ONLINE APPENDIX

"The Cost-Effectiveness of Continuous Glucose Monitoring in Type 1 Diabetes"

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The purpose of this technical appendix is to provide more detail for readers interested in understanding the structure and assumptions of the lifetime complication model for type 1 diabetes. The basic structure of the model is depicted in Figure 1 of the manuscript. For the purposes of this analysis, we simulate the lifetime of cohorts of subjects assigned to CGM or traditional self-monitoring of blood glucose. All simulated subjects run through eight disease modules and a mortality module at one year cycles. Simulated patients can experience multiple disease states and continue to cycle through the model till death occurs.

The microvascular complication modules include retinopathy, nephropathy, and neuropathy. The retinopathy module follows patients across transitions from normal vision, to background diabetic retinopathy, to intermediate states (proliferative diabetic retinopathy and macular edema), and to blindness. Patients can become blind from proliferative diabetic retinopathy and from macular edema. The neuropathy module follows patients across transitions from normal peripheral nerves, to neuropathy, to foot ulcers, to amputation. The nephropathy module follows patients across transitions from normal renal function, to micoalbuminuria, to proteinuria, to end-stage renal disease requiring dialysis.

For all microvascular complications, we used the original DCCT prediction models for intermediate complications that relate HbA_{1C} with the cumulative probability of developing these intermediate complications (courtesy Richard Eastman).(1; 2) Because of the similarities in the distributions of baseline HbA_{1C} levels in the trial populations to that of the intensive arm of DCCT, we used the equations developed for the intensive arm of DCCT. The disease free survival formulas from DCCT have the following functional form

$$\text{Disease Free Survival} = \text{Exp}(-\text{Exp}(B_o)*((\text{HbA1c})\hat{}B_1)*((\text{Duration of diabetes})\hat{}A_1))$$

For the transitions from intermediate to end-stage microvascular complications, we used annual probabilities found in the literature.(3-8)

All probabilities for macrovascular complications come from the United Kingdom Prospective Diabetes Study (UKPDS No.68). The modules for ischemic heart disease, myocardial infarction, and stroke are all single complication equations with no intermediary transition states.

The complication states that were assigned utilities for this analysis included blindness, end-stage renal disease, foot ulcer, lower extremity amputation, myocardial infarction or arrest, angina (Ischemic heart disease), and stroke. We used the average utilities for these states obtained from trial subjects. The myocardial infarction utility comes from the utility for angina. We applied the same average complication utility to control and intervention patients. Quality adjusted life years (QALYs) were calculated using the minimum method. In this method, the lowest utility score for any experienced health state (treatment or complication state) is used for a given year. For example, if a patient experienced a myocardial infarction and a stroke in a given year while using CGM, the utility for that year would be 0.36 which is the lower utility of the three states. If a patient had no complications in a given year the patient receives an everyday utility for life with CGM or SMBG. The total QALY for a given patient is the sum of each year's QALY for the patient's lifetime.

Appendix Table 1. Within-Trial Cost Assumptions

Within Trial Cost Assumptions		
Item	**Unit Cost**	**Source**
Direct CGM Personnel Costs		
Time of investigators/coordinators devoted to training/counseling patient on RT-CGM (sum of time over 6 months)	$51.30/hour ($64/hour for pediatrician, $30/hour for nurse)	Bureau of Labor Statistics http://www.bls.gov/oes/current/oes_nat.htm#b31-0000
Direct Medical Care Costs		
Pump user (infusion set, meter control solution, glucagon)	$1371/year	See Appendix Table 3
MDI user (syringes, meter control solution, glucagon)	$419/year	See Appendix Table 3
Average daily insulin use over 6 months	$0.09/unit of insulin	$91.88/1000 units Lantus Red Book 2007
Average daily fingerstick use over 6 months	$0.23/lancet (assume 6 used during trial) $0.92/test strip	$46.69/200 lancets $46.12/50 test strips Red Book 2007
Daily RT-CGM sensor costs	$13.85/day	See Appendix Table 2
Number of office visits (6 months)	$331	Diabetes Care 2008;31:596-615(9)
Number of ER visits (6 month)	$696	Diabetes Care 2008;31:596-615(9)
Number of 911 calls (6 month)	$415 ($381-$450)	*Ambulance Providers: Costs and Expected Medicare Margins Vary Greatly.* GAO-07-383. Washington, D.C.: May 2007.
Number of hospitalizations (6 month)	$4897/hospitalization	http://www.cms.hhs.gov/HealthCareConInit/02_Hospital.asp#TopOfPage
Number of after hour visits (6 month)	$331	Diabetes Care 2008;31:596-615(9)
Indirect Costs		
Hours per day devoted to diabetes care-patient (6 months)	Age and sex specific median hourly wage	Bureau of Labor Statistics 2007
Days of work/school missed due to diabetes- patient* (6 months)	Age and sex specific median hourly wage	Bureau of Labor Statistics 2007
Hours per day devoted to diabetes care-primary caregiver (6 months)	Age and sex specific median hourly wage	Bureau of Labor Statistics 2007
Days of work/school missed due to diabetes*- primary caregiver months)	Age and sex specific median hourly wage	Bureau of Labor Statistics 2007
Hours per day devoted to diabetes care-secondary caregiver (6 months))	Age and sex specific median hourly wage	Bureau of Labor Statistics 2007
Days of work/school missed due to diabetes*- secondary caregiver (6 months))	Age and sex specific median hourly wage	Bureau of Labor Statistics 2007

* Includes whole days missed and days of underperformance where 50% of a day is lost.

Appendix Table 2. Optimal Protocol Continuous Glucose Monitoring Cost Assumptions

	Medtronic	Abbott	Dexcom	Average daily CGM cost
	Guardian	**Freestyle Navigator**	**Seven**	
Initial Kit	$1,339 with 4 sensors	$1,250 with 0 sensors	$600 with 0 sensors	
Sensors	$350 for Box of 10	$450 for Box of 6	$240 for Box of 4	
FDA approved sensor replacement frequency	3 days	5 days	7 days	
Daily Sensor Cost	$11.67	$15.00	$8.57	
Transmitter Cost	$550	--	$400	
Transmitter Lifespan	1 year	2 years	1.5 years	
Transmitter Daily Cost	$1.51	--	$0.80	
Receiver Cost	0	--	$600	
Receiver Lifespan	4 years	2 years	1.25 years	
Receiver Daily Cost	0	--	$1.32	
Year 1 Daily Cost	$14.95	$16.71	$9.89	$13.85
Year 2 Daily Cost	$13.18	$16.71	$10.11	$13.33
Year 3 Daily Cost	$13.18	$16.71	$10.62	$13.50

* CGM= continuous glucose monitoring; FDA= Food and Drug Administration

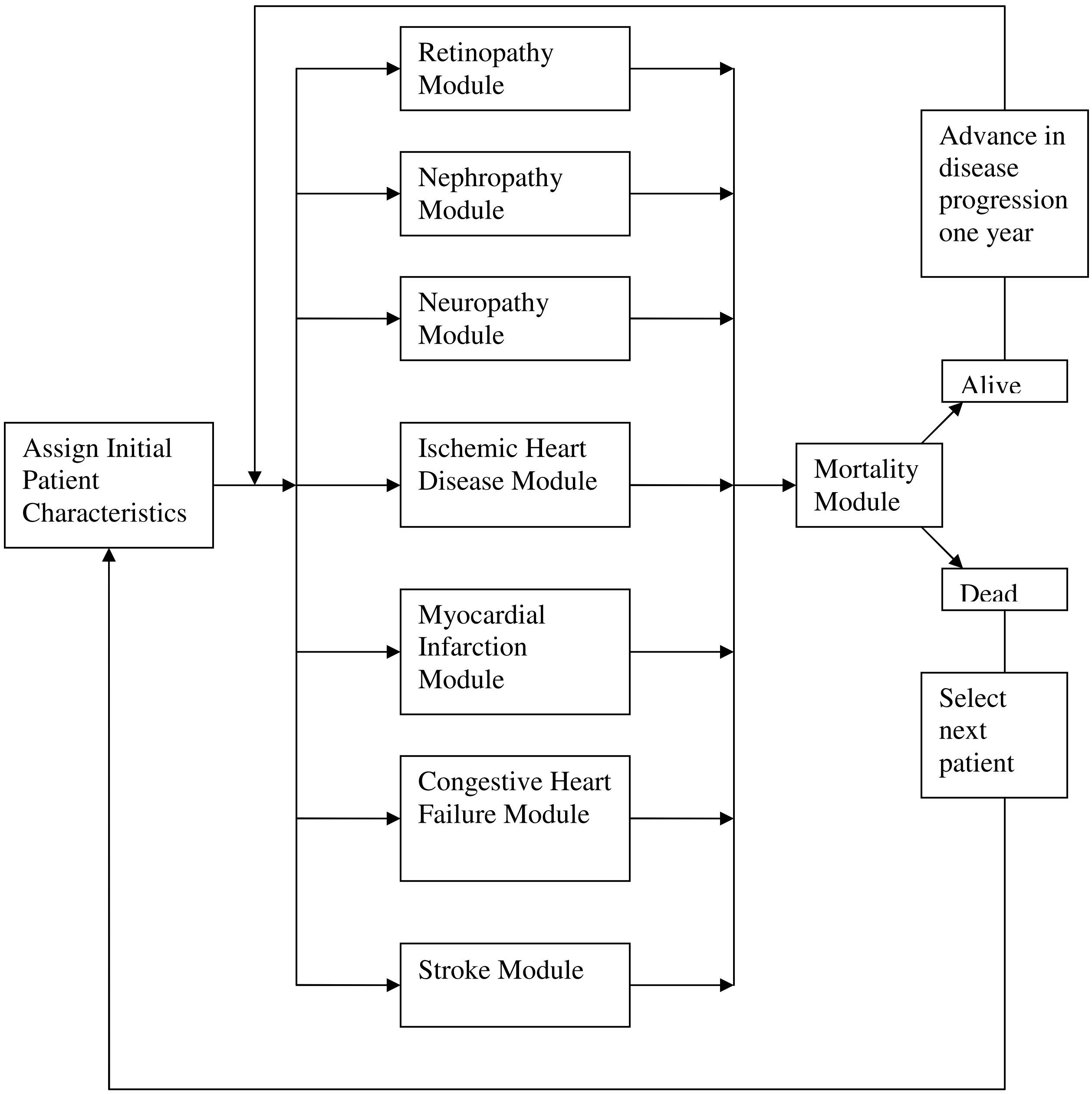
Appendix Table 3. Long-term cost-effectiveness analysis base case model assumptions

Definition	Base-Case Value (Range)		References
Demographics and clinical characteristics			
Age	HbA_{1C}≥7.0% cohort (43 (SD 12, Min 25, Max 73), HbA_{1C}<7.0% cohort (31 (SD 17, Min 8, Max 65))		Study population
Proportion women	HbA_{1C}≥7.0% cohort (56%), HbA_{1C}<7.0% cohort (53%)		Study population
Duration of diabetes	Age and gender specific duration of diabetes for both cohorts		Study population
Blood pressure	Non-diabetic values		NHANES
Cholesterol	Non-diabetic values		NHANES ; Wadwa 2005(10)
Body mass index	Age-gender based values		Study population
Smoking	Age-gender based values		Study Population
Impact of RT-CGM			
	Control	RT-CGM	
Glycosylated hemoglobin distributions, HbA_{1C}≥7.0% cohorts	Mean 7.6, SD 0.4, Min 6.7, Max 8.7	Mean 7.1, SD 0.4, Min 6.2, Max 8.8	Study adjusted results
Glycosylated hemoglobin distributions, HbA_{1C}<7.0% cohorts	Mean 6.8, SD 0.5, Min 5.8, 8.1	Mean 6.5, SD 0.5, Min 5.3, Max 7.7	Study adjusted results
Immediate quality of life (utility) distributions at end of 6 month trial, HbA_{1C}≥7.0% cohorts	Mean 0.8338, Variance 0.0005	Mean 0.8608, Variance 0.0017	Study adjusted results
Immediate quality of life (utility) distributions at end of 6 month trial, HbA_{1C}<7.0% cohorts	Mean 0.8400, Variance 0.0006	Mean 0.8935, Variance 0.0010	Study adjusted results
Annual probability of diabetic retinopathy progression			
No retinopathy to background diabetic retinopathy (BDR)	DCCT equation intensive glucose arm		Eastman 1997(1)
BDR to Macular edema	DCCT equation intensive glucose arm		Eastman 1997(1)
BDR to Proliferative diabetic retinopathy (PDR)	DCCT equation intensive glucose arm		Eastman 1997(1)
Macular edema to blindness with photocoagulation	0.0300		Javitt 1994(3), Vijan 2000(4), ETDRS 1991(11)
PDR to blindness with photocoagulation	0.0148		Javitt 1994(3), Vijan 2000(4), ETDRS 1991(11)
Annual probability of diabetic nephropathy progression			
Microalbuminuria	DCCT equation intensive glucose arm		Eastman 1997(1)
Microalbuminuria to Gross proteinuria	DCCT equation intensive glucose arm multiplied by 3 to obtain conditional probability		Eastman 1997(1), UKPDS 64(12)
Gross proteinuria to end-stage renal disease	0.0042 (0-11 years) 0.0385 (12-24 years) 0.0740 (25 years-).		Humphrey 1989(5)
Annual probability of diabetic neuropathy progression			
Diabetic neuropathy	UKPDS control arm- DCCT equation		Eastman 1997(1)
Neuropathy to foot ulcer	0.0075, without neuropathy 0.0435, with neuropathy		Young 1994(6), Gregg 2004(7)
Foot ulcer to amputation	0, no risk factors		Peters 2001(8)

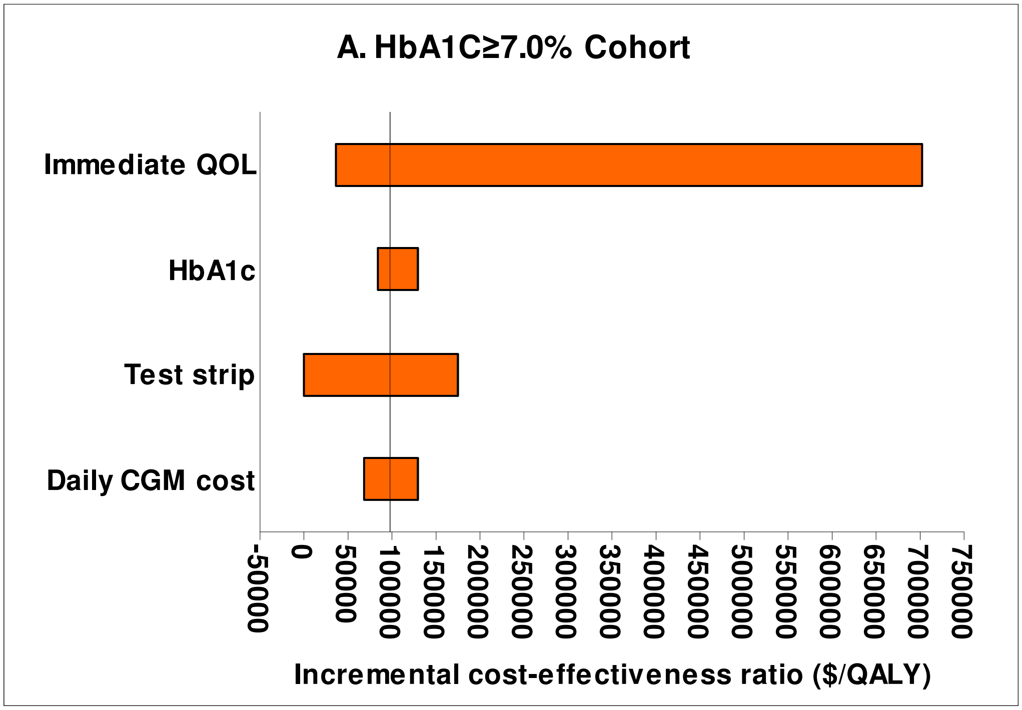
	0, neuropathy 0.0067, neuropathy with foot deformity 0.0697, history of foot ulcer	
Annual probability of cardiovascular complications		
Ischemic heart disease	UKPDS equation	Clarke 2004(13)
Congestive heart failure	UKPDS equation	Clarke 2004(13)
Myocardial infarction	UKPDS equation	Clarke 2004(13)
Stroke	UKPDS equation	Clarke 2004(13)
Annual probability of major hypoglycemic event		
Hypoglycemia requiring medical care	0.26	Study population
Annual probability of death		
First event mortality	UKPDS equation	Clarke 2004(13)
Diabetes mortality	UKPDS equation	Clarke 2004(13)
Background mortality	National Vital Statistics Life Tables ((non-cardiovascular death rate for non-diabetics)*2.75)	CDC, National Center for Health Statistics, 2004(14)
Other assumptions		
Prevalence of foot deformity	0.37 (0.30-0.45)	Rith-Najarian 1992(15)
Prevalence of atrial fibrillation	Gender and age specific prevalence from Kaiser population	Go 2001(16)
Costs, $		
RT-CGM costs		
CGM training costs (Physician and nurse educator)	246 (51-512) (5 hours (1-10) hours: 30% time of physician (64/hour), 100% time of nurse (30/hour))	Study results
Daily CGM costs	13.85 (year 1), 13.33 (year 2), 13.50 (year 3) for intervention group	See Appendix Table 2
Days of CGM use per year	313 (6/7 days per week) for intervention group	See Appendix Table 2
Glucometer costs		
Lancets	0.23/lancet	Redbook 2008
Lancets use per year	12	
Test strips	0.92/strip	Redbook 2008
Test strips use per year	HbA_{1C}≥7.0% cohort (2,190 control; 2,008 intervention); HbA_{1C}<7.0% cohort (2,555 for both arms)	Study adjusted results
Pump and syringe costs		
Pump costs	1,371/year	Study population
Proportion using pumps, %	HbA_{1C}≥7.0% cohort (84), HbA_{1C}<7.0% cohort (86)	Study population
Multiple daily injections, syringe cost	0.26/needle/syringe	Redbook 2008
Syringe utilization	4 syringes/day	
Routine laboratory testing		
Glycosylated hemoglobin	13.56 (11.50-15.00)	2004 Medicare fee schedule
Lipid panel	18.19 (17.00-19.50)	
Urine microalbuminuria	6.27 (5.00-7.50)	
Drugs costs		

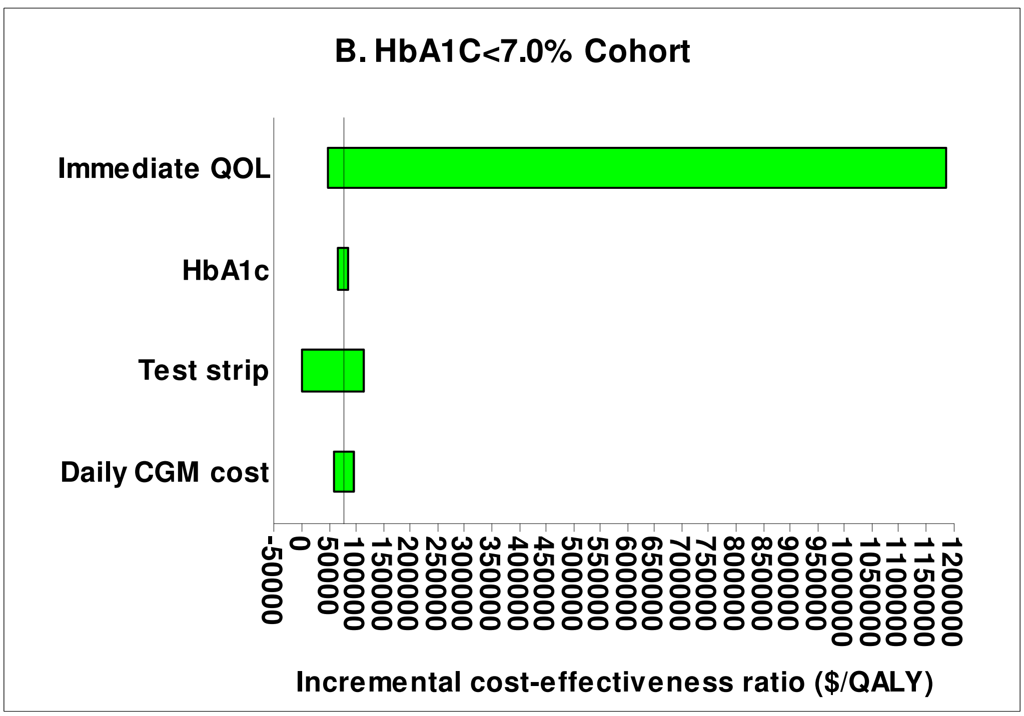
Insulin	$91.88/1,000 units	Redbook 2008
Insulin use	$HbA_{1C} \geq 7.0\%$ cohort (46 units/day), $HbA_{1C} < 7.0\%$ cohort (43 units/day)	
Eye related costs		
Macular edema	916 (event), 90 (state)	O'Brien 2003(17)
Proliferative diabetic retinopathy	1,013 (event), 90 (state)	
Blindness	4,438	
Kidney related costs		
Microalbuminuria	76 (event), 18 (state)	O'Brien 2003(17)
Proteinuria	81 (event), 26 (state)	
ESRD	44,577	
Neuropathy related costs		
Neuropathy	448	O'Brien 2003(17)
Foot ulcer care	9,501 (8,501-10,501)	Diabetes in America(18)
Lower extremity amputation	36,548 (event), 1,314 (state)	O'Brien 2003(17)
Cardiovascular complication costs		
Acute myocardial infarction	36,560 (event), 2,020 (state)	O'Brien 2003(17)
Angina	7,253 (event), 1,874 (state)	
Ischemic stroke	48,414 (event), 16,157 (state)	
Hypoglycemia costs		
Hypoglycemic event requiring medical attention	1,087	Bullano 2008(19)
Indirect costs		
Patient and caregiver time	Age and sex specific median hourly wage	Bureau of Labor Statistics 2007
Utilities		
Quality of life at end of trial	$HbA_{1C} \geq 7.0\%$ cohort (0.86 intervention and control arm); $HbA_{1C} < 7.0\%$ cohort (0.84 control arm)	Subject response-overall cohort
Blindness	0.55	Subject response-overall cohort
End-stage renal disease	0.51	Subject response-overall cohort
Foot ulcer	0.75	Redekop 2004(20), Tennvall 2001(21)
Lower extremity amputation	0.74	Subject response-overall cohort
Myocardial infarction or arrest	0.75	Subject response-overall cohort
Angina (Ischemic heart disease)	0.75	Subject response-overall cohort
Stroke	0.36	Subject response-overall cohort
Discount Rate, %	3 (3-5)	

Appendix Figure 1. Model of Diabetes-Related Complications.



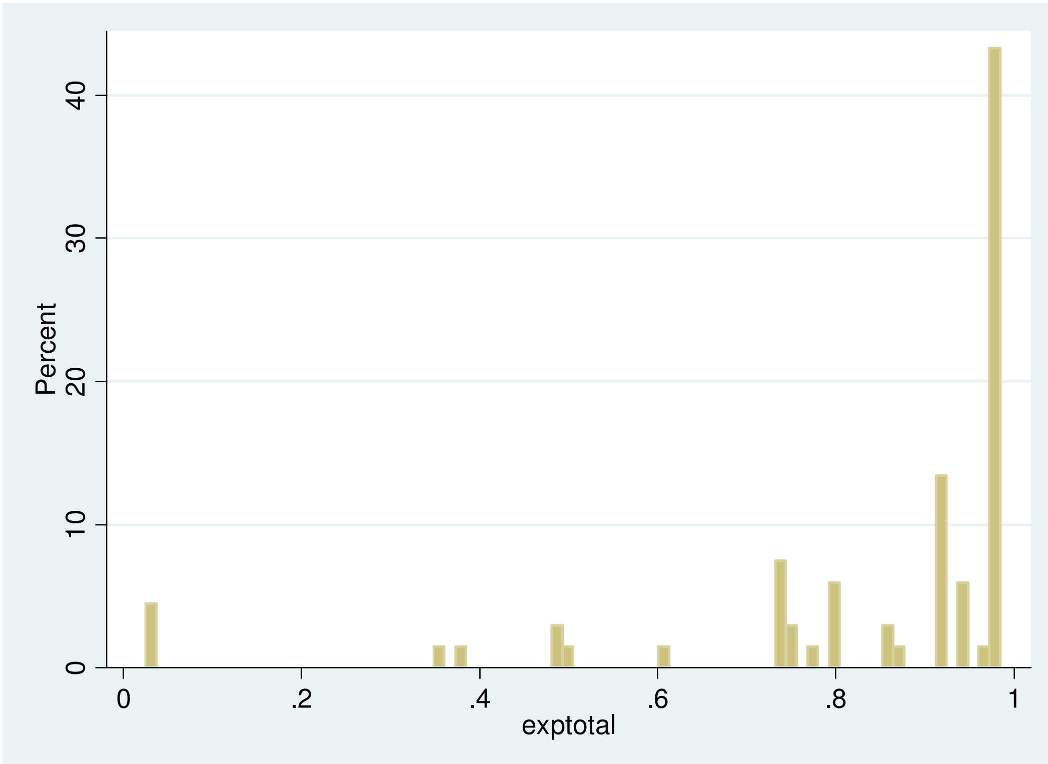
Appendix Figure 2. One-way sensitivity analyses for lifetime analysis





Immediate quality of life (QOL) effect range: 0.1 improvement in utility to no improvement in utility. HbA1c difference range: 1% difference to no difference. Test strip range: 2 test strips per day with continuous glucose monitor (CGM) to 10 test strips per day. Daily CGM cost range: $9.89/day to $16.71/day. QALY = quality-adjusted life year.

Appendix Figure 3. Baseline Time Tradeoff Utilities for A1C<7.0 Cohort Subjects Randomized to the Continuous Glucose Monitor



This figure displays the distribution of baseline experienced time-tradeoff utilities for patients in the treatment group of the A1C<7.0 cohort. The y-axis is the proportion of individuals within utility categories and the x-axis displays the utility on a 0 to 1 scale.

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