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. **(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.[1] 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 (HbA_{1c}) level of <6.0% will reduce the rate of CVD events more than a strategy that targets an HbA_{1c} 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).[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).[2] 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[3–6]) 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.[3–8]) 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.

Table 1
Observed number of Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial participants in the health-related quality of life (HRQOL) and cost-effectiveness analysis (CEA) subsets, by treatment group*

	BP Trial		Lipid Trial†		
Glycemia Trial	SBP <120 mm Hg	SBP <140 mm Hg	Group A	Group B	Total
HbA_{1c} <6.0%					
HRQOL	261	252	259	252	1,204
CEA	535	538	544	538	2,155
Overall	1,178	1,193	1,383	1,374	5,128
HbA_{1c} 7.0%–7.9%					
HRQOL	264	251	259	255	1,029
CEA	544	538	537	537	2,156
Overall	1,184	1,178	1,370	1,391	5,123
Total					
HRQOL	525	503	518	507	2,053
CEA	1,079	1,076	1,081	1,075	4,311
Overall	2,362	2,371	2,753	2,765	10,251

BP = blood pressure; HbA_{1c} = glycosylated hemoglobin; SBP = systolic BP.
* "Overall" reflects the total number of ACCORD randomized participants. The CEA participants are a subset of the overall participants, and the HRQOL participants are a subset of the CEA participants.
† Treatment group assignments were blinded until the end of the trial.

Table 2
Health-related quality of life (HRQOL) hypotheses in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial

Intervention/Event	Outcomes	Instruments
Primary HRQOL hypotheses (main-effects comparisons)		
1. Intensive control of blood glucose will:	a. Reduce symptoms and side effects compared with less intensive control in patients with diabetes mellitus	a. Diabetes Symptoms Distress Checklist[3]
2. Intensive control of BP will:	b. Reduce symptoms and disability associated with cardiovascular events	b. SF-36
3. Treatment of lipids with a statin and a fibrate compared with treatment of lipids with a statin alone will:	c. Increase self-reported treatment satisfaction	c. DTSQ
Secondary HRQOL hypotheses (pairwise "reference case" comparisons)		
4. Intensive control of glucose and BP, compared with standard treatment for glucose and BP will:	a. Reduce symptoms and side effects compared with less intensive control in patients with diabetes	a. Diabetes Symptoms Distress Checklist
5. Intensive control of glucose and treatment of lipids with a fibrate, compared with standard treatment for glucose and placebo will:	b. Reduce symptoms and disability associated with cardiovascular events	b. SF-36
	c. Increase self-reported treatment satisfaction	c. DTSQ
Event-related HRQOL hypotheses		
6. Participants experiencing nonfatal cardiovascular events in the preceding 4 mo	Show greater decreases in health status (pre–post) ratings than those who do not experience nonfatal events	EuroQol Feeling Thermometer*
7. Participants experiencing >3 hypoglycemic episodes in the preceding 4 mo	Show greater decreases in health status ratings than those without hypoglycemic episodes	EuroQol Feeling Thermometer
8. After cardiovascular events, participants in the intensive glucose control group	Show more rapid recovery of health status ratings	EuroQol Feeling Thermometer

BP = blood pressure; DTSQ = Diabetes Treatment Satisfaction Questionnaire[4]; SF-36 = 36-Item Short Form Health Survey, Version 2 (RAND Corporation, Santa Monica, CA).[5]
* From the EQ-5D instrument (EuroQol Group, Rotterdam, Netherlands).[6]

Our hypotheses also differ in the timing of the outcomes addressed. Three time frames are addressed: immediate (event related), short term, and long term.

IMMEDIATE (EVENT RELATED). It is well known that patients adapt over time to the symptoms and disability posed by chronic medical illness. The HRQOL effects of major

Table 3
Health-related quality of life and cost-effectiveness analysis measures used in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial

Instrument	Description	Scales	Time Point	Targeted Use in ACCORD
SF-36	36-item measure of general health status Time frame: past 4 wk	Physical and mental health component scores Range, 0–100 Reliability 0.65–0.94	Baseline; 12, 36, and 48 mo	Assess sustained general health effects from the intervention over several years of follow-up Assess changes in emotional well-being and vitality in response to treatment
DTSQ	8-item inventory assessing treatment satisfaction with diabetes mellitus medical therapy (types 1 and 2) Time frame: past 2 wk	Overall treatment satisfaction (6 items) (a) Satisfaction with metabolic control: highs and lows (single items) (b) Range, 0–36 (a), 0–6 (b) Reliability, >80 (b)	Baseline; 12, 36, and 48 mo	Assess participant treatment satisfaction, including short-term effects of increased treatment complexity and longer-term effects: burden of maintaining regimen over several years
PHQ	9-item inventory assessing the frequency of *DSM-IV* symptoms of depression Time frame: past 2 wk	Depression severity index: 9 items Range: 0–27 Sensitivity 88%, specificity 88%	Baseline; 12, 36, and 48 mo	Assess depressive symptoms as cause and consequence of intensity of diabetes control, diabetes complications, and CVD events
EuroQol Feling Thermometer*	Single-item numerical scale of acute health perceptions Time frame: today	Range, 0–100	Baseline and every 4 mo	Assess acute perceived changes in overall well-being in response to CVD events; more frequent measurement (every 4 mo) allows proximity to clinical events
Diabetes Symptoms Distress Checklist[3]	60-item scale assessing presence of symptom and degree of distress. Time frame: past month	Index of symptoms relevant to diabetes and its treatment Items assess symptom presence (a) and degree of distress (b) Range, 0–60 (a), 0–240 (b)	Baseline; 12, 36, and 48 mo	Assess short-term effects of treatment intensity on diabetes-related symptoms and distress
Effectiveness measure HUI-3	15-item scale assessing general health status	8 scales: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain	Baseline; 12, 36, and 48 mo	Assess the utility of health states using weights derived from the general population

CVD = cardiovascular disease; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition; DTSQ = Diabetes Treatment Satisfaction Questionnaire[4]; HUI-3 = Health Utilities Index Mark 3 (Health Utilities Inc., Dundas, Ontario, Canada)[7]; PHQ = Patient Health Questionnaire (Pfizer Inc, New York, NY)[8]; SF-36 = 36-Item Short Form Health Survey (RAND Corporation, Santa Monica, CA).[5]

* From the EQ-5D instrument (EuroQol Group, Rotterdam, Netherlands).[6]

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),[6] 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),[5] depressive symptoms with the Patient Health Questionnaire (PHQ) (Pfizer Inc, New York, NY),[8] 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 classed 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 (eg, 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 adapted from Testa and Simonson[3] and the World Health Organization (WHO) Diabetes Treatment Satisfaction Questionnaire (DTSQ).[4]

The Diabetes Symptoms Distress Checklist developed by Testa and Simonson[3] 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 coworkers[9] 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 al[10] observed an approximate 8-point DTSQ difference (mean, 24.6; SD, 24 vs mean, 16.8; SD, 17.9) between patients whose HbA_{1c} levels were poorly controlled and those whose HbA_{1c} levels were well controlled. A 17-point difference on the DTSQ was observed between patients with no symptoms and those with moderate symptom scores. Bradley[4] 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 HbA_{1c} 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 colleagues[11] 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 coworkers[9] 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 HbA_{1c}

(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.

Table 4
Cost-effectiveness analysis (CEA) hypotheses in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial

Comparisons	Costs	Effectiveness
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	• 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.	• CVD-free years gained (according to main trial criteria)
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	• 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.	• Life-years gained • QALYs gained (adjusted according to value calculated from HUI-3)
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	• 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
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	• Same as above	
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 placebo		

BP = blood pressure; CVD = cardiovascular disease; HUI-3 = Health Utilities Index Mark 3 (Health Utilities Inc., Dundas, Ontario, Canada)[7]; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

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 of 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, are collected at the clinic site level. The estimated allocation of these resources for each therapy per patient is recorded for each clinic participating in ACCORD. Data on medications, tests, and medical supplies for the therapies are derived from the main trial. Research-related costs will not be included in the cost calculations, so that the cost comparisons between therapies will be for healthcare delivery costs only.

Inpatient care. Data on hospitalization are collected at the patient level. Costs for hospital care represent a disproportionate share of direct medical costs (70%–80%) and show extreme variability.[14] Therefore, it is important to collect hospitalization data from all CEA study patients to derive cost estimates with reasonably narrow confidence intervals. We collect hospital admission data primarily using ACCORD forms and through available administrative data systems. Research staff members at each clinic site obtain copies of the discharge summary for each hospital admission for those patients who participate in the CEA and

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 2×2 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.[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.[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: $\text{ICER}_{\text{CEA}} = (\text{Mean Cost}_{\text{Treatment A}} - \text{Mean Cost}_{\text{Treatment B}})/(\text{Mean Effect}_{\text{Treatment A}} - \text{Mean Effect}_{\text{Treatment B}})$;
- Formula B: $\text{ICER}_{\text{Cost-Utility Analysis}} = (\text{Mean Cost}_{\text{Treatment A}} - \text{Mean Cost}_{\text{Treatment B}})/(\text{Mean QALYs Gained}_{\text{Treatment A}} - \text{Mean QALYs Gained}_{\text{Treatment B}})$

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.[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,[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.[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[19] and statin therapy[20] on HRQOL, there is some concern that combined statin-fibrate therapy may have

serious adverse effects.[21] Our ability to test for interaction effects of the ACCORD interventions on HRQOL will be informative.

Third, the target levels of HbA_{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_{1c} and systolic blood pressure than those targeted in ACCORD. Because the effects of glycemic and blood pressure control on HRQOL may vary and because the effects may increase at more stringent levels of HbA_{1c} or systolic blood pressure control, ACCORD's results 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 interventions have methodologic limitations, such as a lack of a control group, selection bias, and uncontrolled regression to the mean.[20] Moreover, no previous studies have assessed the impact of targeted HbA_{1c} levels <6%, systolic blood pressure levels <120 mm Hg, or the value of fibrate treatment 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 retrospectively. By building in a cost-effectiveness study prospectively, ACCORD will make a major contribution to estimates of cost-effectiveness. Similarly, few previous studies, and none that used empiric analyses, have provided economic analyses that take into account the potential synergistic interactions when care is intensified across multiple clinical domains (HbA_{1c} and systolic blood pressure, HbA_{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 investigation of differences over a prolonged period. In the past, only the United Kingdom Prospective Diabetes Study (UKPDS) 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 rigorous.[22]

In summary, the HRQOL and CEA measures are integrated into the core ACCORD study design. These substudies 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 design 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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