Health-Related Quality of Life and Cost-Effectiveness Components of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial: Rationale and Design

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Diabetes mellitus affects not only life expectancy but also quality of life. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial’s health-related quality of life (HRQOL) and cost-effectiveness components will enable the assessment of the relative importance of the various outcomes from the point of view of patients, provide an understanding of the balance between the burdens and benefits of the intervention strategies, and offer valuable insights into adherence. The HRQOL measures used include the Diabetes Symptoms Distress Checklist; the 36-Item Short Form Health Survey, Version 2 (SF-36) (RAND Corporation, Santa Monica, CA); the Patient Health Questionnaire (PHQ) depression measure (Pfizer Inc, New York, NY); the World Health Organization (WHO) Diabetes Treatment Satisfaction Questionnaire (DTSQ); and the EuroQol Feeling Thermometer (EuroQol Group, Rotterdam, Netherlands). The cost-effectiveness analysis (CEA) in ACCORD will provide information about the relative economic efficiency of the different interventions being compared in the trial. Effectiveness will be measured in terms of cardiovascular event–free years gained and quality-adjusted life-years gained (using the Health Utilities Index Mark 3 [HUI-3] [Health Utilities Inc., Dundas, Ontario, Canada] to measure health-state utility). Costs will be direct medical costs assessed from the perspective of a single-payer health system collected by means of patient and clinic cost forms and hospital discharge summaries. The primary HRQOL and CEA hypotheses mirror those in the main ACCORD trial, addressing the effects of the 3 main ACCORD interventions considered separately. There are also secondary (pairwise reference case) comparisons that do not assume independence of treatment effects on HRQOL. CEA will be done on a subsample of 4,311 ACCORD participants and HRQOL on a subsample of 2,053 nested within the CEA subsample. Most assessments will occur through questionnaires at baseline and at 12, 36, and 48 months. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99[suppl]:90i–102i)

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The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is designed to test the effects of improving the treatment of glucose, blood pressure, and lipids on cardiovascular disease (CVD) in patients with diabetes mellitus. Details regarding the general design of ACCORD are provided elsewhere in this supplement. Briefly, ACCORD is a multicenter study using a double 2 × 2 factorial design, involving 10,251 middle-aged and older participants with type 2 diabetes who are at high risk for CVD events. All participants are in the glycemia trial, which is testing the hypothesis that a therapeutic strategy that targets a glycosylated hemoglobin (HbA1c) level of <6.0% will reduce the rate of CVD events more than a strategy that targets an HbA1c level of 7.0%–7.9%. The lipid trial includes 5,518 of the participants, who will receive double-blinded fenofibrate or placebo in addition to a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) to determine whether the addition of a fibrate to increase high-density lipoprotein and lower triglycerides reduces the rate of CVD events. The blood pressure trial includes the remaining 4,733 participants to examine the hypothesis that a therapeutic strategy that targets a systolic blood pressure level of <120 mm Hg in the context of good glycemic control reduces the rate of CVD events compared with a strategy that targets a systolic blood pressure level of <140 mm Hg. In all, there are 8 treatment groups (Table 1).

The primary outcome of the trial is a composite outcome of death from CVD or nonfatal myocardial infarction (MI) or nonfatal stroke. Should the trial find positive results on this primary outcome, 2 other groups of outcomes will become important to patients and policymakers: health-related quality of life (HRQOL) and the cost-effectiveness of the interventions.

Diabetes affects not only life expectancy but also quality of life. For example, a 40-year-old patient with diabetes will lose 12–14 years from his or her life expectancy. However, if the reduction in quality of life during the years that the patient will live is taken into account, the total loss is 18–22 quality-adjusted life-years (QALYs). The ACCORD trial’s HRQOL component will enable the assessment of the relative importance of the various outcomes from the point of view of patients, provide an understanding of the balance between the burdens and benefits of the intervention strategies, and offer valuable insights into adherence.

The cost-effectiveness analysis (CEA) in ACCORD will provide information about the relative efficiency of the different interventions being compared in the trial. Answering these questions concerning effectiveness requires the measurement of the quality-adjusted and unadjusted health benefits as well as side effects. Answering questions concerning cost requires the measurement of the costs of interventions, the costs of side effects, and the costs of adverse health outcomes during the duration of the trial from the perspective of the healthcare system.

HRQOL may be a significant determinant of patients’ willingness to undertake the burden of more intensive control of glucose and other cardiovascular risk factors. The CEA will give an assessment of the feasibility of adopting these strategies in the health system. The ACCORD study, therefore, has prospectively planned a careful assessment of HRQOL and cost-effectiveness within the structure of the main trial. This report describes the hypotheses for these 2 components of the trial, the analytical frameworks and designs, and measurements. The HRQOL and CEA hypotheses have been written so that they are parallel. They include primary (main effects) and secondary (pairwise reference case) comparisons. The primary hypotheses mirror those in the main ACCORD trial, addressing the effects of the 3 main ACCORD interventions considered separately.

### Health-Related Quality of Life Assessment

**Introduction:** The goal of the ACCORD trial’s HRQOL investigation is to assess the overall effect of the ACCORD interventions from patients’ point of view in a randomly selected subsample of 2,053 participants (a subset of the subsample of 4,311 selected for the CEA study) from each of the 8 ACCORD treatment groups at baseline and at 12, 36, and 48 months. The distribution of CEA and HRQOL randomized participants across the 8 treatment groups is depicted in Table 1.

The HRQOL assessment will address (1) effects on perceived quality of life related to acute health events (eg, acute MI, stroke) to which patients may adapt over time (response shift); (2) short-term symptoms and side effects mediated largely through the level and intensity of glycemic, blood pressure, or lipid control treatment and possible interactions between the glycemic and lipid control or blood pressure control treatments; and (3) long-term effects on general health and well-being mediated through potential differences in the reduction of cardiovascular events, hypoglycemic events, and other diabetes complications among the ACCORD treatment strategies.

The HRQOL hypotheses (Table 2) are thus designed to address immediate (event-related), short-term, and long-term differences in HRQOL that may be caused by the different ACCORD interventions. (The specific measures and instruments being used are listed in Table 3.) We distinguish between primary hypotheses, which concern the main effects of treatment and parallel those of the main study, and secondary hypotheses, which are unique to the HRQOL and CEA substudies. The secondary hypotheses, which compare individual treatment cells, have been included for 2 reasons. First, it is not known whether the ACCORD interventions will have independent effects on all dimensions of HRQOL or cost. Second, the inclusion of “reference case” comparisons is standard practice in cost-effectiveness research. This is because it is very important to understand how costs and the effectiveness of the various intervention combinations differ from the usual-care or reference-case scenario.
Our hypotheses also differ in the timing of the outcomes addressed. Three time frames are addressed: immediate (event related), short term, and long term.
health events, such as paralysis or MI, can fade significantly over a period as short as a year, because of recovery from or adaptation to the effects of illness. This poses a challenge for the ACCORD HRQOL substudy, in which assessments will take place at baseline and at 12, 36, and 48 months. We have therefore included a single-item assessment of “event-related HRQOL” using the EuroQol Feeling Thermometer from the EQ-5D instrument (EuroQol Group, Rotterdam, Netherlands), applied to all participants at each 4-month clinic visit.

SHORT TERM. Symptoms from an underlying disease or from treatments for the disease can be transient but important factors in HRQOL. It is important that these assessments be sensitive and specific to the disease and treatments in question. In ACCORD, disease-specific symptoms and medication-related effects on HRQOL are assessed primarily with a symptom inventory developed and refined empirically from a database of multiple previous diabetes, lipid, and blood pressure treatment trials.3

LONG TERM. A chronic disease such as diabetes has cumulative effects on the health status of patients from diverse causes, including falls and neurologic sequelae from hypoglycemia. It is important to capture these cumulative effects using validated measures that will allow comparisons among the ACCORD intervention groups and with patients with other chronic medical conditions. In ACCORD, health states known to be influenced by macrovascular and microvascular disease processes and events are of primary interest. Participant ratings will be assessed for general health (eg, physical, social, and psychologic well-being) using the 36-Item Short Form Health Survey, Version 2 (SF-36) (RAND Corporation, Santa Monica, CA), depressive symptoms with the Patient Health Questionnaire (PHQ) (Pfizer Inc, New York, NY), and health-state utilities with the Health Utilities Index Mark 3 (HUI-3) (Health Utilities Inc., Dundas, Ontario, Canada).7 Hypotheses address mean score differences on overall scales and established subscales.
among groups. Individual item analysis, if conducted, will be exploratory.

In addition to asking ACCORD participants about the effects of treatments on their health status, it is important to assess how well the treatments are meeting their needs and expectations. This treatment satisfaction will likely be related to the rates of treatment adherence and dropout noted throughout the trial.

**HRQOL measures:** The ACCORD HRQOL study was designed to detect meaningful HRQOL benefits and burdens of intensive risk factor management compared with less intensive management. These potential benefits are expected to accrue as the preservation of general health status mediated by primary and secondary CVD prevention achieved through intensified control of blood glucose and lipids or blood pressure. However, undergoing intensive risk factor treatment to achieve optimal control may itself place on patients greater treatment burden through the use of more medications with more side effects, stricter regimens, and more frequent adjustments to achieve optimal glucose and blood pressure targets. The ACCORD HRQOL study was designed to assess 3 distinct outcomes: general health, treatment satisfaction, and diabetes-related symptoms. These outcomes are classified as potentially short-term and long-term effects on the basis of when they might occur after randomization.

**SHORT-TERM REGIMEN EFFECTS.** Once patients are randomized to intensive or less intensive treatment of glucose and either combination lipid or intensive blood pressure therapy, the treatment regimen effects that emerge first might be those related to treatment burden and the effectiveness of symptom control (e.g., such as through hyperglycemia and hypoglycemia). Throughout the study, ACCORD participants undergo repeated treatment adjustments to reach and maintain targets specific to their treatment arms. To capture the effects of these repeated adjustments on general health status, ACCORD includes the Diabetes Symptoms Distress Checklist developed by Testa and Simonson and the World Health Organization (WHO) Diabetes Treatment Satisfaction Questionnaire (DTSQ).4

The Diabetes Symptoms Distress Checklist developed by Testa and Simonson3 was selected to record changes in symptom burden in response to the ACCORD treatments. In an earlier randomized, double-blind, placebo-controlled clinical trial of diet and either 5 or 20 mg of glipizide, this instrument was able to show differences between treatment regimens.3 ACCORD includes a 60-item version of this instrument. Effect sizes on the Diabetes Symptoms Distress Checklist ranged from 0.6 to 0.2 standard deviation (SD) units in the glipizide trial. There is evidence from previous treatment trials that hypoglycemic, lipid-lowering, and antihypertensive drug effects and their reflection in patient-rated HRQOL will show nonadditive properties. Therefore, it is of interest to compare individual cells of the 2 × 2 design, assessing different combinations of interventions individually, rather than just the marginal (main) effects of each intervention. To allow us to address possible nonadditive treatment effects, a sample of participants randomized to each 2 × 2 trial will be assessed for HRQOL. Sample-size calculations used an analysis of variance model and assumed similar treatment effects within each trial (glycemia plus lipids or glycemia plus blood pressure). To detect a 0.3-SD difference between the group that receives intensive therapies and the group that receives no intensive therapies, an estimated 250 participants per cell would provide approximately 90% power. The total sample size would thus be 2,000 of the 10,251 randomized participants (250 × 8 treatment groups). Ultimately, this target was exceeded by 53 participants, providing the ACCORD HRQOL study with 2,053 participants.

There are no norms for the DTSQ, but in published research, the mean score for patient samples has been reported to be about 24–28 (SD, 6–7).4 Reza and coworkers9 found a 5-point improvement in DTSQ score after 4 weeks of insulin treatment, which may be considered a moderate effect. In a sample of patients with type 2 diabetes, Anderson et al10 observed an approximate 8-point DTSQ difference (mean, 24.6; SD, 24 vs mean, 16.8; SD, 17.9) between patients whose HbA1c levels were poorly controlled and those whose HbA1c levels were well controlled. A 17-point difference on the DTSQ was observed between patients with no symptoms and those with moderate symptom scores. Bradley4 also found a score difference of 2–5 points for the DTSQ with interventions that produced small improvements in glycemic control.

**SUSTAINED GENERAL HEALTH EFFECTS.** Achieving targeted HbA1c levels and CVD risk factor control over many months is expected to affect daily functioning and well-being by preserving and enhancing health and functioning through the prevention of cardiovascular events. To capture effects of this nature, ACCORD includes the SF-36.5 Component scores will be used to represent global dimensions of HRQOL of psychologic and physical functioning. Measures such as the SF-36 provide an average assessment of health states over the past month. Population norms for the physical component score of the SF-36 for type 2 diabetes show a mean of 67.7 (SD, 28.7).

In published research, a difference of about 10 points on the physical component score of the SF-36 appears to discriminate groups that can be reasoned to have small to moderate patient-reported differences in health related to diabetes. Camacho and colleagues11 in a community sample of patients with diabetes, found a 10-point difference in the SF-36 Physical Function scale between patients who rated their health as good and those who rated their health as very good or excellent and a similar difference between patients taking insulin and those taking oral medications. Reza and coworkers9 found an approximate 6-point difference in SF-36 Physical Function scale scores in patients with poorly controlled type 2 diabetes after 4 weeks of insulin therapy that co-occurred with a mean change of 1.3 units in HbA1c.
(9.8%–8.5%). Taken together, these reports suggest that a range of 5–10 points corresponds to treatment effects that represent clinically significant effects. Power to detect the lower estimate of 5 points will provide ACCORD with the ability to detect small effects from treatment on HRQOL.

DEPRESSION. Because of documented relation of depression with cardiovascular events and glycemic control, depressive symptoms will also be measured. The 9-item depression measure from the PHQ will be used. The PHQ is the self-report version of the Primary Care Evaluation of Mental Disorders (Pfizer Inc), a well-validated psychiatric diagnostic interview for use in primary care settings.8 The PHQ depression measure offers the briefest measure that provides diagnostic information, severity information, and responsiveness to depression treatment.

ACUTE EFFECTS. Patients adapt to health events over time. Much of the effect on HRQOL of even dramatic events, such as paraplegia, disappears over the period of 1 or 2 years for many patients. The phenomenon has been called HRQOL “response shift.”12 Retrospective estimates of HRQOL may therefore underestimate initial (acute) effects from clinical events (eg, acute MI, stroke). To enhance the ability of ACCORD to fully capture HRQOL effects prospectively, a single-item visual analogue scale, the EuroQol Feeling Thermometer from the EQ-5D instrument, was included as part of the interval history form (assessed every 4 months) for the full sample.6 Participants rate their health states from 0 (the worst imaginable health state) to 100 (the best imaginable health state). The EuroQol Feeling Thermometer will allow the assessment of HRQOL change related to many different kinds of medical events already recorded in the ACCORD database.

Cost-Effectiveness Analysis

Introduction: CEA seeks to describe and compare the cost per clinical benefit for different healthcare interventions. The cost-effectiveness sample comprises a total of 4,311 randomly selected participants from the 8 treatment cells in the ACCORD study population. The primary economic research questions to be addressed are as follows: (1) Is intensive glycemic therapy more cost-effective than less intensive glycemic therapy? (2) Is lipid treatment with a statin and a fibrate more cost-effective than lipid-lowering therapy with a statin alone? (3) Is intensive blood pressure therapy more cost-effective than less intensive blood pressure therapy? We will also examine the secondary question: Is intensive glycemic therapy in combination with intensive blood pressure therapy or intensive glycemic therapy in combination with combined statin-fibrate lipid therapy more cost-effective than less intensive therapy? The specific hypotheses are listed in Table 4. To answer these questions, we will estimate incremental cost-effectiveness ratios (ICERs) to compare the cost-effectiveness of the intensive therapy relative to the less intensive therapy. The perspective of this economic evaluation will be that of a single-payer national healthcare system. The perspective of a national healthcare system dictates that regardless of where care is provided, all direct medical costs associated with the treatment of patients with type 2 diabetes and its complications and costs for treating adverse effects of the therapy are relevant and will be considered. Nonmedical and productivity costs (such as lost income for patients and their informal caregivers) are not considered.13

Effectiveness measures: The end points defined by the main trial are considered primary outcome measures for this economic evaluation. Three effectiveness measures are identified: (1) CVD-free years gained, (2) life-years gained, and (3) QALYs gained. The primary effectiveness measure of CVD-free years gained is derived from the primary outcome of the main ACCORD trial and is defined as the time until the first occurrence of CVD end points. The measure of life-years gained is determined by the difference in the number of life-years between intensive therapy and standard therapy. QALYs will be calculated using utility values derived from our health utility measure, the HUI-3.7

Health-state utility measure: The HUI-3 is a questionnaire that will be used to assess health-state utilities for ACCORD participants.7 These utilities will be combined with the mortality rates for the different treatment groups to determine the QALYs gained (or lost) by the intensive interventions compared with the less intensive interventions. The HUI-3 has 8 attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain), with 5 or 6 levels per attribute. With the recent release of a multiplicative, multiattribute utility function for the HUI-3 system, users are now able to generate population-based utility scores for HUI-3 health state relating patient outcomes to health utilities derived from the general population. The HUI-3 scoring function is based on preference measurements obtained from a random sample of the general population (aged >16 years) in Hamilton, Ontario, Canada. There is a high level of agreement between directly measured utility scores for HUI-3 health states and scores obtained using the multiplicative function.

The HUI-3 is a self-administered, 15-item instrument that takes approximately 8 minutes to complete. It will be administered to the full ACCORD sample at the same intervals as the HRQOL instrument is administered to the subsample. The HUI-3 is administered at baseline; at 12, 36, and 48 months; and at study exit. This is important for the following reasons. First, it allows the subsample assessed for HRQOL and the subsample assessed for cost-effectiveness to be linked in analysis. Second, it allows the detection of the HRQOL effects of diabetes complications occurring in a minority of ACCORD participants, which requires a large sample size. Third, it allows the calculation of valid incremental cost-utility scores for the various intensities of treatments to be tested in ACCORD.
The ICER of intensive control of blood glucose, in the presence of lipid therapy or BP control, will not be larger than the maximum acceptable “ceiling” level compared with less intensive control.

The ICER of intensive lipid treatment (adding a fibrate to a statin), in the presence of control of glucose, will not be larger than the maximum acceptable “ceiling” level compared with less intensive control.

The ICER of intensive BP control, in the presence of control of glucose, will not be larger than the maximum acceptable “ceiling” level compared with less intensive control.

The ICER of intensive control of blood glucose and BP will not be larger than the maximum acceptable “ceiling” level compared with standard treatment for glucose and BP.

The ICER of intensive control of blood glucose and lipids (with a fibrate) will not be larger than the maximum acceptable “ceiling” level compared with less intensive control.

Costs: Therapies are conceptualized as having 3 stages: (1) the initiation of the therapy, (2) the monitoring and maintenance of the ongoing therapy, and (3) the treatment of side effects and complications. All healthcare resource consumption will be classified into these 3 stages: items such as ambulatory service and diabetes treatment supplies will be classified into monitoring and maintenance costs, and inpatient costs will be classified as the treatment of side effects and complications. Total cost and costs in different stages will be assessed for each intervention.

Because the ACCORD CEA is conducted from the perspective of a national healthcare system, all direct medical costs associated with the treatment of patients with type 2 diabetes and its complications and costs for treating adverse effects of the therapy will be considered. These costs will include the costs of inpatient care, outpatient care, medications, and laboratory tests. Participants’ costs, such as waiting time, transportation, lodging, and informal care arising from the disease, will not be included. Likewise, opportunity costs of premature death, productivity loss, and long-term disability will not be considered in this study, because of the cost and complexity of monitoring these costs.

Cost data collection. To reduce the burden of data collection for economic analysis, data being collected from the main trial will be used whenever possible. Much of the data, such as primary end points and resources for the initial and the ongoing therapy, are routinely collected. The following sections describe methods for use in the collection of medical resource consumption data, which are not collected by the trial.

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

Data on hospitalization will be collected at the patient level. Research staff members at each clinic site will obtain a copy of the discharge summary for each hospital admission.

Primary (main-effects) hypotheses

1. The ICER of intensive control of blood glucose, in the presence of lipid therapy or BP control, will not be larger than the maximum acceptable “ceiling” level compared with less intensive control.

2. The ICER of intensive lipid treatment (adding a fibrate to a statin), in the presence of control of glucose, will not be larger than the maximum acceptable “ceiling” level compared with less intensive control.

3. The ICER of intensive BP control, in the presence of control of glucose, will not be larger than the maximum acceptable “ceiling” level compared with less intensive control.

Secondary “reference case” hypotheses

4. The ICER of intensive control of blood glucose and BP will not be larger than the maximum acceptable “ceiling” level compared with standard treatment for glucose and BP.

5. The ICER of intensive control of blood glucose and lipids (with a fibrate) will not be larger than the maximum acceptable “ceiling” level compared with standard treatment for glucose and BP.

Table 4

Cost-effectiveness analysis (CEA) hypotheses in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Costs</th>
<th>Effectiveness</th>
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<tr>
<td>Primary (main-effects) hypotheses</td>
<td>● Under the perspective of a national healthcare system, all direct medical costs associated with treatment of type 2 diabetes and its complications and costs for treating adverse effects of the therapy are relevant and will be considered. ● Labor and fringe benefits of providers, overhead, and resources used for patient management, including telephone calls, letters, team meetings, and adherence activities, will be collected at clinic site level. The estimated allocation of these resources to each therapy per patient will be recorded on the clinic resource and cost questionnaire. Data on medications, tests, and medical supplies for the therapies will be derived from the main trial. ● Data on hospitalization will be collected at the patient level. Research staff members at each clinic site will obtain a copy of the discharge summary for each hospital admission. ● Same as above</td>
<td>● CVD-free years gained (according to main trial criteria) ● Life-years gained ● QALYs gained (adjusted according to value calculated from HUI-3) ● Same as above</td>
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BP = blood pressure; CVD = cardiovascular disease; HUI-3 = Health Utilities Index Mark 3 (Health Utilities Inc., Dundas, Ontario, Canada); ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
send copies of these discharge summaries to the Coordinating Center, where diagnostic and procedural information are abstracted. All study patients are requested to consent to the release of their medical records when they participate in the study. The period for the collection of hospitalization data by the hospitalization form is at each follow-up visit. A specially trained medical coder at the Coordinating Center will map diagnoses and procedures into diagnosis-related groups.

**Ambulatory care.** The use of ambulatory care services outside of ACCORD-related visits is collected for all patients through self-reporting at each follow-up visit and is recorded using the clinic follow-up questionnaire. The data include the number of clinic and/or physician office visits, the number of emergency room visits, and number and types of outpatient diagnostic tests and procedures. Data on medication use are collected by the main trial.

**Unit cost.** Primary and secondary data sources are used to calculate the unit costs of resources used to reflect the cost for consuming an itemized service. Unit costs of hospital stays are based on the diagnosis-related groups used by Medicare. Unit costs for outpatient services, outpatient procedures, laboratory tests, and physician services are estimated using Medicare payment rates published by the Centers for Medicare and Medicaid Services (CMS). The unit costs of medications will derive from average wholesale prices using the Medical Economics Data Red Book. The total cost is the product of the multiplication of resource use and unit cost summed over all types of services involved. A discount rate of 3% is used to adjust for the preferences of patients for current rather than future benefits. All costs are adjusted for inflation over the study years.

**Estimated sample size for cost-effectiveness.** Although 4,311 participants were recruited for the cost substudy, the original targeted sample size was 4,288, on the basis of the following assumptions: (1) Patients are randomized in a double $2 \times 2$ layout, and each cell has the same expected sample size. (2) The decision rule in any healthcare system is that the intensive treatment should be implemented instead of the standard treatment if the ICER of the intensive treatment is less than the maximal willingness to pay for additional health effects. A maximal acceptable “ceiling” level for cost per QALY gained of $50,000 has been used in many other studies.\(^\text{15}\) A cost-effectiveness ratio $<$50,000 per life-year added is generally acceptable in the United States because it approximates the annual cost of patients receiving renal dialysis, a publicly supported program. Ratios $>$100,000 per life-year added are generally considered unacceptable, although this threshold is controversial. (3) There is no correlation between cost and health effects. (4) The test of interest is that the observed ICER derived from the trial is significantly less than the ceiling cost-effectiveness ratio.

**Data analysis for cost-effectiveness.** ICERs will be calculated separately for quality-adjusted health benefit and unadjusted health benefit.\(^\text{16}\) These ratios provide a summary of the cost-effectiveness of one intervention relative to the other.

Two formulas are used. In formula A, the effect is a measure of clinical effectiveness (eg, cardiovascular event–free years gained) without quality-of-life adjustment. In formula B, QALYs gained are derived from combining mortality rates with health-state utility (eg, HUI-3 score derived from patient reports). The formulas are as follows:

- **Formula A: ICER\textsuperscript{CEA}**
  
  $$\text{ICER}_{\text{CEA}} = \frac{(\text{Mean Cost}\text{Treatment A} - \text{Mean Cost}\text{Treatment B})/(\text{Mean Effect}\text{Treatment A} - \text{Mean Effect}\text{Treatment B})}{H11002}$$

- **Formula B: ICER\textsuperscript{Cost-Utility Analysis}**
  
  $$\text{ICER}_{\text{Cost-Utility Analysis}} = \frac{(\text{Mean Cost}\text{Treatment A} - \text{Mean Cost}\text{Treatment B})/(\text{Mean QALYs Gained}\text{Treatment A} - \text{Mean QALYs Gained}\text{Treatment B})}{H11005}$$

The ratio of incremental cost to incremental effectiveness represents the cost-effectiveness of the specific treatment. This ratio is a point estimate. Bootstrap methods will be used to calculate confidence intervals for cost-effectiveness ratios.\(^\text{17}\) In addition, sensitivity analyses will be performed to examine the effects of key demographic and clinical parameters on cost-effectiveness ratios.

**Conclusion**

Measuring the impact of the intensive treatment of patients with diabetes in ACCORD on the quality of life and cost-effectiveness addresses an important question that has been only partially resolved in previous studies. Although there is limited evidence from short-term studies that improved glycemic control may improve some HRQOL measures,\(^\text{2}\) most published research suggests only a weak effect of improved glycemic control on HRQOL. In large randomized trials, patients receiving intensive glycemic control interventions usually observed no significant differences in HRQOL relative to those receiving standard care.\(^\text{18}\)

The ACCORD HRQOL evaluation will provide important new information because of the following study design features. First, the ACCORD study is powered to detect differences in major cardiovascular events. If the intensive treatment in ACCORD decreases major cardiovascular events, there may be a measurable positive impact on HRQOL as well. The planned HRQOL analyses may enable us to identify factors that mediate the impact of intensive diabetes control on HRQOL. For example, is there a benefit associated with changes in glucose, lipids, and blood pressure in all study participants, or are HRQOL benefits mediated primarily by large HRQOL changes in the subset of participants with major cardiovascular events?

Second, a strength of ACCORD is its study design, which conjointly targets multiple clinical domains. Although studies suggest minimal adverse impacts of blood pressure therapy\(^\text{19}\) and statin therapy\(^\text{20}\) on HRQOL, there is some concern that combined statin-fibrate therapy may have
serious adverse effects.\textsuperscript{21} Our ability to test for interaction
effects of the ACCORD interventions on HRQOL will be
informative.

Third, the target levels of HbA\textsubscript{1c} (<6\%) and systolic
blood pressure (<120 mm Hg) in the intervention groups
have not been previously achieved in large clinical trials of
adults with type 2 diabetes. Previous evaluations of the
effect of more intensive diabetes care on HRQOL were
done in groups of patients who achieved substantially
higher levels of HbA\textsubscript{1c} and systolic blood pressure than
those targeted in ACCORD. Because the effects of glycemic
and blood pressure control on HRQOL may vary and be-
cause the effects may increase at more stringent levels of
HbA\textsubscript{1c} or systolic blood pressure control, ACCORD’s re-
sults will contribute important new information on this
topic.

CEA is a key feature of ACCORD and will contribute
important new knowledge on this topic. Many previous
studies of the cost-effectiveness of diabetes care interven-
tions have methodologic limitations, such as a lack of a
control group, selection bias, and uncontrolled regression
to the mean.\textsuperscript{20} Moreover, no previous studies have assessed
the impact of targeted HbA\textsubscript{1c} levels <6\%, systolic blood
pressure levels <120 mm Hg, or the value of fibrate treat-
ment in terms of cost-effectiveness. Furthermore, existing
published research on the cost-effectiveness of intensive
glycemic control and/or blood pressure control is often
based on simulation models or on data collected retrospec-
tively. By building a cost-effectiveness study prospecti-
vatively, ACCORD will make a major contribution to esti-
mates of cost-effectiveness. Similarly, few previous studies,
and none that used empirical analyses, have provided eco-
nomic analyses that take into account the potential syner-
gistic interactions when care is intensified across multiple
clinical domains (HbA\textsubscript{1c} and systolic blood pressure, HbA\textsubscript{1c}
and low-density lipoprotein).

For the CEA and HRQOL components of ACCORD, the
length of patient follow-up, with >1,000 study participants
having >7 years of follow-up, and a mean follow-up for the
full cohort of 10,251 of over 5 years, will allow the inves-
tigation of differences over a prolonged period. In the past,
only the United Kingdom Prospective Diabetes Study (UK-
PDS) has had comparable data with long follow-up periods
on large numbers of patients. However, several classes of
oral agents and newer insulins were not available at the time
of the UKPDS, and the treatment targets were less rigor-
ous.\textsuperscript{22}

In summary, the HRQOL and CEA measures are inte-
grated into the core ACCORD study design. These substud-
ies allow the assessment of the effects of the ACCORD
interventions from the patients’ point of view (HRQOL) and
in terms of the resources needed to achieve these effects
(CEA). The systematic collection of data to adequately
assess these domains, along with the ambitious overall de-
sign of ACCORD and the targeted levels of glycemic, blood
pressure, and lipid control by study participants, suggests
that the results of the HRQOL and CEA analyses will
significantly advance our knowledge concerning the value
and cost of the more intensive treatment of cardiovascular
risk factors in patients with type 2 diabetes.

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Appendix


* No longer affiliated with study unit.
† Deceased.