

**ACCORD Eye Study**  
**Protocol**

**Version: January 30, 2004**

# ACCORD Eye Study

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# ACCORD Eye Study

(January 30, 2004)

## I. Introduction and Background

### A. Design of the ACCORD Trial

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) is a randomized clinical trial with 3 components, determining the effects of blood glucose lowering, blood pressure lowering, and lowering of serum triglycerides plus raising serum high density lipoprotein cholesterol levels on cardiovascular disease (CVD) in patients with type 2 diabetes. 10,000 participants will be randomly assigned in equal numbers to two glycemic management treatment arms. An intensive treatment arm will aim to achieve and maintain hemoglobin A1C level < 6.0%. A conventional treatment arm will target an A1C range of 7.0-7.9% with an expected mean value of approximately 7.5%.

4,200 of these participants will simultaneously be randomized to one of two hypertension management protocols. The intensive treatment arm targets a systolic blood pressure (SBP) < 120 mmHg and the conventional treatment arm targets a SBP <140 mmHg.

5,800 dyslipidemic ACCORD participants (HDL < 40 mg/dl) will be randomly assigned in a double masked fashion to either a placebo or fenofibrate 160 mg daily for reduction of triglyceride levels and increase in high-density lipoprotein cholesterol levels, after low-density lipoprotein cholesterol has been lowered with statin therapy (simvastatin 20 mg daily) to target LDL levels of approximately 100 mg/dl or lower.

The primary endpoint of the ACCORD Trial is death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke. Secondary outcomes include: the combination of the primary outcome plus any revascularization for coronary artery disease plus hospitalization for congestive heart failure; total mortality, cardiovascular mortality; any one of the specific coronary heart disease endpoints noted above, and fatal and non-fatal strokes. Other microvascular complications will also be assessed in this study. A study designed to evaluate the effects of treatment on diabetic retinopathy within the ACCORD Trial is described here.

## **B. 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 diabetic patients.

Many patients in the older type 2 diabetes population studied in ACCORD have both DR and 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.

In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the 10 year incidence of development of any retinopathy increased 30% and 60% for each absolute 1% higher baseline A1C, in older onset diabetic patients not taking or taking insulin respectively.<sup>1</sup> Progression to proliferative retinopathy increased 50% and 90% for each absolute 1% increase in A1C in the same patient groups. The United Kingdom Prospective Diabetes Study (UKPDS) established conclusively that glycemic control strongly influences the development and progression of DR (as the predominant microvascular endpoint studied) in newly diagnosed patients with type 2 diabetes followed for 10-11 years.<sup>2</sup> The UKPDS study was conducted in individuals with newly diagnosed diabetes who were at relatively low risk of cardiovascular disease. To date, no studies of the effect of glucose lowering on DR have been reported in individuals at high risk for CV disease who have established diabetes. In the UKPDS, intensive treatment which maintained a median A1C of 7.0% led to a 25% reduction in DR as assessed largely by requiring photocoagulation therapy, compared to an A1C of 7.9% with conventional treatment. A 21% risk reduction in 2 step progression on a modified Early Treatment Diabetic Retinopathy Study (ETDRS) scale was also produced by intensive glycemic management. Epidemiological analysis of the UKPDS data revealed no

glycemic threshold for risk of retinopathy in the diabetic range of glycemia. The actual microvascular event rates/1,000 person was 9.1, 6.1, and 3.9 in the A1C ranges of 7.0 - < 8.0, 6.0 - < 7.0 and < 6.0% respectively.<sup>3</sup> From the above, it is reasonable to hypothesize that intensive treatment of glycemia in ACCORD will reduce the risk of DR.

The UKPDS also demonstrated that lowering blood pressure from a mean of 154/87 to 144/82 reduced the risk of DR by 37%.<sup>4</sup> This benefit was independent of whether an ACE inhibitor or a beta blocker was randomly assigned to the patients as the initial antihypertensive drug. Progression of DR on the modified ETDRS scale was decreased 34%. After 7.5 years of follow-up, visual acuity loss of  $\geq 3$  lines on the logarithmic visual acuity chart was decreased by 47%. Epidemiological analysis of the UKPDS data showed that there was no threshold in the relationship between systolic blood pressure (SBP) and microvascular complications (largely composed of photocoagulation events). For each 10 mmHg decrease in SBP, there was a 13% decrease in risk of microvascular events down to a median SBP of 114 mmHg. Notably, this risk gradient was similar to that relating the risk of myocardial infarction to SBP. The event rate of myocardial infarction was, however, double the event rate of microvascular complications over the 10-11 years of follow-up. From the above data, it is also reasonable to hypothesize that reducing SBP to < 120 mm Hg will decrease the risk of DR.

The ETDRS study has shown a relationship between progression to high risk proliferative DR over 5 years and baseline serum triglycerides in the age group 50-69.<sup>5</sup> Progression was 23% higher in those with serum triglycerides > 190 mg/dl versus those whose serum triglycerides were normal, after adjustment for 11 significant covariates. It might be noted parenthetically that in the type 1 diabetes DCCT Trial, although reduction in A1C levels appeared to be the major mechanism for the decrease in retinopathy produced by intensive glycemic management, the latter treatment also produced a significant decrease in serum triglyceride levels over the 6.5 years of follow-up. It is therefore reasonable to hypothesize that fibrate therapy which decreases serum triglycerides will reduce the risk of DR.

In the ACCORD trial, between January and June 2001, 1,184 have been recruited in the Vanguard Phase. At baseline the patients enrolled in the Vanguard Phase had a

mean A1C of 8.7% and a mean duration of diabetes of 12.6 years. Many of the ACCORD Trial cohort can be expected already to have DR of some degree at baseline but some participants will not have DR. Therefore, both initial development of DR as well as its progression from a baseline level of DR can be assessed in ACCORD. The ACCORD Trial therefore offers the opportunity to answer four important questions regarding DR in type 2 diabetic patients at great risk for CVD events over the ensuing 5 years.

## **II. Aims of Eye Study**

1. Will lowering A1C to < 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%?
2. 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?
3. 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?
4. Is DR an independent risk factor for CVD in type 2 diabetes?

## **III. Eye Study Design**

The ACCORD Eye Study consists of 2 eye exams with fundus photography of 7 stereoscopic fields, scheduled for baseline and year 4 of follow-up. The projected sample size is 4065 patients. The main ACCORD Trial, which follows the Vanguard Phase, will recruit and randomize patients from February 2003 through June 2005. The length of follow-up for subjects in the diabetic retinopathy study will range from 4 to 6 years. The patients enrolled in the Vanguard Phase, however, will not participate in the Eye Study because baseline fundus photographs were not collected. All clinical centers from all clinical networks will be encouraged to participate in the Eye Study.

Baseline fundus photographs will be obtained within four months of randomization, preferably as close to baseline as possible. The clinical coordinator of each clinical site will schedule the patient and obtain the informed consent for the eye exam and fundus photographs with the ophthalmologist's office. This can be scheduled at baseline but also at the one month visit for the eye exam to be performed within the 4 month window. The clinical coordinator will enter the appointment information on a web-based form residing at the coordinating center. The fundus photographs and the completed eye exam form will be sent to the central Fundus Reading Center at the University of Wisconsin. The Reading Center will inform the Coordinating Center of receipt of photographs and eye exam forms using a web-based form residing at the Coordinating Center immediately upon receipt. 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.

#### **A. Primary Hypotheses for the ACCORD Eye Study**

In middle aged or older people with type 2 diabetes at high risk for having a CVD event:

1. A glycemic therapeutic strategy that targets A1C < 6.0% will reduce the rate of development or progression of DR more than a strategy that targets A1C range of 7.0-7.9% with the expectation of achieving a median A1C of 7.5%.
2. In the context of good glycemic control, a therapeutic strategy that uses a fibrate to lower triglyceride levels and raise HDL cholesterol levels in patients already receiving a statin drug for treatment of LDL cholesterol levels, will reduce the rate of development or progression of DR compared to a strategy that only uses a statin drug for treatment of LDL cholesterol levels.
3. In the context of good glycemic control, a therapeutic strategy that targets systolic blood pressure of < 120 mmHg will reduce the development and progression of DR compared to a strategy that targets a systolic blood pressure < 140 mmHg.

## **B. Secondary Hypothesis for the ACCORD Eye Study**

1. Baseline DR is a risk factor for CVD events independent of:
  - a. other CVD risk factors,
  - b. treatment effects of glycemic, blood pressure, and lipid control.

## **C. Subgroup Hypotheses**

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

1. Effects of glycemic control on the primary outcome are the same across baseline levels of A1C, and
2. Effects of glycemic control on the primary outcome are independent of effects due to the blood pressure and lipid interventions.
3. Effects of glycemic control on primary outcome are independent of baseline retinal status.

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

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

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

## **IV. Analysis Plan:**

### **A. Primary Outcome**

The primary outcome variable of the Eye study is the combined outcome of progression of diabetic retinopathy of at least 3 stages on the ETDRS scale,

photocoagulation, or vitrectomy. Analysis will be according to the intention-to-treat principle and only subjects with data at both baseline and follow-up will be used in the primary analysis.

The relationship of power and sample size is shown in the table below. We have assumed that the proportions of Eye study participants in the lipid and blood pressure trials will mirror the study-wide proportions of 58% and 42%, respectively. The sample sizes below were calculated to achieve 80, 85, and 90% power for all three primary aims.

<b>Number of Patients Recruited</b>	<b>Power</b>		
	<b>Glycemia</b>	<b>Lipid</b>	<b>BP</b>
4065	88.3%	90.9%	80.0%
4684	92.3%	94.2%	85.2%
5443	95.4%	96.8%	90.0%

#### **B. Exclusion Criterion**

Subjects who have had laser photocoagulation or vitrectomy for diabetic retinopathy in either eye at baseline will be excluded from the eye study.

#### **C. Analysis Exclusion**

Subjects 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. However, they may still be eligible for the endpoint of the development of diabetic macular edema or laser photocoagulation.

#### **D. 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.

#### **E. Statistical Analysis for Primary Hypotheses**

For the primary hypotheses listed in III. A., separate models will be used to test the primary hypothesis associated with each intervention. The main comparisons of the intervention groups with respect to the 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 glycemia control, lipid use, and blood pressure control.

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. Our reasoning for including term (f) is that secondary prevention participants should have higher event rates than primary prevention participants. Likewise, term (g) will be included because the clinical networks contain very different types of participants that may have different event rates. For example, the VA clinics will primarily consist of men. The main comparison in this model will be based on the chi-square statistic from a likelihood ratio test obtained from 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).

## **F. Secondary Hypothesis**

Testing the secondary hypothesis specified in III. B. for glycemic, blood pressure and lipid control involves comparisons of CVD incidence rates. The planned analysis for

the secondary hypothesis will use logistic regression models similar to those described above for the primary hypotheses. We will add ETDRS score, hypertension, dyslipidemia, and obesity at baseline as additional predictor variables to these models.

### **G. Subgroup Hypotheses**

Testing each of the subgroup hypotheses specified in III. C. will be carried out using logistic regression, as all subgroup hypotheses involve the primary outcome. For each subgroup hypothesis, the logistic regression model used to address the primary hypotheses will serve as the base model to which additional terms will be added to test each subgroup hypothesis.

To address the glycemia subgroup hypothesis to determine if relative risks for the primary outcome are the same across baseline levels of A1C, a term representing A1C levels will be entered into the logistic regression model. A test of the interaction between this term and the term representing the glycemetic intervention effect will address this initial subgroup hypothesis. To address the second glycemia subgroup hypothesis, whether the effects of glycemetic control on the primary outcome are independent of effects due to the blood pressure and lipid interventions, the significance of interactions between the terms representing each of the interventions will be investigated.

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

Finally, consistency of effect in demographic and primary/secondary prevention participants, and in the separate 2 X 2 subrandomizations, 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.

### **H. Sensitivity Analyses**

We recognize that there will be subjects 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 our analysis, we will look for systematic differences

between subjects who were and were not seen at follow-up. This comparison of those who do and do not return for their follow-up eye exam will focus on baseline characteristics, but may also include follow-up data from other scheduled ACCORD visits as appropriate. In secondary analyses, we will also attempt to model the impact of the missing data. One approach to such modeling might be to build a prediction model based on baseline measures and post-randomization visual acuity measurement without incorporating treatment information. A missing observation then would be replaced with the calculated probability of progression conditional on the covariate pattern for that observation. We would then compute a t-statistic using all data (which consists of 1s and 0s for people with complete data and calculated probabilities for people with missing follow-up data), and do a permutation test to evaluate statistical significance. This type of approach is valid as long as the data are missing at random.

## V. Power Considerations

### A. Summary

With a sample of 4065 recruited participants, the ACCORD Eye study is designed to have:

- 88% power to detect a 15% treatment effect of intensive glycemic control compared with conventional glycemic control on the primary outcome,
- 91% power to detect a 20% treatment effect of lipid control through LDL-C lowering and fibrates compared with lipid control using LDL-C lowering alone,
- 80% power to detect a 20% treatment effect of intensive blood pressure control compared with conventional blood pressure control.

To achieve a study of the above power, **4065** patients will need to be recruited to ensure that **3211** patients will have follow-up measurements (assuming 10% mortality, 10% drop-out, 1% failure to have fundus photographs). The 10% drop out rate is, if anything, a slightly high estimate which would be conservative. In the DCCT/EDIC study, the proportion of patients who underwent eye examinations was mostly above 90%. In studies of diabetic retinopathy, such as the Early Treatment Diabetic Retinopathy Study (ETDRS), less than 5% of subjects missed their eye exams. The table

in section IV. A. shows the sample sizes required for a range of power for the eye study, again assuming a 21% drop-out rate.

## **B. Computational Details for Power Calculations**

The population event rate was based on the WESDR study which showed a 38.4% 4-year rate of progression of retinopathy<sup>6</sup>. This event rate was for the group of older-onset diabetics taking insulin whose glycosylated hemoglobin is in the range of 5.9-8.8 using the WESDR A1C assay. Converting this to the Seattle lab assay yields a range of 5.52-8.21.<sup>7</sup> We have assumed that this is the incidence rate in subjects who receive the less intensive glycemic control and either the less intensive blood pressure control or the less intensive lipid control. We have assumed the same relative risks for glycemia, lipid, and blood pressure treatments as in the main ACCORD trial. These are  $RR_{gly}=0.85$ ,  $RR_{lip}=0.8$ , and  $RR_{bp}=0.8$  such that the intensive interventions are protective against DR. The UKPDS study found a relative risk of 0.83 for six-year incidence of DR for subjects with intensive glycemia control as compared with conventional therapy<sup>8</sup>. This was based on progression rates of 23.0% for the intensive group and 27.8% for the conventional group. This corresponds to a relative risk of

$RR_{gly} = 0.819 = \left(1 - (1 - 0.23)^{4/6}\right) / \left(1 - (1 - 0.278)^{4/6}\right)$  for four-years. Our assumption of  $RR_{gly}=0.85$  is close to this and is slightly conservative ( $RR=1$  is no effect). The strategy for power calculations is to estimate cumulative event rates for each of the 8 cells of the design and then average the event rates for the “+” and “-” intervention cells appropriate for comparing the more and less intensive levels of the intervention (i.e., 4 cells with “+” versus 4 cells with “-” for glycemia, 2 cells with “+” versus 2 cells with “-” for fibrates, and 2 cells with “+” versus 2 cells with “-” for blood pressure control). This results in assumed 4-year incidence rates of 0.346 vs. 0.294 for glycemia and 0.355 vs. 0.284 for both lipid and blood pressure. Finally, a simple binomial power calculation was performed based on the two averaged event rates using a two-sided test at the 5% level of significance.

These calculations indicate that we need to observe 3211 subjects at follow-up to have at least 80% power for the three main hypotheses (glycemia, BP, and lipid). This sample size will provide 88.3% power for the glycemia hypothesis, 90.9% power for the lipid hypothesis, and 80.0% for the blood pressure hypothesis.

In order to observe 3211 subjects at follow-up we will need to recruit considerably more subjects to account for mortality, dropout, and ineligibility (primarily because of failure of pupils to dilate sufficiently to allow for fundus photography). We will assume that we will have at most a 10% dropout due to patients being unwilling to participate at follow-up. In the UKPDS, the all-cause mortality rate was observed to be 17.9/1000 patient-years for the intensive group and 18.9 deaths/1000 patient years for the conventional group (UK Prospective Diabetes Study Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes)<sup>3</sup> These correspond to death rates over 5 years of 9.0% and 9.5%, respectively. In subjects with A1C levels of 7-8% the all cause mortality was 18.7 deaths/1000 patient years and 15.8 deaths/1000 patient years in subjects with A1C levels of 6-7%. These correspond to death rates over 4 years of 7.4% and 6.3%, respectively. To be conservative, we have assumed a maximum death rate of 10% over 4 years. With some adjustment for possible lack of dilation of the pupils in 1% of patients, the total percentage of patients missing final evaluations is expected to be approximately 21%. Consequently, we need to recruit 4065 ( $=3211/0.79$ ) subjects to ensure sufficient sample size at follow-up.

Other secondary endpoints include the development of diabetic macular edema, visual loss and cataract extraction. There is insufficient power for these endpoints but we will examine for trends. If we were to use the entire remaining cohort of 8700 subjects we would barely have 80% power for the glycemic effect on diabetic macular edema.

## **VI. Logistical Considerations**

The clinical coordinator has the option of obtaining the signed informed consent and scheduling the patient for an eye exam and fundus photography either at the baseline or one month visit. The eye exam should occur within 4 months of baseline. It is encouraged to have the eye exam as close to baseline as possible. The rationale for scheduling the visit as close to baseline as possible is the potential for intensive treatment to cause early worsening of existing diabetic retinopathy. It is essential to try to have the severity of retinopathy measured as close to baseline, prior to treatment, as possible.

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, to schedule it, and to obtain the informed consent at baseline or the one month visit. During the scheduling of the visit, the clinical coordinator will provide the subject's study ID number to the ophthalmologist's office and hand the subject an appointment card that will also contain the study id. The clinical coordinator will use the ACCORD website to enter data about the scheduled appointment including the study ID, date of visit, and the ophthalmologist's name and address (we expect that the latter will be done via a drop-down menu). The Reading Center will then use this information to prepare study packets which will be sent directly to the ophthalmologists. The completed forms and fundus photographs will be sent from the ophthalmologist's office to the Reading Center. The data entry from these forms and the photographic grading will be done by the Reading Center. Upon receipt of data the Reading Center will enter the administrative data into a form that will reside on the ACCORD website. 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 and eye exam data 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. The Coordinating Center will generate a report that will have names and addresses of the ophthalmologists who have seen study participants. The CCNs will issue checks to these 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.

## **VII. Safety Monitoring**

We will monitor potential adverse effects of the measurements, including allergic reactions, infections, acute glaucoma, cornea abrasions, and all other adverse events. All adverse events will be reported to the DSMB on a regular basis. The role and composition of the Data and Safety Monitoring Board are described in Section 13.8 of the main ACCORD protocol. Up-to-date statistical analyses will be provided to the DSMB at approximately 6-month intervals for review at their regular meetings. The analyses will include data on recruitment, outcome measures, any side- or safety effects, adherence, and quality control, and will be designed in collaboration with the DSMB. Interim analyses of the intervention effectiveness on the primary outcome of the eye study (composite of 3-stage progression of retinopathy, photocoagulation, or vitrectomy) will be performed at times coinciding with the meetings of the DSMB, and will be controlled to protect the overall Type I error of the trial. These results will be for the use of the DSMB and will not be revealed to the investigators. This information will be examined in conjunction with the efficacy monitoring data from the trial's primary outcome (composite of MI, stroke, or cardiovascular death), as well as safety analyses and other monitoring of the trial, to inform the DSMB's deliberations regarding trial continuation.

## **VIII. Appropriateness of Study Design compared to other Studies of Diabetic Retinopathy**

The ACCORD Eye Study design will have adequate power to evaluate the effects of the treatments on the progression of diabetic retinopathy. The outcomes proposed have been evaluated in the ETDRS, the DCCT/EDIC, and the UKPDS. The photographic methods used in the UKPDS utilized only 3 stereoscopic fields while the ACCORD Eye Study is using the standard 7 stereoscopic fields, which were used in previous studies of diabetic retinopathy. The retinopathy classification is also similar to that used in these important trials of diabetic retinopathy. The Fundus Reading Center at the University of Wisconsin, Madison is experienced with large multi-center trials because it served as the reading center for many of

these trials in the past as well as being the leaders who developed the classification of diabetic retinopathy severity.

## **IX. Eye Examination Procedures**

### **A. Introduction**

The procedures for carrying out the eye examinations required in the study 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 are described in the appendices.

### **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. If visual acuity is worse than 20/40, a pinhole should be added.

### **C. Intraocular Pressure**

Intraocular pressure (IOP) should be measured using an applanation tonometer by personnel experienced in the procedure. A pneumatonometer may be used if an applanation tonometer is not available.

### **D. 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-synephrine 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. See Appendices 1 and 2 for the fundus photography procedures for the clinical centers

### **E. 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 (see Appendix 2 for the Eye Exam Form):

- 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.

#### **F. 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.

#### **G. 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.

#### **X. Organizational Aspects of the ACCORD Eye Study:**

This study is funded by the National Eye Institute/National Institutes of Health. Funding will be provided for the baseline ophthalmic exams which include stereoscopic fundus photographs of the standard 7 fields of for subjects in ACCORD Eye Study. NEI will also provide the funding for the centralized grading of all the fundus photographs at a Fundus

Reading Center. The staff of the NEI will play an active role in the Eye Study of diabetic retinopathy in ACCORD.

The funds for the Reading Center will be administered through the Coordinating Center. The funds for the eye exams will be administered to each clinical center through the Clinical Network. Money will be provided for the eye exam, fundus photographs, support for the clinical coordinator's efforts, and possibly travel for each patient.

## **XI. References**

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