the allotted time period. Each member is expected to actively participate in the preparation of the manuscript. Selection of the journal for initial submission of the manuscript is delegated to the Writing Group, with input from the P&P Subcommittee and the Steering Committee, as needed.

12.3 Final Review of Finished Manuscripts

Prior to submission for publication, manuscripts will be reviewed by the Steering Committee, not for final approval but for scientific content, accuracy, and interpretation. At this stage, Steering Committee members may make comments. The notion is that the Steering Committee is the governing body of the study and wants all ACCORDION publications to be of the highest quality. This process will also provide the Writing Group with comments that would likely improve the paper and its chances for acceptance.

However, if there is a general consensus by the Steering Committee members that the finished manuscript has serious flaws, the Coordinating Center will send the manuscript back to the Writing Group with the instruction that the paper should not be submitted to the journal until the comments are addressed. The P&P Chair and the CoC representative on the paper will review the final, revised manuscript to ensure that the comments were appropriately addressed and will then inform the Writing Chair that the paper may be submitted.

Although the Steering Committee does not routinely approve/disapprove manuscripts thought to be ready for submission, any manuscript with NHLBI co-authors must be approved by NHLBI before submission to a journal. After revision, a final copy of the manuscript should be sent to the Coordinating Center and to all co-authors.

12.4 Abstracts and Presentations

The ACCORDION Coordinating Center, with the assistance of the Steering Committee, will maintain a current list of all relevant meetings and their deadlines for submission of abstracts. No abstract shall be submitted to any national or international organization for consideration prior to review and approval by the P&P Subcommittee and NHLBI Project Office (if abstract includes an NHLBI co-author). Abstracts of papers for presentations are expected to be based on active manuscripts.

Abstracts should be submitted to the P&P Subcommittee at least two weeks prior to the abstract deadline. Abstracts not submitted within this timeframe may not be reviewed/approved. If the P&P Subcommittee review is favorable, the Writing Group Chair will be given approval to submit the abstract.

Any ACCORD investigator who receives a personal invitation to make a presentation should notify the P&P Subcommittee of the sponsor, date and topic of the presentation. If information is to be presented that is not based on previously approved reports, prior approval of the abstract must be granted by the P&P Subcommittee.

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

A standard set of PowerPoint slides presenting the ACCORD/ACCORDION designs and results will be placed on the ACCORDION website for downloading. Presenters are encouraged to use these slides as part of any presentation.

12.5 Promoting Collaboration with Non-ACCORDION Investigators

The ACCORDION investigators will promote any use of this study by any researcher, including for paper writing activities. The ACCORDION investigators understand that a collaborative approach to research is advantageous to ACCORDION- and non-ACCORDION investigators alike.

Promoting collaboration with others will be accomplished through at least the following:

- In a prominent place on the ACCORDION website homepage, there will be a statement inviting investigators to use ACCORD/ACCORDION data for paper writing activities
- A link will be placed on the website providing instructions on how to propose a manuscript idea, including proposal application forms
- ACCORDION investigators will participate in future national meetings with other observational studies, during which collaborators are recruited from a variety of backgrounds

- It will be required that all ACCORD or ACCORDION presentations (oral or poster) include information regarding how to contact us with ideas for collaboration.

Although not required, non-ACCORD investigators who include ACCORD Investigators in their manuscript preparation are able to take advantage of their considerable knowledge of the ACCORD participants and data as well as knowledge of research and analytic methodologies appropriate for the data.

Chapter 13

ACCORDION Data Sharing Plan

13.1 Overview

ACCORDION supports the timely public dissemination of study results by the Coordinating Center/Investigators and will grant public access to the ACCORDION data according to NIH Policies. Specifically, ACCORDION will adhere to institutional policies, local IRBs, as well as local, state and federal laws and regulations (including the HIPAA Privacy Rule), as outlined in the NIH policy of February 2003 policy for the data generated from NIH-sponsored research.

There are three levels of data sharing that together comprise the Data Sharing Plan. Both ACCORDION and non-ACCORDION investigators may apply to the ACCORDION Coordinating Center for one or more of the following: 1) a Limited Data Set with Data Use Agreement, 2) de-identified data, and 3) fully identified data sets (requires participant authorization and IRB approval). In some cases, under recent guidance from OHRP, a de-identified dataset can be declared to be “not human subjects” and thus not subject to the recipient’s IRB review.

13.2 Preparing Data to be Shared

Because ACCORDION will have a broad, more public data share, it is planned that the data will be de-identified (i.e. stripped of all Personal Health Information (PHI) in compliance with the HIPAA privacy rule). This will make the data free of identifiers that would permit linkages to the research participants and free of content that would create unacceptably high risks of participant identification. The ACCORDION Coordinating Center (CoC) is part of a covered entity and all CoC personnel are required to maintain yearly HIPAA training.

Under the HIPAA Privacy Rule, PHI will be stripped from the database. Based on previous experience, other data, often not listed as PHI are indirect identifiers and could lead to what the NIH data sharing workbook calls “deductive disclosure” of participants’ identities. This is more likely in small, geographically limited or specialized populations. Examples of data that is often considered for de-identification on a variable or field level are comment fields, optional fields, other specified fields, site number, investigator, and site name. In ACCORDION, these data will either be recoded or removed to prevent identification.

13.3 Additional Measures to be Taken to Protect Data

As referred to in the Coordinating Center Systems Security Plan (available separately) and in discussions on the specific applications used for managing data for ACCORDION, the Coordinating Center will take full measures to minimize the risk of breaching the confidentiality of data. These include but are not limited to the following:

- electronic firewalls and locked storage facilities
- password authentication of users
- audit trails
- disaster prevention and recovery plans
- security measures for backup tapes
- systems certification
- yearly HIPAA training for all employees

13.4 When Data will be Shared

Data for each clinic exam cycle will be shared within 3 years of completion of that cycle or within 2 years of freezing data for analysis, whichever comes first. In collaboration with the NHLBI, the Coordinating Center will develop a process to facilitate providing other investigators with access to de-identified ACCORDION data in the format that is most helpful to them.

13.5 How Data Will be Provided

It is recognized that interested parties will desire “access to the data” in different formats. Some may benefit from having the actual study database, others may want specific statistical output (analyses and tables), and still others may desire opportunities for collaboration with the ACCORDION study group.

Documentation will also be provided. The documentation will include electronic versions of the protocol, data collection forms (with instructions for scoring if needed), data dictionary, data code book, labels, and formats. Documentation will be provided in a standard format (such as .pdf files) readable on a variety of platforms. An appendix to the documentation will include a separate section on derived variables that were not part of the original data collection forms.

The ACCORDION data provided, whether it is in SAS data sets or already programmed tables and listings, will be made available to the user under an agreement containing the following stipulations:

1. data will be used for research purposes and not to identify individual participants
2. data must be secured using appropriate computer technology
3. data must be destroyed or returned after any analysis is complete
4. authors of any manuscript resulting from this data must acknowledge the source of the data upon which their manuscript is based and follow all authorship guidelines developed by the ACCORDION Publication Committee
5. any analyses for the purposes of presentations, abstracts, and/or publications must be coordinated through the ACCORDION Publications Committee, to ensure coordination of analyses and prevent redundant analyses from being performed independently
6. all coauthors must be given a chance for review and approval of a draft manuscript prior to submission for publication as outlined in the ACCORDION publication guidelines developed by the Publications Committee.

13.6 Procedures for Requesting Data and Biospecimens

A procedure for applying for data and biospecimens has been developed and request forms will be posted on the ACCORDION website. Requests will be reviewed by the ACCORDION Steering Committee according to criteria established by that committee. Requests by ACCORDION investigators and those with peer review funding will be prioritized.

Chapter 14

Study Organization

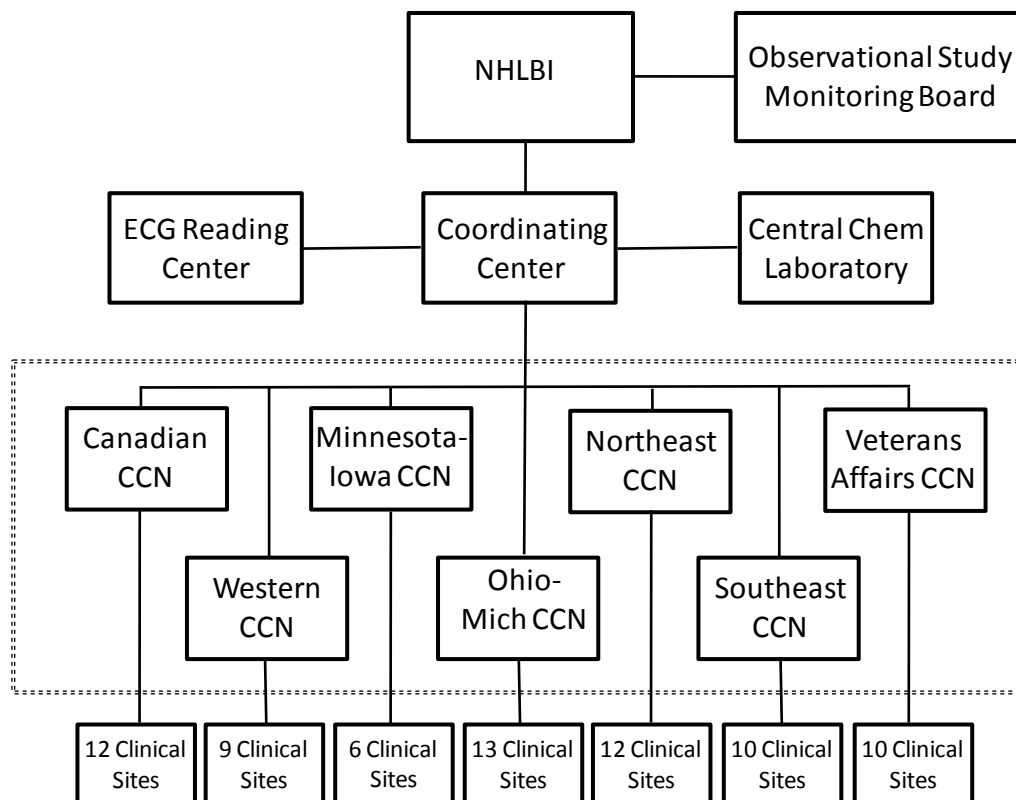
14.1 Administrative Organizational Structure

The ACCORDION organizational structures and responsibilities mirror those previously used with great success in ACCORD and are similar to those of other, large multicenter clinical trials sponsored by government or industry. (See Figure 14.1 below.) There are 72 clinical sites (medical facilities and/or private practices) administratively located under 7 Clinical Center Networks (CCNs). In addition, there is a Coordinating Center (CoC), a Central Chemistry Laboratory and an ECG Reading Center. The NIH study sponsors are described below in Section 14.2. Scientific leadership is provided by the Steering Committee, which is described below in Section 14.3. Of the 77 clinical sites operating during most of ACCORD, one clinic closed a year before the scheduled end of the trial and four clinics subsequently merged with other clinics, leaving 72 operating clinics in ACCORDION.

At least 8000 ACCORDION participants will be recruited from the clinical sites from which they were randomized, treated, and followed in ACCORD. CCN investigators, in conjunction with the CoC, will work with their clinical sites during the trial on issues related to recruitment, adherence to protocol, retention and quality control. While these clinical sites will interact principally through their CCNs, for matters such as data collection, the sites will transmit their data directly to the Coordinating Center and the other central units. Similarly, data queries will be sent directly to the clinical sites, with copies to the appropriate CCN.

The Coordinating Center, with input from the ACCORD Steering Committee, will be responsible for coordinating the protocol writing activities; developing and distributing the Manual of Procedures; training the core CCN trial personnel in the standardized protocol implementation and data collection; providing rapid feedback to the CCNs and Core Laboratories on the quality of data submitted and proposing corrections; collecting all trial data, including clinical outcomes; analyzing all data; and preparing reports for the OSMB. The CoC will also plan, organize and coordinate all Steering Committee meetings. Specifically related to the Lab and ECG Centers, the CoC will monitor the timeliness of their data gathering and analysis, quality control measures and performances, review the quality of all data transmitted, and report these and related matters to the NHLBI Project Office. CoC investigators and staff are also active members of each of the Steering Committee subcommittees.

Figure 14.1: ACCORDION Organizational Structure (for administrative purposes)



The CoC, working through the CCNs, will assure that the clinical sites perform the following tasks by providing frequent oversight, and if necessary, provide assistance to the clinical sites: follow *Good Clinical Practice* (GCP) guidelines; attend and participate in all training sessions and meetings/calls; obtain annual IRB approval and follow any other legal and ethical requirements related to the conduct of human subject research; ensure that all procedures are conducted as described in the protocol and MOP; implement procedures to maximize participant retention; accumulate and maintain participant study files; ensure the documentation of all participant encounters with prompt collection, completion and entry of data forms; maintain confidentiality and security of the participant study files; complete study data forms; answer data queries in a timely fashion; capture outcomes; complete and enter data forms and provide documentation of outcomes to the CoC in a timely fashion; identify and promptly report unanticipated problems to the CoC leadership, IRB and any regulatory agencies; make participants' records and study files available for site visits by the CCNs, CoC and the NHLBI; and perform other tasks as needed to implement and complete the study.

The ECG Reading Center and the Central Chemistry Laboratory, both which participated in the original ACCORD trial, will provide central interpretation of resting ECG, HbA1c, lipid values and other blood measurements on trial participants. Each core unit is responsible for development and distribution of specific measurement procedures, timely data gathering, and analysis.

14.2 NHLBI Project Office and Other Government Representatives

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

NHLBI will establish an external Observational Study Monitoring Board (OSMB), which will report directly to NHLBI. This committee is described below in Section 14.4.

14.3 ACCORDION Steering Committee, Executive Committee, and Subcommittees

The Steering Committee (SC) will be the main governing body of the study, providing leadership and establishing scientific and administrative policy. This committee will oversee all levels of conduct of the study, including study design, study protocol development, establishment of data collection practices, forms and MOP approval, analyses, publications/presentations, etc. The nine voting members of the SC include the 7 CCN PIs, the Coordinating Center PI, and the NHLBI Project Officer. The Chair can make or break a tie. This model was followed in ACCORD and provided an excellent and efficient means of decision and policy making. Key members of the CCNs, the CoC, Central Laboratory, ECG Reading Center, the MIND Substudy, Eye Substudy and NIH (including NHLBI, NIDDK, NIA, NEA, and CDC) can also attend all meetings and calls of the SC and contribute to the discussions. The CoC will serve as the secretariat for the SC and its subcommittees. This will require close collaboration of the CoC staff and the SC chair in planning agenda and distributing minutes. The CoC will arrange conference calls and keep minutes as required. The CoC will have a representative on each subcommittee and will meet deadlines for preparing and distributing minutes. During the first year of the study, the SC will have calls at least

monthly. Thereafter, the SC will have quarterly calls and annual face-to-face meetings in the Bethesda area.

The Executive Committee will serve as an extension of the SC to ensure a faster and efficient means of monitoring the study on a more frequent basis and making quicker operational decisions of minor study issues. If necessary, the Executive will vet more complicated study issues prior to presentation to the full SC. This committee will have monthly conference calls, as they did during ACCORD. Members of this committee include CoC staff (including the Principal Investigator), ACCORDION Chair and Vice-Chair, Project Office Staff (including the Program Director and representatives of the Contract Office), other NIH investigators (e.g., from at least NIDDK, NIA, and NEI), and an annually rotating CCN PI representative and CCN Coordinator representative. Other investigators and staff may be invited as needed. The CoC Principal Investigator, in conjunction with the study chair and Project Office, will develop the agendas and lead the discussions.

The ACCORDION Steering Committee will have four standing subcommittees. These are the Morbidity and Mortality Subcommittee, the Ancillary/Substudy Proposals Subcommittee, the Publications and Presentations Subcommittee, and the Operations/Retention Subcommittee. Their charges are described below. Other committees and task forces may be constituted whenever a need develops.

Using the definitions presented in Chapter 5 of this protocol, the Morbidity and Mortality Subcommittee will be responsible for reviewing and classifying the pre-specified outcome events reported by the clinics. These include all deaths, nonfatal myocardial infarction, and nonfatal stroke. Guidelines and rules for these processes will be based upon the ACCORD experience and will constitute a chapter in the ACCORDION Manual of Procedures. Initially, they will review and classify only 10% of the events, as described in Protocol Section 4.7. However, this committee, with the assistance of study statisticians, will develop sensitivity analyses that will compare their classifications with the clinic classifications. If thresholds of disagreement (to be developed and approved in advance by the Steering Committee) are crossed, the proportion of events to be reviewed and classified will be increased incrementally up to 100%.

The Ancillary/Substudy Proposals Subcommittee is charged with developing procedures for review and approval of substudies funded by contract as well as ancillary studies funded by alternate mechanisms. As outlined in Protocol Chapter 11, ACCORDION will devote statistical support to the development of many ancillary studies through this committee. The ACCORDION investigators are eager to promote and develop ancillary

studies, as evidenced by the embedded ACCORDION-MIND and ACCORDION Eye Substudies presented in Protocol Chapters 5 and 6, respectively.

Using the successful processes developed during ACCORD, the ACCORDION Publications and Presentations (P&P) Subcommittee is charged with developing and implementing policies and procedures designed to stimulate productivity in these important areas. As described in detail in Protocol Chapter 12, the goal is to analyze these data and to disseminate the ACCORD/ACCORDION results and messages in an efficient and timely manner.

The ACCORDION Operations/Retention Subcommittee is a merger of the former ACCORD Recruitment and Retention (R&R) Subcommittee and Operations Subcommittee. The activities of this new, combined subcommittee will mirror those conducted by the parent subcommittees during the trial. During the trial portion of the original ACCORD, the R&R developed trial eligibility criteria, as well as the screening and recruitment strategies for participant accrual. It monitored screening and recruitment, and identified/assisted the CCNs (and their component clinics) experiencing recruitment difficulties. Subsequently, during the ACCORD post-trial event monitoring period (September 2009 through December 2010), that subcommittee monitored all aspects of participant retention, including visit, intervention and procedure adherence. The new subcommittee will adapt these activities, with the new/slightly altered goal of recruiting and retaining former ACCORD participants for and in ACCORDION. Also during the trial, the ACCORD Operations Subcommittee worked with the CoC to facilitate communication among the clinical sites with respect to overall study coordination and implementation of procedures. The Operations Subcommittee was comprised of all CCN Coordinators, selected individual clinic personnel, as well as representatives from the CC and the Project Office. Together with CoC personnel, this subcommittee coordinated training of the Project Coordinators on trial procedures. All of these activities will be continued during ACCORDION. The CCN Coordinators, who are most aware of the day-to-day issues at their sites, are an invaluable resource to the trial and will be invited to make recommendations regarding the conduct of the trial to the Steering Committee for review and consideration.

14.4 The ACCORDION Observational Study Monitoring Board (Figure 14.1)

At the end of the ACCORDION protocol development phase, an external and independent Observational Study Monitoring Board (OSMB) will review the scientific merit and feasibility of the ACCORDION Protocol. Members of the Committee, appointed by the Director of NHLBI, will be senior experts in the areas of cardiovascular

medicine, diabetes, biostatistics, epidemiology, and bioethics. The ACCORDION Study Chair, Vice-Chair, senior Coordinating Center staff, CCN PI's, and representatives from the NHLBI and other sponsoring Federal agencies and Institutes will participate in OSMB meetings as non-voting members. If acceptable, the OSMB will make a recommendation to the NHLBI that the ACCORDION protocol be approved.

Following the initiation of ACCORDION participant contact, the OSMB will provide oversight of the study and its ancillary studies. Specifically, the OSMB will review and evaluate data on recruitment of former ACCORD trial participants, retention, adherence, quality control, outcomes, and participant burden. This panel will report directly to NHLBI and may recommend corrective action, changes in the protocol, early stopping of the study or parts of the study. The OSMB will also review and advise on proposed changes in the protocol and review ancillary study proposals. The CoC will be the primary study unit interacting with the OSMB, scheduling meetings, preparing reports, and responding to queries.

OSMB meetings or calls are planned to occur generally annually, following an established schedule. Hard copy reports will be generated by the CoC for the OSMB and the Project Office. Regular reports will also be sent to the SC, and a subset of these will be continually updated on the study website. These will permit verification of completeness, timeliness, reliability, and accuracy of collection and coding of data. Comprehensive data on all QC activities will be included. Also included will be comparisons of measures of distribution of values over time, and among CCNs, technicians, or instruments. The CoC will develop and maintain standards to identify outliers, and initiate and coordinate separate review of these for accuracy.

14.4 Conflict of Interest Policy

To manage any real or perceived conflicts of interest, the ACCORDION investigators will abide by the posted policies of the International Committee of Medical Journal Editors (ICMJE). The full policy can be found at http://www.icmje.org/ethical_4conflicts.html.

All key study staff will be required to complete and submit an ICMJE form (found at http://www.icmje.org/coi_disclosure.pdf and reproduced as Protocol Appendix F) at least annually, and more often as relationships change. Additionally, investigators with potential conflicts must also notify their institutions, according to local policies, and notify study participants of their relationships.

Information received from ICMJE forms will be reviewed annually, or more often as needed, by the Steering Committee Chair, Coordinating Center Principal Investigator, and the NHLBI Project Officer. Findings will be shared with the ACCORDION Steering Committee at least annually to ensure that relationships are fully disclosed.

Chapter 15

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Appendix A

Original Entry Criteria for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial

The original entry criteria for ACCORD are presented in this appendix. The objective of setting specific inclusion/exclusion criteria in ACCORD was to identify a trial population that would likely have 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 needed 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 was required to be assessed and if eligible for subcomponents, then a computer program probabilistically assigned the participant.

I) Original ACCORD 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 in HbA1C 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 represented secondary prevention participants. Categories B and C together represented primary prevention participants.

II) Original ACCORD 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 μ mol/l) obtained within the previous 2 months
7. Transaminase >2 times upper limit of normal or active liver disease
8. Any ongoing medical therapy with known adverse interactions with the glycemic interventions (e.g., corticosteroids, protease inhibitors)
9. Cardiovascular event or procedure (as defined for study entry) or hospitalization for unstable angina within last 3 months
10. Current symptomatic heart failure, history of NYHA Class III or IV congestive heart failure at any time, or ejection fraction (by any method) < 25%
11. A medical condition likely to limit survival to less than 3 years or a malignancy other than non-melanoma skin cancer within the last 2 years
12. Any factors likely to limit adherence to interventions. For example,
 - dementia
 - alcohol or substance abuse
 - plans to move in the next 2 years.
 - history of unreliability in medication taking or appointment keeping
 - significant concerns about participation in the study from spouse, significant other, or family members
 - lack of support from primary health care provider
13. Failure to obtain informed consent from participant
14. Currently participating in another clinical trial. Note: Patient must wait until the completion of his/her activities or the completion of the other trial before being screened for ACCORD
15. Living in the same household as an already randomized ACCORD participant.
16. Any organ transplant
17. Weight loss > 10% in last 6 months
18. Pregnancy, currently trying to become pregnant, or of child-bearing potential and not practicing birth control
19. Participants with recurrent requirements for phlebotomy or transfusion of red blood cells.

III) Additional Eligibility Criteria for Participants in the ACCORD Lipid Trial

Participants eligible for the glycemic component of the trial were also eligible for the lipid component if the following criteria were met. Screening lipids may have either been measured at a local laboratory or obtained from medical records. If obtained from medical records, the most recent values recorded within the previous 12 months were used. If there were no lipid values recorded in the medical records within the previous 12 months, a blood test had to 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 needed 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 was 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, and possibly harmful levels. The rationale for the upper LDL-C limit was 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 was 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 were:

- 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)

IV) Additional Eligibility Criteria for Participants in the ACCORD Blood Pressure Trial

Participants eligible for the glycemic component of the trial were also eligible for the blood pressure component:

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

and

If:

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

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

Appendix B

Model Informed Consent Document

ACCORDION

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study

(Consent Version Date: March 18, 2011)

You are invited to join in a research study called Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study, also called ACCORDION. It is sponsored by the several agencies in the National Institutes of Health, including the National Heart, Lung and Blood Institute (NHLBI), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Eye Institute (NEI), and the National Institute on Aging (NIA). These agencies are part of the U.S. Federal Government.

Research studies are designed to gain knowledge that may help other people in the future. Your participation is voluntary. You may refuse to participate, or may stop participating at any time, and for any reason, without putting your future care at this institution or your relationship with your doctor at risk.

You are being invited to participate in this study because you were in the main ACCORD trial. We expect about 8,000 former ACCORD participants across the United States and Canada to join this study. The study will involve approximately [local number] participants at this clinical site.

Study Summary

People with diabetes have a higher rate of heart attacks and strokes than people who do not have diabetes. The ACCORD study was designed to see if medical treatments could reduce the heart attack and stroke rate in people with diabetes. ACCORDION is an observational follow up study that will be done over the next 3½ years to see if the effects of the ACCORD treatments change over time.

Please note that ACCORDION is not a treatment for your diabetes, blood pressure, or cholesterol. It is not a substitute for diabetes care. You should continue to see your personal health care provider for all of your medical care, including medications.

ACCORDION will last until 2014. However, the study will be reviewed regularly to see if it should be stopped earlier than this.

Visit Schedule and Measurements

If you decide to participate in ACCORDION, you will have 3 clinic visits with 4 follow-up phone calls (called “phone visits”) over a period of about 3½ years. These visits will be approximately six to eight months apart. About half of the ACCORDION participants will have a clinic visit first, and then will alternate between phone and clinic visits. The other half will

have a phone visit first and then alternate between clinic and phone visits. Everyone is scheduled to have the same number of phone and clinic visits, only the order will be different.

At each clinic visit, your health will be reviewed, and a short physical exam will be performed. You will be asked about your medical conditions, medications, treatments, health habits, and the quality of your life. You will also be asked about any hospitalization or other illnesses you may have had. If you have had a hospitalization or other event (such as a heart attack), your study staff will ask your permission to obtain medical records.

At your first and last clinic visit, about five teaspoons of blood will be drawn for laboratory testing. You will need to fast before this visit, which means you should have nothing to eat after midnight the night before. After the blood draw, you may have something to eat or drink. You will also have an electrocardiogram, which is a recording of the electrical activity of the heart, also called an ECG or an EKG. Additionally, at your last visit you will be asked to read an eye chart.

During phone visits, the study staff will ask you the same types of questions that are covered in the clinic visits. You will be asked about your medical conditions, treatments, health habits, and the quality of your life. If you have had a hospitalization or other event (such as a heart attack), your study staff will ask your permission to obtain medical records.

Study staff will ask you to provide contact information from people who may know how to get in touch with you if you cannot be located. These people may also be asked about your health status, for instance, if you have been hospitalized. If you are not comfortable having other people speak for you, you may refuse to provide this information.

Potential Risks

The risk involved with being in this research study is not expected to be more than the risk you may encounter in daily life, or from routine physical or psychological examinations or tests.

During the blood draws, you may experience discomfort, bruising and/or bleeding where the needle is inserted. Sometimes people become dizzy, lightheaded or feel faint. Infection may also occur, but it is very rare.

Potential Benefits

There is no guarantee that participating in ACCORDION will benefit you. However, knowledge will be gained that may benefit others, or may benefit you, in the future.

Study Costs and Compensation

There will be no charge to you for any of the required study tests and procedures performed during this study. Costs for study clinic visits, physical exams, laboratory tests, electrocardiograms and any other procedures associated with your participation are covered by the study.

You will not be paid for your participation in this study.

Alternative Treatments

ACCORDION is not a treatment study. A number of treatments are available for diabetes, high blood pressure, or high cholesterol. These treatments should be discussed with your personal healthcare provider.

New Information

You will be given any new information about the study that might affect your willingness to participate. Results of your laboratory tests will be provided to you to share with your personal physician.

Privacy and Confidentiality

We need to collect your health information to do this study. All information collected will be kept confidential as required by law. NHLBI is authorized to collect this information under Title 42 of the United States Code [42 USC 285b].

Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. We will ask you to provide information about your medical conditions, treatments, health habits, and the quality of your life. We may collect medical record information related to any hospitalizations you may have while participating in this study.

Wake Forest University Health Sciences is the Coordinating Center for ACCORDION. Study data from all study clinics will be sent to the Coordinating Center by secure internet connection. A code number assigned just to you will be used on all your study data and samples. You will not be identified in any report or publication about this study.

The key that connects you to your code number will be kept by your local study staff. It will be stored in a locked file or a password-protected computer. Your study records will also be stored in a locked area at your clinical site.

As part of this study, your name, address, phone number, email address, and social security number will be collected. It will be stored in a locked file or a password-protected computer and is for study use only. Only the local study staff members and approved staff members at the Coordinating Center will have access to your identifying information.

The local study staff will use your identifying information to contact you for study related purposes such as scheduling visits and study phone call visits. The Coordinating Center may use your information to help locate you during the study or to search the Death Index at the end of the study.

Your records for this study may be reviewed by authorized representatives from agencies within the National Institutes of Health, the Food and Drug Administration (FDA), the Centers for Disease Control (CDC), Wake Forest University Health Sciences, and monitoring personnel for the study at ___[Name of CCN Institution]___ and by the committee in charge of protecting research participants at ___[Name of Local Site Institution]___.

At the end of the study, the Coordinating Center will provide data and materials to the NIH agencies listed above. These data and materials will not include personal identifying

information. The NIH agencies may share your data and materials with other scientists who meet strict requirements regarding confidentiality, approval from human subjects review boards, and agreement to not further share the data or materials with other parties.

[Sites may insert additional local HIPAA Authorization language, as applicable]

Your Rights as a Research Participant

You may refuse to participate in this study or stop being in the study at any time. Regardless of your choice, you will not be penalized and you will not lose any benefits. The care you get from your doctor will not change.

This study has been reviewed and approved by an Institutional Review Board (IRB). The IRB is a group of people who review the research to protect your rights. If you would like to ask questions about your rights as a research participant, discuss problems or concerns, offer input, and/or obtain additional information, you should contact the Chairman of the IRB at [phone number] .

For questions about the study or in the event of a research-related injury, contact the study investigator, [Name] at [telephone number, including after hours number]

Agreement to Participate in the ACCORDION Study:

I have read the information provided above and had the opportunity to ask questions. I voluntarily consent to participate in the ACCORDION study.

Participant's signature: _____ Date: _____

Printed name of participant: _____

Agreement of LAR in regard to the ACCORDION Study: (if applicable)

I affirm that I am the Legally Authorized Representative (LAR) for the participant named above. I have read the information provided above and had the opportunity to ask questions. I voluntarily consent for the above-named person to participate in the ACCORDION study.

LAR's signature: _____ Date: _____

Printed name of LAR: _____

Relationship to participant: _____

Statement of Person Obtaining Consent:

I affirm that I have reviewed this consent with the above-named participant and, if applicable, his/her LAR. I have given the participant (and/or LAR) the opportunity to ask questions and have answered their questions to the best of my ability and to their satisfaction.

Signature: _____

Date: _____

Printed name of person obtaining consent:

Appendix C

Model Informed Consent Document Addendum

ACCORDION MIND Substudy **A Substudy of the Action to Control Cardiovascular Risk** **in Diabetes (ACCORD) Follow-On Study** *(Consent Version Date: March 18, 2011)*

You are invited to join in a substudy of ACCORDION called ACCORDION MIND. This substudy is only for people who took part in the MIND substudy of ACCORD. If you were not in ACCORD-MIND, you are not eligible to participate in ACCORDION MIND.

In addition to the main ACCORDION consent form, which you should already have read, this document explains the procedures, risks and possible benefits of participating in the ACCORDION MIND substudy. You do not have to be in the ACCORDION MIND study to participate in ACCORDION.

We expect about 2,500 former ACCORD MIND participants across the United States and Canada to join this study. The study will involve approximately ___ participants at this clinical site.

Study Summary

The effects of medical treatments for diabetes may have an impact on memory and thinking skills. The purpose of the ACCORDION MIND substudy is to measure long-term changes in memory and thinking skills, and to evaluate how these changes were affected by the medical treatment you received in the ACCORD study. This will be done through memory testing.

Visit Schedule and Measurements

If you agree to participate in ACCORDION-MIND, you will have your memory and thinking skills tested at one of your in-clinic ACCORDION visits. The tests include tasks that involve memory, concentration, and drawing. These are the same tests that you did for ACCORD-MIND.

Potential Risks

There are no risks associated with the memory-testing portion of the study. If you are uncomfortable with a question or task you may decline to answer or stop the task.

Potential Benefits

There is no guarantee that you will benefit from participating in this study. There may be benefit to you in that the early diagnosis of memory problems allows for earlier treatment. You will be notified of problems so you may discuss them with your primary care provider.

While you may or may not benefit by participating in this study, knowledge will be gained that may benefit others, or may benefit you in the future.

Confidentiality

All information collected from you will be treated as strictly confidential. Information collected as part of ACCORDION-MIND will be treated in the same manner as described in the main ACCORDION consent form.

As part of our training process, your memory tests may be recorded and sent to the Coordinating Center at Wake Forest University Health Sciences. These recordings will not identify you in any way and they will be destroyed immediately after use.

Right to Discontinue

You may refuse to participate or stop being in this substudy at any time. Regardless of your choice, you will not be penalized and you will not lose any benefits. The care you get from your doctor will not change.

Agreement to Participate in the ACCORDION MIND Sub-Study:

I have read the information provided above and had the opportunity to ask questions. I voluntarily consent to participate in the ACCORDION MIND Sub-Study.

Participant's signature: _____ Date: _____

Printed name of participant: _____

Agreement of LAR in regard to the ACCORDION MIND Sub-Study: (if applicable)

I affirm that I am the Legally Authorized Representative (LAR) for the participant named above. I have read the information provided above and had the opportunity to ask questions. I voluntarily consent for the above-named person to participate in the ACCORDION MIND Sub-Study.

LAR's signature: _____ Date: _____

Printed name of LAR: _____

Relationship to participant: _____

Statement of Person Obtaining Consent:

I affirm that I have reviewed this consent with the above-named participant and, if applicable, his/her LAR. I have given the participant (and/or LAR) the opportunity to ask questions and have answered their questions to the best of my ability and to their satisfaction.

Signature: _____ Date: _____

Printed name of person obtaining consent: _____

Appendix D

Model Informed Consent Document Addendum

ACCORDION MIND Follow-up Study - MRI Portion **A Substudy of the Action to Control Cardiovascular Risk** **in Diabetes (ACCORD) Follow-On Study (ACCORDION)** *(Consent Version Date: March 18, 2011)*

As part of your participation in ACCORDION-MIND, you are also invited to participate in the Magnetic Resonance Imaging (MRI) portion of the ACCORDION-MIND Follow-up Study.

In addition to the main ACCORDION and ACCORDION-MIND consent forms, which you should already have read, this document explains the procedures, risks and possible benefits of participating in the MRI portion of ACCORDION-MIND. You do not have to participate in the MRI portion to be in ACCORDION-MIND or to participate in ACCORDION.

We expect about 500 former ACCORD-MIND participants across the United States and Canada to join this portion of the study and have an MRI. The study will involve approximately ____ participants at this clinical site.

Study Summary

The effects of medical treatments for diabetes may have an impact on your brain. The purpose of the MRI portion of ACCORDION-MIND is to measure long-term changes in your brain, and to evaluate how these changes were affected by the medical treatment that you received in the ACCORD study.

Visit Schedule and Measurements

Because you agreed to participate in ACCORD-MIND you will undergo evaluations of your memory and thinking skills at one of your ACCORDION clinic visits. If you agree to the MRI portion of the study, you will also receive an MRI scan within approximately 45 days of your ACCORDION follow-up visit.

For the MRI, you will lie on a table and be placed inside of a large device that will take pictures of your head using magnetic fields. The study will require that you remain in the testing room for 30-45 minutes so that the pictures can be taken. The MRI machine does not use radiation (such as x-rays), and is considered safe. No needles or injections are used and there is also no discomfort or physical pain.

Prior to having the MRI exam, you will be asked questions about your medical history including whether you have:

- metal clips or fragments in your eyes, brain or spinal cord,
- a pacemaker, artificial heart valve, ear implant, or spinal cord stimulator
- had prior surgery for an aneurysm (a bulging blood vessel)
- are currently pregnant (females only)

If any of these factors are present, the MRI will not be performed.

Potential Risks

MRI scans can sometimes cause claustrophobia, a fear of tight spaces. MRIs are risk-free for those who do not have metal parts in their bodies. No serious biological effects have been reported from MRI scans. If you experience a fear of the confined space while in the scanner, you may stop the test. Trained medical personnel are always in attendance during these tests.

Potential Benefits

There is no guarantee that you will benefit from participating in this study. There may be benefit to you in that the early diagnosis of memory problems allows for earlier treatment. You will be notified of abnormalities so you may discuss them with your primary care provider.

While you may or may not benefit by participating in this study, knowledge will be gained that may benefit others, or may benefit you in the future.

Confidentiality

All information collected from you will be treated as strictly confidential. Information collected in the MRI portion of ACCORDION-MIND will be treated in the same manner as described in the main ACCORDION consent form.

In addition to those listed on the main ACCORDION consent form, the results of your MRI scan will be transmitted to the MRI Reading Center at the University of Pennsylvania.

Right to Discontinue

You may refuse to participate or stop being in this substudy at any time. Regardless of your choice, you will not be penalized and you will not lose any benefits. The care you get from your doctor will not change.

Agreement to Participate in the MRI portion of the ACCORDION-MIND Substudy:

I have read the information provided above and had the opportunity to ask questions. I voluntarily consent to participate in the MRI portion of the ACCORDION-MIND Substudy.

Participant's signature: _____ Date: _____

Printed name of participant: _____

Agreement of LAR in regard to the MRI portion of the ACCORDION-MIND Substudy: (if applicable)

I affirm that I am the Legally Authorized Representative (LAR) for the participant named above. I have read the information provided above and had the opportunity to ask questions. I

voluntarily consent for the above-named person to participate in the MRI portion of the ACCORDION-MIND Substudy.

LAR's signature: _____ Date: _____

Printed name of LAR: _____

Relationship to participant: _____

Statement of Person Obtaining Consent:

I affirm that I have reviewed this consent with the above-named participant and, if applicable, his/her LAR. I have given the participant (and/or LAR) the opportunity to ask questions and have answered their questions to the best of my ability and to their satisfaction.

Signature: _____ Date: _____

Printed name of person obtaining consent: _____

Appendix E

Model Informed Consent Document Addendum

ACCORDION EYE Substudy **A Substudy of the Action to Control Cardiovascular Risk** **in Diabetes (ACCORD) Follow-On Study** *(Consent Version Date: March 18, 2011)*

You are invited to join a substudy of ACCORDION called ACCORDION EYE. This substudy is only for people who took part in the EYE substudy of ACCORD.

In addition to the main ACCORDION consent form, which you should have already read, this document explains the procedures, risks and possible benefits of participating in the ACCORDION EYE substudy. You do not have to be in the ACCORDION EYE Sub-study to participate in ACCORDION.

We expect about 2,700 former ACCORD EYE participants across the United States and Canada to join this substudy. The substudy will involve approximately ____ participants at this clinical site.

Study Summary

The effects of medical treatments for diabetes may have an impact on the progression of diabetic retinopathy, the eye condition associated with diabetes. The purpose of the ACCORDION EYE sub-study is to see if there are any long-term effects of the medical treatment that you received in the ACCORD study.

Visit Schedule and Measurements

If you agree to participate in the ACCORDION EYE sub-study, you will have one clinic visit with an ophthalmologist (eye doctor) in addition to your ACCORDION clinic visits. At this visit you will have your vision tested and the pressure in your eyes measured. Your eyes will be dilated with drops so that your eyes can be thoroughly examined. You will also have pictures taken of the inside of your eyes.

Potential Risks

The procedures used in this sub-study are standard examination techniques that are used in a comprehensive clinical eye exam. All of the risks are very rare and are the same as the risks involved in standard eye care. Should any of these occur, treatment will be immediately available and there are usually no lasting effects.

The risks include:

- A stinging sensation when the dilating drops are put in your eye. The drops may also cause an allergic reaction or, if contaminated, can cause an infection
- A sudden increase in eye pressure from the dilating drops (acute glaucoma)
- Scratching the cornea (clear tissue at the front of the eye) while measuring eye pressure

- Discomfort from the bright camera flash when taking photographs

Potential Benefits:

There is no guarantee that you will benefit from participating in this study. There may be benefit to you in that the early diagnosis of retinopathy allows for the best chance to avoid blindness from diabetes. You will be notified of abnormalities so you may discuss them with your primary care provider.

While you may or may not benefit by participating in this study, knowledge will be gained that may benefit others, or may benefit you in the future.

Confidentiality

All information collected from you will be treated as strictly confidential. Information collected as part of ACCORDION-EYE will be treated in the same manner as described in the main ACCORDION consent form.

In addition to those listed on the main ACCORDION consent form, the results of your eye examinations and your eye photographs will be transmitted to the Fundus Photograph Reading Center at the University of Wisconsin.

Right to Discontinue

You may refuse to participate or stop being in this substudy at any time. Regardless of your choice, you will not be penalized and you will not lose any benefits. The care you get from your doctor will not change.

Agreement to Participate in the ACCORDION EYE Sub-Study:

I have read the information provided above and had the opportunity to ask questions. I voluntarily consent to participate in the ACCORDION EYE Sub-Study.

Participant's signature: _____ Date: _____

Printed name of participant: _____

Agreement of LAR in regard to the ACCORDION EYE Sub-Study: (if applicable)

I affirm that I am the Legally Authorized Representative (LAR) for the participant named above. I have read the information provided above and had the opportunity to ask questions. I voluntarily consent for the above-named person to participate in the ACCORDION EYE Sub-Study.

LAR's signature: _____ Date: _____

Printed name of LAR: _____

Relationship to participant: _____

Statement of Person Obtaining Consent:

I affirm that I have reviewed this consent with the above-named participant and, if applicable, his/her LAR. I have given the participant (and/or LAR) the opportunity to ask questions and have answered their questions to the best of my ability and to their satisfaction.

Signature: _____

Date: _____

Printed name of person obtaining consent: _____

Appendix F

Sample ICMJE Form for Disclosure of Potential Conflicts of Interest

(Downloaded February 11, 2011)



ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) 2. Surname (Last Name) 3. Effective Date (07-August-2008)

4. Are you the corresponding author? Yes No

5. Manuscript Title

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
2. Consulting fee or honorarium	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X

ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
7. Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X

ICMJE Form for Disclosure of Potential Conflicts of Interest

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD
9. Royalties	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
10. Payment for development of educational presentations	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
11. Stock/stock options	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
13. Other (err on the side of full disclosure)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Hide All Table Rows Checked 'No'

SAVE