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OPTIMAL THERAPY REPORT

COMPUS

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Cost-Effectiveness of Blood Glucose Test Strips in the Management of Adult Patients with Diabetes Mellitus

Supporting Informed Decisions

À l'appui des décisions éclairées

This report was prepared by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS), a service of the Canadian Agency for Drugs and Technologies in Health (CADTH).

This report, which was prepared with the advice and assistance of economic and clinical experts, is a comprehensive review of the public literature available to CADTH. The authors have also considered input from other stakeholders. The information in this report should not be used as a substitute for the application of professional judgment in any decision-making process. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

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ABBREVIATIONS

A1C	glycosylated hemoglobin
BMI	body mass index
CAC	COMPUS Advisory Committee
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	confidence interval
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CORE	Center for Outcomes Research
DiGEM	Diabetes Glycaemic Education and Monitoring
EQ-5D	EuroQol 5-dimension index
HRQoL	health-related quality of life
ICD-9	International Classification of Diseases, 9th edition
ICUR	incremental cost-utility ratio
QALY	quality-adjusted life-year
QPC	quality priority conditions
RCT	randomized controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
SMBG	self-monitoring of blood glucose
UKPDS	United Kingdom Prospective Diabetes Study

GLOSSARY

A1C: A glycosylated form of hemoglobin, formed by the attachment of sugars to the hemoglobin molecule when glucose levels are elevated. A1C levels increase with the average concentration of glucose in the blood.

Absolute risk reduction: The difference in event rates between treatment and control groups. It is the inverse of the number needed to treat.

Bootstrapping: A technique that is used to approximate the accuracy (e.g., standard error, confidence interval) of a statistical estimate.[1]

Cohort study: A longitudinal observational study (prospective or retrospective) in which participants are selected according to exposure status (before the outcome is determined), followed over time, and the outcomes for each group compared.

Confidence interval: The interval in which a population parameter lies, based on a random sample of the population. The most commonly reported confidence interval is the 95% confidence interval.

Congestive heart failure: A condition in which abnormal cardiac structure or function is responsible for the inability of the heart to fill with or eject blood at a rate to meet the requirements of the metabolizing tissues.

Cost-effectiveness acceptability curve: A method used to represent the uncertainty of cost-effectiveness results. A cost-effectiveness acceptability curve presents the probability that one treatment is more cost-effective than another treatment, as a function of willingness to pay for one additional unit of effectiveness (or efficacy).

Diabetes mellitus: A group of common metabolic disorders characterized by hyperglycemia and caused by insufficient insulin secretion, reduced insulin sensitivity of target tissues, or both.

Discounting: A method used to adjust future costs and benefits to their present market value. For instance, the present value of $100 one year from now (assuming a discount rate of 5%) is equal to $100/(1 + 0.05)^1 = \$95.24$.

Effectiveness: The extent to which an intervention, procedure, regimen, or service produces the intended outcomes when deployed under routine ("real world") circumstances.

Efficacy: The extent to which an intervention, procedure, regimen, or service produces a beneficial outcome under ideal circumstances (e.g., in a randomized controlled trial).

Funnel plots: A graphical method used to detect publication bias. Funnel plots are simple scatter plots where treatment effects estimated from individual studies are plotted on the horizontal axis against some measure of study size on the vertical axis.

Gestational diabetes mellitus: Defined as glucose intolerance with first onset during pregnancy; usually a temporary condition.

Health-related quality of life: A broad theoretical construct developed to explain and organize measures concerned with the evaluation of health status, attitudes, values, and perceived levels of satisfaction and general well-being with respect to either specific health conditions or life as a whole from the individual perspective.

Heterogeneity (I^2): This statistic describes the degree of variation, as a percentage, between the results of individual studies within a meta-analysis.

Hyperglycemia: A qualitative term used to describe blood glucose that is above the normal range.

Hypoglycemia: A qualitative term used to describe blood glucose that is below the normal range. Definitions vary across studies, although one or more of the following is usually required to define a hypoglycemic event: autonomic or neuroglycopenic symptoms characteristic of low blood glucose (e.g., trembling, sweating, hunger, confusion, weakness) that respond to carbohydrate intake, and/or a plasma glucose level below a specific value (threshold is usually between 3.4 mmol/L to 4.0 mmol/L).

Ischemic heart disease: Heart disease, due to inadequate blood perfusion of the myocardium, which causes an imbalance between oxygen supply and demand.

Less intensive education: Patients were trained on the blood glucose meter but were not provided with instructions regarding self-interpretation and application of their self-monitored blood glucose results, or the educational components of the trial were not specified.

Meta-analysis: Statistical synthesis of the results of individual studies that examine the same question to produce a single estimate of effect.

More intensive education: Patients were provided with training in the self-interpretation and application of their self-monitored blood glucose results to facilitate dietary and lifestyle modifications.

Myocardial infarction: The death of a portion of heart muscle resulting from a sudden loss of blood supply due to occlusive coronary artery thrombus, atherosclerotic plaque, vasospasm, inadequate myocardial blood flow (e.g., hypotension), or excessive metabolic demand. Also called heart attack.

Number needed to treat: The number of patients who need to be treated with a new treatment rather than the standard (control) treatment in order for one additional patient to benefit. It is calculated as the inverse of the absolute risk reduction.

Overall hypoglycemia: Overall hypoglycemia is defined by either symptoms or signs of hypoglycemia and/or blood glucose < 4 mmol/L.

Quality-adjusted life-year (QALY): A health outcome measure that combines both quantity (mortality) and quality of life (morbidity). This measure enables comparisons across diseases and programs.

Randomized controlled trial: A prospective experimental study designed to test the efficacy of an intervention in which patients are randomly allocated to either a treatment group or the control group.

Relative risk: The ratio of the absolute risk of a disease among the exposed group to the absolute risk of the disease among the unexposed group in an epidemiological study.

Standard deviation: A measure of the variability or spread of the data.

Severe hypoglycemia: An event with characteristic hypoglycemic symptoms requiring assistance of another person.

SIGN 50: A quality assessment tool developed for the assessment of the methodological quality of randomized control trials and observational studies.

Systematic review: A summary of the medical literature that uses explicit methods to identify, select, appraise, and analyze studies relevant to a particular clinical question.

Type 1 diabetes mellitus: Diabetes characterized by a lack of insulin secretion caused by pancreatic beta cell destruction. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.

Type 2 diabetes mellitus: Diabetes characterized by insulin resistance and varying degrees of insulin deficiency, especially as the diabetes progresses.

Utility: A quantitative expression of an individual's preference for a particular health state.

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1 INTRODUCTION

In March 2004, the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) was launched by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) — now the Canadian Agency for Drugs and Technologies in Health (CADTH) — as a service to federal, provincial, and territorial jurisdictions and other stakeholders. COMPUS is a nationally coordinated program, funded by Health Canada.

The goal of COMPUS is to optimize drug-related health outcomes and cost-effective use of drugs by identifying and promoting optimal drug prescribing and use. Where possible, COMPUS builds on existing applicable Canadian and international initiatives and research. COMPUS goals are achieved through three main approaches:

- identifying evidence-based optimal therapy in prescribing and use of specific drugs
- identifying gaps between evidence-based optimal therapy and clinical practice, then proposing evidence-based interventions to address these gaps
- supporting the implementation of these interventions.

Direction and advice are provided to COMPUS through various channels, including the following:

- the COMPUS Advisory Committee (CAC): includes representatives from the federal, provincial, and territorial health ministries and related health organizations
- the COMPUS Expert Review Committee (CERC): an advisory body that makes recommendations related to the identification, evaluation, and promotion of optimal drug prescribing and use in Canada
- stakeholder feedback.

1.1 COMPUS Expert Review Committee

The COMPUS Expert Review Committee (CERC) consists of eight Core Members appointed to serve for all topics under consideration during their term of office and three or more Specialist Experts appointed to provide their expertise in recommending optimal therapy for one or more specific topics. For the insulin analogues and blood glucose test strips, four endocrinologists / diabetes specialists were appointed as Specialist Experts. Two of the Core Members are Public Members who bring a lay perspective to the committee. The remaining six Core Members hold qualifications as physicians, pharmacists, or health economists or have other relevant qualifications with expertise in one or more areas such as, but not limited to, family practice, internal medicine, institutional or community clinical pharmacy, pharmacoeconomics, clinical epidemiology, drug utilization expertise, methodology, affecting behaviour change (through health professional and/or patient and/or policy interventions), and critical appraisal. The Core Members including Public Members are appointed by the CADTH Board of Directors.

The mandate of CERC is advisory in nature and consists of providing recommendations and advice to CADTH's COMPUS Directorate on assigned topics that relate to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada. The overall perspective used by CERC members in producing recommendations is that of public health care

policy-makers in pursuit of optimizing the health of Canadians within available health care system resources.

2 ISSUE

The COMPUS Advisory Committee (CAC) has identified management of diabetes mellitus as being a priority area for optimal practice initiatives based on the following criteria:

- large deviations from optimal utilization (overuse or underuse)
- size of patient populations
- impact on health outcomes and cost-effectiveness
- potential to effect change
- benefit to multiple jurisdictions
- measurable outcomes.

Within diabetes mellitus management, optimal use of blood glucose test strips in patients with type 1, type 2, and gestational diabetes mellitus was identified by CAC as a priority topic.

Despite widespread use, there is controversy regarding the benefits of self-monitoring of blood glucose (SMBG), especially in patients with type 2 diabetes mellitus not using insulin.[2-5] Moreover, the optimum frequency of testing has not been defined in any population.[6,7] A need exists for the identification of clinical and economic evidence relating to the optimal prescribing and use of SMBG. Costs associated with SMBG are rising because of the increasing prevalence of diabetes in Canada and higher rates of self-monitoring.[8] In 2005/2006, the Nova Scotia Seniors' Pharmacare Program spent $4 million on blood glucose test strips, approximately 60% of which was spent on beneficiaries who were not using insulin agents.[9] In Saskatchewan, of the $6.5 million spent on diabetic testing supplies in 2001 (most of it on blood glucose test strips), approximately half was for people who were not using insulin agents.[10] Evidence relating to the optimal prescribing and use of SMBG may assist policy decision-makers, consumers, and health care providers in making informed decisions for patients with type 1, type 2, and gestational diabetes mellitus.

2.1 Diabetes Mellitus

Diabetes mellitus is a chronic disease characterized by the body's inability to produce sufficient insulin and/or properly use insulin.[11] Type 1 diabetes mellitus occurs in approximately 10% of patients with diabetes, and it results when little or no insulin is produced by the body.[12] Type 2 diabetes mellitus is a metabolic disorder caused by varying degrees of insulin resistance; the body usually produces insulin but is unable to use it properly.[12] When inadequately managed, diabetes is likely to result in poor glycemic control.[11] Impaired glycemic control, if prolonged, may result in diabetes-related complications (e.g., ischemic heart disease, stroke, blindness, end-stage renal disease, lower limb amputation).[13,14]

The global prevalence of diabetes is estimated to be 246 million and is projected to increase to 380 million by 2025.[15] In 2004/2005, approximately 1.8 million (5.5%) Canadians aged 20 years and older had diagnosed diabetes.[16] However, it is estimated that 2.8% of the general adult population

has undiagnosed type 2 diabetes mellitus,[6] and the true prevalence of diabetes may approach 2.0 million.[17]

2.1.1 Management of blood glucose levels in diabetes mellitus

One goal of diabetes mellitus management is to maintain control of blood glucose levels to reduce the patient's risk of developing long-term diabetes-related complications. Lifestyle modifications (i.e., weight control, proper nutrition, and adequate exercise), the use of medications (e.g., insulin and oral antidiabetes drugs), and SMBG are recommended approaches in improving glycemic control.[6] This project focuses on the use and frequency of blood glucose testing by patients with diabetes.

2.1.2 Technology description — self-monitoring of blood glucose

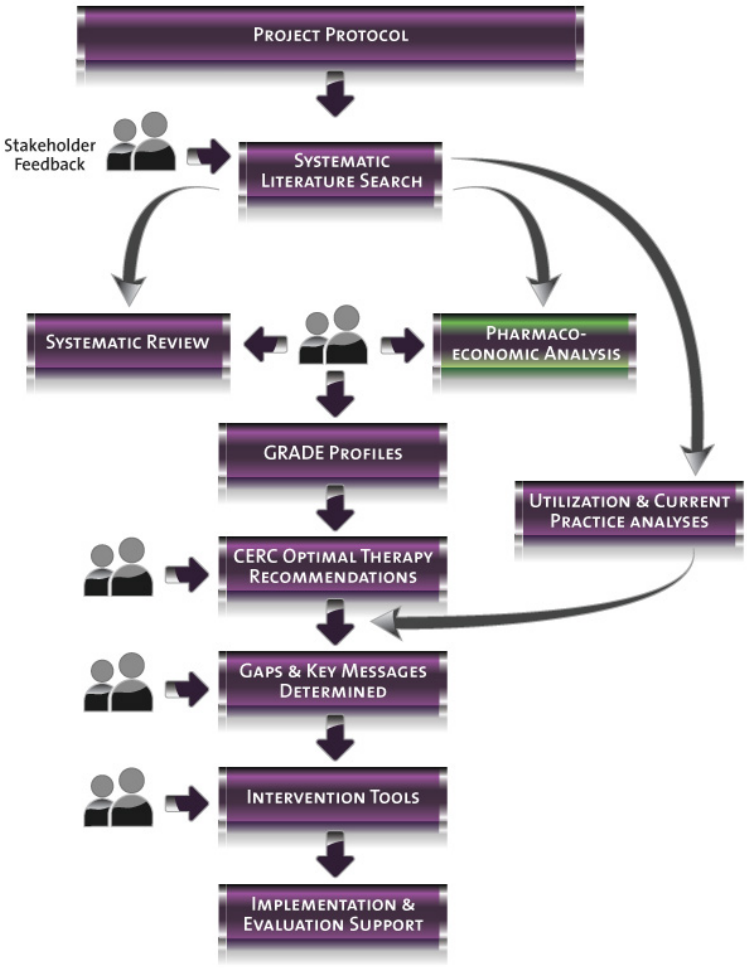
The purpose of SMBG is to collect detailed information about glucose levels across various time points each day and take appropriate action should those levels be outside the desired range.[8,18] SMBG requires that patients prick their finger with a lancet device to obtain a small blood sample (0.3 µL to 5 µL).[8,18] The blood is applied to a reagent strip or blood glucose test strip, and glucose concentration is determined by inserting the blood-laden strip into a reflectance photometer or an electrochemical sensor.[8] Results, based on an automated reading, are available from the photometer within 5 to 30 seconds.[8] The results can be stored in the glucose meter's electronic memory or recorded in the patient's logbook. It has been suggested that patients can adjust food intake, physical activity, and pharmacotherapy in response to their blood glucose readings and thus are better able to maintain optimal glycemic control on a day-to-day basis.[8,18]

3 PROJECT OVERVIEW

Once a topic is selected, COMPUS undertakes activities related to key areas in the COMPUS procedure. CAC provides advice and guidance throughout the process, from topic identification through to supporting interventions and evaluation tools. CERC, as described in Section 1.1, provides expert advice and recommendations on the topic area relating to the identification, evaluation, and promotion of optimal prescribing and use of drugs. A broad range of stakeholders are invited to provide feedback at various stages in the COMPUS process.

To identify and promote the implementation of evidence-based and cost-effective optimal therapy in the use of blood glucose test strips, COMPUS follows the process outlined in the flow chart to the right.

This report represents the draft pharmacoeconomic analysis for stakeholder feedback.



4 METHODS

Prior to conducting this economic analysis, a systematic review[19] was conducted to identify primary studies that compared SMBG with no SMBG, or different frequencies of SMBG, in patients with diabetes. Results from this systematic review are presented in detail elsewhere.[19] In general, this systematic review elicited few studies that explored the effect of SMBG in patients with insulin-treated diabetes. However, the evidence was more robust for patients with non–insulin-treated type 2 diabetes mellitus.

The current analysis reports clinical- and cost-effectiveness findings for patients with:

- non–insulin-treated type 2 diabetes mellitus, and
- insulin-treated type 2 diabetes mellitus.

An economic evaluation of SMBG in patients with type 1 diabetes mellitus was not performed. This decision was based on the following considerations:

- A systematic review of the literature identified only three studies that compared the effect of SMBG on glycemic control: one small crossover randomized controlled trial) (RCT)[20] (n = 25) and two database studies;[21,22] the three studies were deemed to be of low methodological quality when assessed with the Scottish Intercollegiate Guidelines Network (SIGN) 50 instruments.[23,24]
- The systematic review did not identify any studies that assessed the impact of SMBG on prevention of severe hypoglycemic episodes. The incidence of severe hypoglycemia is higher in patients with type 1 diabetes mellitus, relative to those with type 2 diabetes mellitus.[25-27]
- There may be considerable variability among patients with type 1 diabetes mellitus. Patients with type 1 diabetes mellitus typically use multiple daily insulin injections;[6,28,29] consequently, they have more personal control over the modification and enhancement of insulin dosing regimens, in response to SMBG readings.
- The United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model,[30] the mathematical model that was used for other economic evaluations, is specific to patients with type 2 diabetes mellitus. Use of this model for patients with type 1 diabetes mellitus may underestimate the incidence of diabetes-related complications and, in-turn, bias cost-effectiveness estimates against SMBG.[31]
- The prevalence of type 1 diabetes mellitus is much lower than that of type 2 diabetes mellitus. Moreover, the incidence of type 2 diabetes is increasing at a much more rapid rate.[16]
- Patients with type 1 diabetes mellitus in Canada, in general, are not using blood glucose test strips in excess of clinical practice guidelines.[32] In privately funded drug plans in Canada in 2006, patients who are using insulin claimed, on average, 3.18 test strips per day. In the Ontario Drug Benefits Program (ODBP) in 2006, patients claimed, on average, 2.76 test strips per day.[32]

Also, a cost-effectiveness evaluation of SMBG in patients with gestational diabetes mellitus was not performed. Insufficient evidence precluded such an evaluation from being conducted.

4.1 Type of Evaluation

An incremental cost-utility analysis of SMBG using blood glucose test strips, compared with not performing SMBG, was conducted using the UKPDS Outcomes Model.[30]

4.2 Model Structure and Validation

The UKPDS Outcomes Model[30] is a computer simulation model that is used to forecast long-term health outcomes and cost consequences in patients with type 2 diabetes mellitus (Figure 1). The risk of developing seven diabetes-related complications (i.e., fatal or non-fatal myocardial infarction, other ischemic heart disease, stroke, heart failure, amputation, renal failure, and blindness) is estimated based on data from 3,642 patients with type 2 diabetes mellitus who were enrolled in the UKPDS. Each equation[30] estimates the absolute risk of developing a complication, based on patient characteristics (e.g., age and sex, glycosylated hemoglobin [A1C], systolic blood pressure, cholesterol, body mass index [BMI], smoking history, history of diabetes-related complications). Simulations are based on a probabilistic discrete-time illness model with annual cycles.[30] Model projections have been validated against published clinical and epidemiological studies.[33]

4.3 Population

4.3.1 Patients with non–insulin-treated type 2 diabetes mellitus

Simulated patients with non–insulin-treated type 2 diabetes mellitus were reflective of those enrolled in the seven RCTs[5,34-39] that were included in the meta-analysis (Table 1).[5,34-39] Data on history of diabetes-related complications were not reported for patients in the seven RCTs.[5,34-39] The base-case analyses therefore assumed that patients with non–insulin-treated diabetes[5,34-39] had no history of diabetes-related complications. This assumption was based on the following rationale:

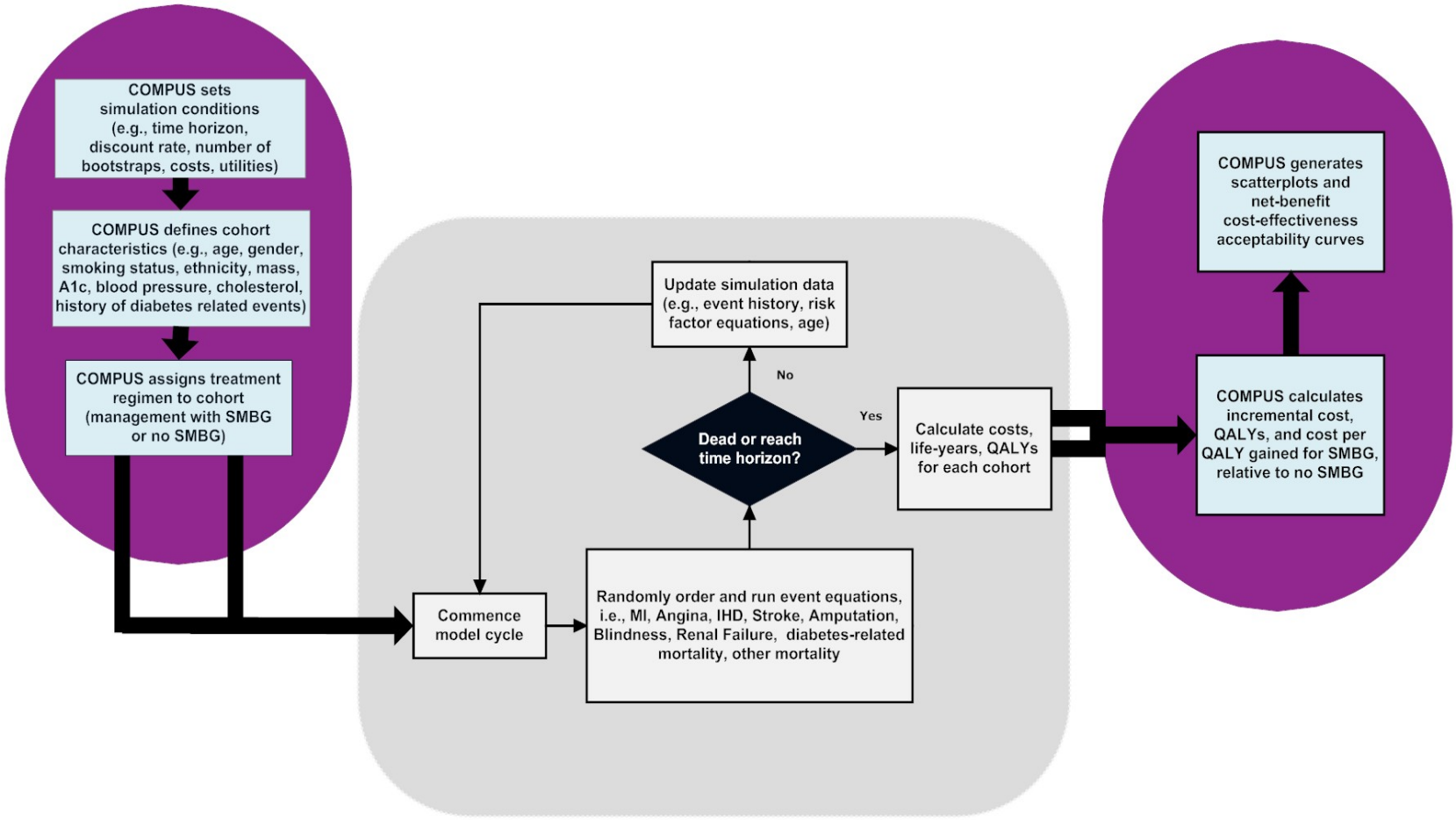
- Most RCTs[5,34-39] excluded patients with impending diabetes-related complications or history of serious disease, and
- • 1% of patients in Canada, with type 2 diabetes mellitus and aged 45 to 65 years have history of stroke, blindness, amputation, or renal disease.[40-42]

4.3.2 Patients with insulin-treated type 2 diabetes mellitus

Patients with insulin-treated diabetes are typically older and have more advanced diabetes than those with non–insulin-treated type 2 diabetes. Consequently, the simulated cohort in Table 1 was modified accordingly. It was assumed that patients with insulin-treated diabetes have a mean age of 63 years (standard deviation = 6.8 years of age), mean duration of diabetes of 12.8 years (standard deviation = 9.3 years), and a baseline A1C of 8.5% (standard deviation = 1.5%).[43] Karter et al.[21,43] found no significant differences between other patient characteristics (e.g., BMI, weight, blood pressure); consequently, these parameters were not modified. History of diabetes-related complications among patients is based on data from Karter et al.,[21,43] the Diabetes in Canada

Evaluation (DICE) Study,[42,44] and Ontario and Alberta Atlases[40,41] (i.e., 1% of patients were assumed to have history of blindness,[40-42] renal disease,[40-42] amputation;[40-43] 4%[45,46] and 2%[43] of patients had history of atrial fibrillation and peripheral vascular disease on diagnosis of diabetes; 2% had history of stroke; 9% had history of myocardial infarction;[40-42] 4% had congestive heart failure;[40-42] and 10% had a history of ischemic heart disease[40-42]). The average time since diabetes-related complication was obtained from the Ontario Diabetes Economic Model.[47]

Figure 1: Schematic of United Kingdom Prospective Diabetes Study Outcomes Model[30] and Its Application in the Current Economic Analysis



A1C = glycosylated hemoglobin; COMPUS = Canadian Optimal Medication Prescribing and Utilization Service; IHD = ischemic heart disease; MI = myocardial infarction; QALYs = quality-adjusted life-years; SMBG = self-monitoring of blood glucose.

Table 1: Baseline Characteristics of Simulated Cohort of Adults with Type 2 Diabetes Mellitus not Requiring Insulin Therapy	
Characteristic	**Baseline Value* (standard deviation)**
Patient demographics	
Age (years)[5,34-39]	60 (9.4)†
Duration of diabetes (years)[5,34-39]	4.6 (4.2)‡
Proportion male (%)[5,34-39]	56
Risk factors	
A1C (%)[5,34-39]	8.4 (1.2)†
Systolic blood pressure (mm Hg)[35,38]	139.4 (14.4)†
Total cholesterol (mmol/L)[38,48]	5.0 (1.12)†
High density lipoprotein cholesterol (mmol/L)[43,49]	1.06 (0.3)†
Mass (kg)[35,35,38,48,50]	84.9 (16.4)†
Height (m)[5,35,48]	1.65 (0.16)†
Ethnicity (%)	
White Caucasian[51,52]	92
Afro-Caribbean[51,52]	4
Asian-Indian[51,52]	4
History of smoking (%)	
Never[38]	37
Past[38]	51
Current[38]	12

A1C = glycosylated hemoglobin.
*Patient-level data were not available for randomized controlled trials included in the meta-analysis.[19] A random number generator (RNG) was used to estimate characteristics. The RNG sampled from probability distributions for each baseline characteristic, using respective mean and standard deviation. Baseline characteristics were not reported for patients at diagnosis[19]; consequently, the model assumes equivalent baseline characteristics at diagnosis.
† RNG sampled from a normal distribution.
‡ RNG sampled from a gamma distribution; gamma distribution confined to be positive, as duration of diabetes ≥ 0 years.

4.4 Comparators

SMBG was compared with no SMBG in the management of patients with non–insulin-treated and insulin-treated type 2 diabetes mellitus.

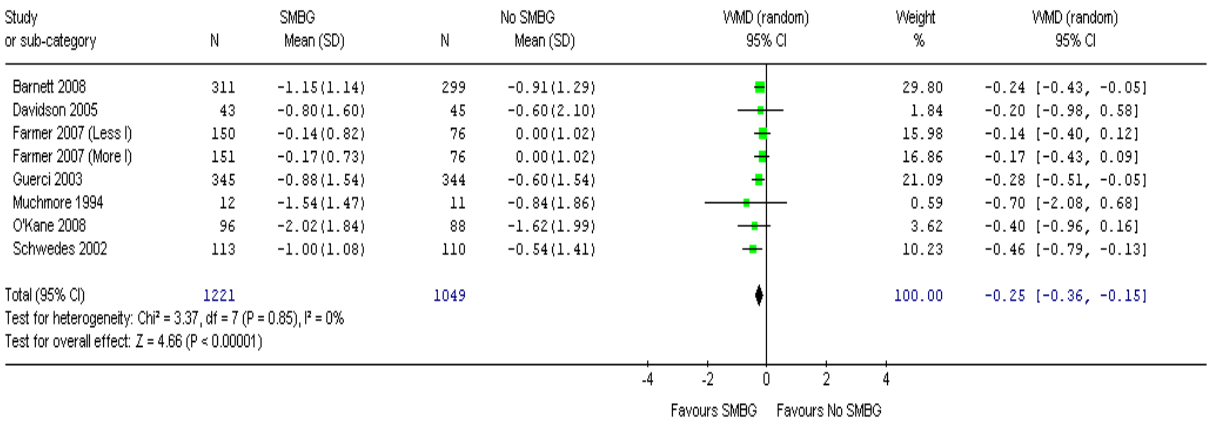
4.5 Clinical Evidence

4.5.1 Patients with non–insulin-treated type 2 diabetes mellitus

Patient-relevant and clinical outcomes associated with SMBG in adults with type 2 diabetes mellitus who do not use insulin therapy were derived from a systematic review[19] of seven RCTs.[5,34-39] The systematic review included all RCTs[5,34-39] that compared SMBG with no SMBG in patients with either newly and previously diagnosed type 2 diabetes mellitus. A heterogeneity statistic (I^2)

value of 0% was observed in the systematic review, indicating statistical consistency in results between RCTs. The systematic review included 2,270 patients (Figure 2) and found a weighted mean A1C difference favouring SMBG of -0.25% (95% confidence interval [CI], -0.36, -0.15). Estimates of A1C treatment effect in the model were assumed to follow trajectories, as outlined in UKPDS Outcomes Model.[30]

Figure 2: Forest Plot of Randomized Controlled Trials Examining the Use of Self-Monitoring of Blood Glucose versus No Self-Monitoring of Blood Glucose in Adult Patients Who Are Not Using Insulin Therapy — Glycosylated Hemoglobin, Weighted Mean Difference of Differences[19]



CI = confidence interval; SD = standard deviation; SMBG = self-monitoring of blood glucose; RCT = randomized controlled trial; WMD = weighted mean difference in glycosylated hemoglobin.

Other critical or important outcomes (e.g., weight/BMI, health-related quality of life [HRQoL]) were reported to be not statistically significant[19] or could not be incorporated into the UKPDS Outcomes Model (e.g., overall hypoglycemia). Therefore, these variables were not included in the reference case analysis. Extensive sensitivity analyses, however, were performed to examine robustness of findings to inclusion of other outcomes.

4.5.2 Patients with insulin-treated type 2 diabetes mellitus

A recent systematic review[19] reported results on the clinical-effectiveness of SMBG in adults with type 2 diabetes mellitus who were treated with insulin. Only a few studies were identified, all of which were of low methodological quality when assessed using the SIGN 50 instrument.[23,24] Moreover, estimates of A1C treatment effect differed between studies (Table 2) and with respect to SMBG testing frequency.

Because of this heterogeneity, cost-effectiveness estimates for a range of plausible estimates of A1C estimate of effect were reported:

- A1C difference = 0.25% favouring SMBG
- A1C difference = 0.50% favouring SMBG
- A1C difference = 1.00% favouring SMBG
- A1C difference = 1.50% favouring SMBG.

A1C treatment effects for all plausible scenarios were assumed to follow trajectories, as outlined in UKPDS Outcomes Model.[30] Other critical or important outcomes (e.g., weight/BMI, HRQoL) were either not reported or could not be incorporated into the UKPDS Outcomes Model (e.g., hypoglycemia). Therefore, these parameters were not included in the current cost-effectiveness analyses.

Table 2: Glycosylated Hemoglobin for Self-Monitoring of Blood Glucose versus No Self-Monitoring of Blood Glucose in Adults with Type 2 Diabetes Mellitus Using Insulin (with or without oral antidiabetes drugs)

Comparison	Sample Size Analyzed	Effect Estimate in Mean Difference of A1C (%) (95% CI)
Patients treated with insulin alone (non-randomized trial[53])		
SMBG 4 per day x 1 day per week versus no SMBG	71	−1.00%× (−1.68 *f*) −0.32)
SMBG 4 per day x once every 2 weeks versus no SMBG	55	−0.70%× (−1.41 *f*) 0.01)
SMBG 4 per day x 1 day per month versus no SMBG	36	−0.20%× (−1.08 *f*) 0.68)
Patients treated with insulin and oral antidiabetes drugs (retrospective cohort study[21])		
SMBG ≥ 1 per day versus no SMBG	4,061	−0.69%† (−0.84 *f*) −0.54)
SMBG < 1 per day versus no SMBG	2,541	−0.13%† (−0.30 *f*) 0.04)

A1C = glycosylated hemoglobin; CI = confidence interval; SMBG = self-monitoring of blood glucose.
*Baseline patient characteristics, including age, sex, disease duration, duration of insulin treatment, hypoglycemia, and rate of complications of retinopathy, nephropathy, and neuropathy, were significantly different between comparator groups. Unadjusted results were reported.
†Adjusted for age, sex, ethnicity, educational attainment, annual income and occupational class, years since diabetes diagnosis, diabetes therapy refill adherence, number of daily insulin injections, clinic appointment "no show" rate, annual eye exam attendance, self-reported exercise and diet as diabetes treatment, smoking status, alcohol consumption, and hospitalization and emergency department visits during baseline year.

4.6 Perspective

This economic evaluation took the perspective of a Canadian publicly funded ministry of health.[54] Therefore, only direct costs to the publicly funded health care system were considered.

4.7 Time horizon

As recommended by CADTH guidelines,[54] the reference case uses a lifetime time horizon (i.e., 40 years). Because clinical outcomes were based on extrapolated data using surrogate outcomes (i.e., A1C), results for time horizons of one, five, 10, 15, and 25 years are also reported.

4.8 Valuing outcomes

The primary outcome measure in the current analysis was the quality-adjusted life-year (QALY).[1,55] A QALY is an outcome measure that simultaneously captures quantity and quality of life (i.e., mortality and morbidity).[1,55] Moreover, QALYs also enable one to capture multiple outcomes of interest and combine them into a single outcome measure. Thus, use of QALYs enables decision-makers to make comparisons across a broad range of health care interventions. Utility scores, or quality weights for the QALY, for health states in the model were obtained from a US catalogue of EuroQol 5-dimension (EQ-5D) scores for chronic conditions.[56,57] The EQ-5D[58] is a widely used preference-based instrument for the measurement of health status.[1] The US catalogue[56,57] was generated using nationally representative data from the Medical Expenditure Panel Survey.[59] Preference scores in the US catalogue should be generalizable to Canadians, as instrument scores are typically applicable in other countries.[54,55] The use of preference-based measures is recommended by CADTH, the National Institute of Clinical Excellence (NICE), and the Washington Panel on Cost-Effectiveness in Health and Medicine.[56,57]

Patients with non–insulin-dependent type 2 diabetes mellitus without history of diabetes-related complications were assumed to have an EQ-5D score of 0.753.[56,57] Disutilities for diabetes-related complications (Table 3), during the year of the event, were based on EQ-5D scores for relevant International Classification of Diseases, 9th edition codes.[56] For subsequent years, disutilities were based on quality priority conditions (QPC) estimates.[56,57] QPC estimates correspond to individuals who have *ever* received a diagnosis of the condition, whereas estimates based on the International Classification of Diseases, 9th edition correspond only to individuals in whom diabetes has been diagnosed within the past year. When QPC estimates[56,57] were unavailable, it was assumed that the disutility for the health state in the first year remained constant over time. When disutility estimates were not available from the EQ-5D catalogue,[56,57] they were obtained from other sources that utilized the EQ-5D instrument.[60]

Mortality, the other key element in the QALY, was based on three regression equations built within the UKPDS Outcomes Model.[30] The first equation estimates the likelihood of death in the first year after the occurrence of a diabetes-related complication. The second equation estimates diabetes-related mortality in subsequent years for patients who have a history of a diabetes-related complication, whereas the third equation estimates the probability of non–diabetes-related mortality (e.g., cancer, accidents).

Table 3: Disutilities for Health States in the Economic Evaluation of Self-Monitoring of Blood Glucose versus No Self-Monitoring of Blood Glucose in the Management of Adult Patients with Type 2 Diabetes Mellitus

Health State	Disutility of Health State	Disutilities Derived From	Technique
Myocardial infarction, year of event[56]	−0.0409222	US survey — 38,678 adults	EQ-5D
Myocardial infarction, subsequent years[57]	−0.012	US survey — 38,678 adults	EQ-5D
Ischemic heart disease, year of event[56]	−0.0412	US survey — 38,678 adults	EQ-5D
Ischemic heart disease, subsequent years[57]	−0.024	US survey — 38,678 adults	EQ-5D
Heart failure, year of event[57]	−0.0546	US survey — 38,678 adults	EQ-5D
Heart failure, subsequent years[57]	−0.018	US survey — 38,678 adults	EQ-5D
Stroke, year of event[56]	−0.0523513	US survey — 38,678 adults	EQ-5D
Stroke, subsequent years[56]	−0.040	US survey — 38,678 adults	EQ-5D
Amputation[60]	−0.280	3,192 adults in the UK with type 2 diabetes mellitus	EQ-5D
Blindness and low vision[56]	−0.0497859	3,192 adults in the UK with type 2 diabetes mellitus	EQ-5D
Renal failure[60]	−0.263	3,192 adults in the UK with type 2 diabetes mellitus	EQ-5D

EQ-5D = EuroQol 5-dimension.

4.9 Resource Use and Costs

4.9.1 Daily utilization of blood glucose test strips

a) Patients with non–insulin-treated type 2 diabetes mellitus

In the reference case, patients with type 2 diabetes mellitus not using insulin therapy were assumed to use 1.29 test strips per day. Daily use of blood glucose test strips was derived using the weighted average from the seven RCTs[35-39,50] included in the systematic review. The current economic analysis used actual testing frequency, when reported. If actual frequency was not reported in the RCT, the current economic analysis assumed that patients in the RCT adhered to testing frequencies outlined in the study protocol. Sensitivity analyses were performed to test robustness of results to varying SMBG frequency.

b) Patients with insulin-treated type 2 diabetes mellitus

Studies identified in the systematic review[19] differed with respect to SMBG testing frequency. Consequently, cost-effectiveness results for several plausible testing frequencies are presented:

- four SMBG tests per week
- seven SMBG tests per week
- 14 SMBG tests per week
- 21 SMBG tests per week.

4.9.2 Price of blood glucose test strips

Unit costs for blood glucose test strips were obtained from the ODBP Formulary/Comparative Drug Index, July 28, 2008.[61] For the reference case, a unit cost of $0.73 per test strip was used, and a $7.00 dispensing fee was applied for every 100 test strips claimed.[62] A mark-up was not applied, because test strips are not eligible for a mark-up in the ODBP.[61] The cost of glucose meters and lancet devices were not incorporated, as they are often provided for free[63] or covered under other diabetes funding programs.[64] Sensitivity analyses were performed to test robustness of results to varying the unit cost of blood glucose test strips.

4.9.3 Costs of managing diabetes-related complications

The average annual cost for patients without diabetes-related complications and who were not performing SMBG was $1,507.[47] Resource utilization and costs (Table 4) associated with managing diabetes-related complications were obtained from the Ontario Ministry of Health and Long-Term Care.[47] Inpatient, outpatient, and emergency department visits and subsequent prescription drug claims, long-term care, and home care costs for managing diabetes-related complications were included.[47] Costs were inflated to 2008 Canadian dollars using the Health Component of the Canadian Consumer Price Index.[65]

4.10 Discount rate

In the reference case, both costs and QALYs were discounted at a rate of 5%, as recommended by CADTH guidelines.[54] Sensitivity analyses were performed for discount rates of 0% and 3%.[54]

Table 4: Management Costs of Diabetes-Related Complications, in 2008 Canadian Dollars	
Diabetes-Related Complication	**Cost of Diabetes-Related Complications (C$ 2008)***
Myocardial infarction	
Myocardial infarction, year of event, fatal[47]	9,039
Myocardial infarction, year of event, non-fatal[47]	17,324
Myocardial infarction, each subsequent year[47]	2,695
Ischemic heart disease	
Ischemic heart disease, year of onset[47]	5,394
Ischemic heart disease, each subsequent year[47]	3,114
Heart failure	
Heart failure, year of onset[47]	15,766
Heart failure, each subsequent year[47]	4,420
Stroke model	
Stroke, year of event, fatal[47]	8,505
Stroke, year of event, non-fatal[47]	23,475
Stroke, each subsequent year[47]	3,257
Amputation	
Amputation, year of onset[47]	36,416
Amputation, each subsequent year[47]	4,987
Blindness	
Blindness, year of onset[47]	2,884
Blindness, each subsequent year[47]	2,055
Renal Failure	
Renal failure, year of onset[47]	23,365
Renal failure, each subsequent year[47]	10,604

* Inflated to 2008 Canadian dollars using the health component of the Consumer Price Index.

4.11 Handling Uncertainty and Variability

a) Patients with non–insulin-treated type 2 diabetes mellitus

Sensitivity analyses were performed to examine robustness of results to variation of parameters and model assumptions. Variability analyses were also performed to explore heterogeneity in the cost-effectiveness of SMBG, by patients' diabetes treatment regimen (i.e., oral antidiabetes drugs versus no pharmacotherapy). A non-parametric bootstrapping* method,[1,66] in which 999 bootstrap iterations of 100 patients, was used to estimate the mean life expectancy, quality-adjusted life-expectancy, and costs for each treatment arm. Incremental costs and effectiveness between SMBG and no SMBG, as derived from the 999 bootstrap iterations, were plotted on the cost-effectiveness plane (scatter plot) to convey uncertainty of results. Net-benefits cost-effectiveness

*Bootstrapping is a technique that is used to approximate the accuracy (e.g., standard error, confidence interval) of a statistical estimate. (Berger ML, Bingefors K, Hedblom EC, Pashos CL, Torrance GW, editors. *Health care cost, quality, and outcomes: ISPOR book of terms*. Lawrenceville: International Society for Pharmacoeconomics and Outcomes Research; 2003.)

acceptability curves were generated based on the proportion of bootstrap iterations with a positive incremental net-monetary benefit[67] across a range of willingness-to-pay thresholds:

Incremental net monetary benefit[67] = λ*• E - • C
λ = decision-maker's willingness to pay per QALY gained; • E = difference in QALYs between SMBG versus no SMBG arm; • C = difference in lifetime costs between SMBG versus no SMBG arm.[67]

b) Patients with insulin-treated type 2 diabetes mellitus

Given the paucity and quality of clinical data, the estimate of A1C treatment effect for SMBG is unknown. Moreover, testing frequencies reported in studies identified in this systematic review[19] differ from those in the Canadian clinical care setting. Consequently, results for a reference case are not presented but, rather, cost-effectiveness estimates for several hypothetical plausible scenarios are provided. Net-benefits cost-effectiveness acceptability curves were also generated for each scenario to convey uncertainty.

5 RESULTS

5.1 Patients with Non–insulin-Treated Type 2 Diabetes Mellitus

5.1.1 Reference case

For patients with type 2 diabetes mellitus who are not using insulin, SMBG generated an additional 0.02385 QALYs and increased costs by $2,711, resulting in an incremental cost-utility ratio (ICUR) of $113,643 per QALY gained (Table 5).

Table 5: Results for Reference Case Analysis Comparing Self-Monitoring of Blood Glucose with no Self-Monitoring of Blood Glucose in Patients with Type 2 Diabetes Mellitus Who Are Not Using Insulin Therapy

	No SMBG	SMBG	Difference Between SMBG and No SMBG
Life-years gained*	9.87038	9.89812	0.02774
Quality-adjusted life-years gained*	7.29806	7.32191	0.02385
Total direct costs [C$]*	$27,997	$30,708	$2,711
Incremental cost per life-year gained (ICER)*			$97,729†
Incremental cost per QALY gained (ICUR)*			$113,643‡

• = difference; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SMBG = self-monitoring of blood glucose.
*Discounted at 5% per year.
† Cost in $C per incremental life-year gained.
‡ Cost in $C per incremental quality-adjusted life-year gained.

The model projects that patients using SMBG (• A1C% = -0.25% [95% CI, -0.36 to -0.15]) will have a slightly lower cumulative incidence of diabetes-related complications over a 40-year period, compared with patients who do not perform SMBG. Absolute risk reductions for diabetes-related complications, which represent differences in cumulative incidence rates between cohorts, range

from 0.08% to 0.40%. Consequently, the number of patients who need to be treated with SMBG, relative to no SMBG, to avert one diabetes-related complication over a 40-year period ranges from 228 to 1,299, depending on the outcome. The number of patients who need to be treated is equivalent to the inverse of the absolute risk reduction between cohorts (i.e., 1/absolute risk reduction).

Table 6: Number Needed to Treat by Self-Monitoring of Blood Glucose Over a 40-Year Time Horizon to Avert One Diabetes-Related Complication, Compared With No Self-Monitoring of Blood Glucose, in Patients with Type 2 Diabetes Mellitus Who Are Not Using Insulin Therapy

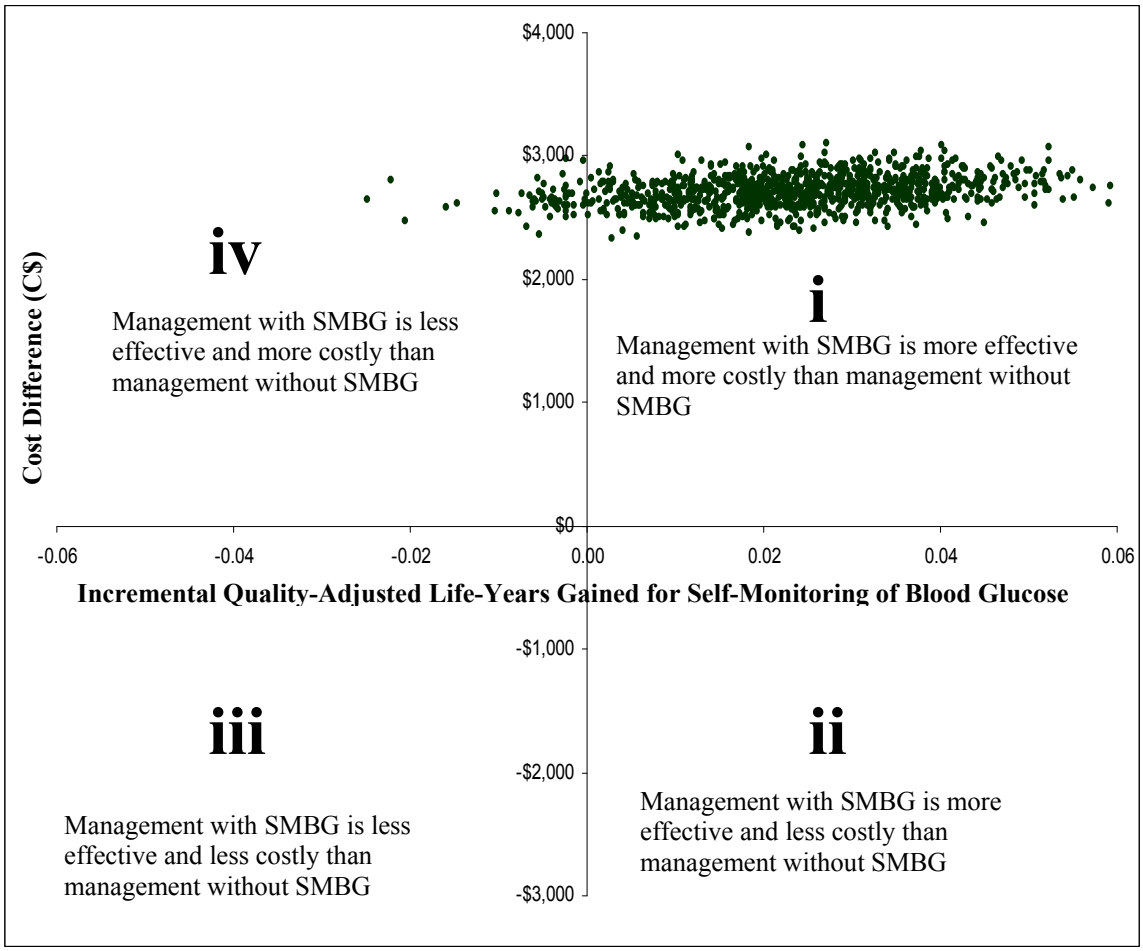
	Cumulative Incidence (%) in No SMBG Arm	Cumulative Incidence (%) in SMBG Arm	ARR (%)	NNT to Avert One Complication Over 40 Years with SMBG
Heart failure	17.6%	17.2%	0.40%	228
Myocardial infarction	36.58%	36.21%	0.38%	266
Amputation	3.55%	3.34%	0.21%	467
Stroke	16.34%	16.14%	0.20%	500
Blindness	8.69%	8.49%	0.19%	518
Ischemic heart disease	13.12%	13.04%	0.09%	1,136
End-stage renal disease	2.29%	2.21%	0.08%	1,389

ARR = absolute risk reduction; NNT = number needed to treat; SMBG = self-monitoring of blood glucose.

5.1.2 Cost-effectiveness scatter plot

Figure 3 presents a scatterplot of the mean differences in costs and QALYs between SMBG and no SMBG in the reference case. The horizontal axis depicts incremental gain in QALYs, and the vertical axis depicts incremental cost of SMBG, relative to no SMBG. The high concentration (94.7% of points) in quadrant (i) indicates that it is very likely that SMBG is more effective and more costly, relative to no SMBG. However, the small scatter of points (5.3%) in quadrant (iv) indicate that there is a slight possibility that SMBG is more costly and less effective (i.e., dominated), relative to no SMBG.

Figure 3: Incremental Cost-Utility Scatter Plot of Self-Monitoring of Blood Glucose, Relative to No Self-Monitoring of Blood Glucose, in the Management of Patients with Type 2 Diabetes Mellitus Who Are Not Using Insulin Therapy



SMBG = self-monitoring of blood glucose.

5.1.3 Sensitivity analyses

Results from sensitivity and variability analyses are presented in Table 7. Parameter(s) in the model were varied within plausible ranges, whereas other parameters in the model were held constant.

a) Glycosylated hemoglobin effect size

ICURs ranged from $189,376/QALY to $47,512/QALY when A1C treatment effects were varied between -0.15% (lower limit of 95% CI from meta-analysis of seven RCTs) and -0.57% (estimate from an observational study[21]).

b) Self-monitoring of blood glucose testing frequency

ICURs ranged from $6,322/QALY to $152,095/QALY when mean testing frequency of SMBG was varied between one and 12 strips per week.

c) Cost of blood glucose test strips

When the cost of blood glucose test strips ($0.71 per strip) is decreased by 25%, 50%, and 75%, ICURs decreased to $86,129, $58,615, and $31,101 per QALY gained, respectively. When the cost of the least expensive test strip in the ODBP is applied, the ICUR decreased to $63,892/QALY. In contrast, ICURs increased to $123,143/QALY when an alternative price from other publicly funded drug plans in Canada was used in the analysis.

d) Time horizon

ICURs were $1.1 million per QALY, $303,339 per QALY, $178,184 per QALY, $125,057 per QALY, and $120,054 per QALY for one-year, five-year, 10-year, 15-year, and 25-year time horizons, respectively.

e) Discount rates

ICURs were $104,020 per QALY and $90,225 per QALY when discount rates of 3% and 0% were used for both costs and effects.

f) Management costs of diabetes-related complications

The ICUR decreased to $112,901 per QALY when the cost of all diabetes-related complications was increased by 15%. The ICUR decreased to $109,378 per QALY when the cost of stroke and end-stage renal disease was doubled.

g) Other parameter(s)

ICURs ranged from $89,656 per QALY to $161,262 per QALY when other parameters (e.g., history of diabetes complications, duration of disease, level of glycemic control) in the model were varied within plausible ranges.

h) Two-way sensitivity analyses

The ICUR increased from $81,654 per QALY to $169,120 per QALY, when testing frequency was increased from < 1 SMBG tests per day (• A1C = -0.20%; frequency = 0.77 SMBG tests/day)[5,35,38] to > 2 SMBG tests per day (• A1C = -0.47%; frequency = 3.5 SMBG tests/day). [37,39] When baseline A1C was restricted to RCTs with < 8.0%, the ICUR increased to $213,502 per QALY, whereas the ICUR decreased to $94,443 per QALY for RCTs with baseline A1C between 8.0% to 10.5%.

i) Multi-way sensitivity analyses (scenario analyses)

ICURs ranged from $91,373 per QALY in the Canadian-specific model to $166,758 per QALY in the model that incorporates other outcomes (i.e., weight per BMI, and HRQoL).

j) Subgroups, by treatment type

For patients not using diabetes pharmacotherapy, the ICUR for SMBG was $292,114 per QALY, relative to no SMBG. For patients using oral antidiabetes drug(s), the ICURs for SMBG, versus no SMBG, was $91,724 per QALY.

5.1.4 Cost-effectiveness acceptability curves

Figures 4 to 9 present cost-effectiveness acceptability curves for SMBG versus no SMBG for:

- A1C effect size
- SMBG testing frequency
- price of blood glucose test strips
- two-way sensitivity analyses
- multi-way sensitivity analyses (scenario analyses)
- treatment type.

The horizontal axis depicts the decision-makers' willingness to pay for each QALY gained, and the vertical axis depicts the probability that SMBG is cost-effective, relative to not performing SMBG. For example, in the reference case (green line with solid square in Figures 4 to 9), if a decision-maker in a publicly funded ministry of health is prepared to pay $0, $50,000, $100,000, or $150,000 per QALY gained, then the probability that SMBG is cost-effective is 0%, 2%, 40%, and 67%, respectively.

Table 7: Results from Sensitivity Analyses and Variability Analyses

	• Cost (C$)	• QALYs	ICUR (C$/QALY)
Reference Case	$2,711	0.02385	$113,643/QALY
One-way sensitivity analyses			
a) A1C treatment effect size; reference case, • A1C = -0.25% (95% CI -0.36 to -0.15)			
Lower limit of 95% CI for WMD in A1C from 7 RCTs[5,34-39]	$2,644	0.03403	$77,706/QALY
Upper limit of 95% CI for WMD in A1C from 7 RCTs[5,34-39]	$2,769	0.01462	$189,376/QALY
WMD in A1C from good quality RCTs[34,36,38] (• A1C = -0.21%[21])	$2,735	0.02043	$133,829/QALY
• A1C estimate from observational study[21] (• A1C = -0.57%[21])	$2,523	0.05311	$47,512/QALY
WMD in A1C from RCTs[37,38] that used intensive education (• A1C = -0.28%[21])	$2,694	0.02696	$99,916/QALY
b) Frequency of SMBG; reference case, ~9 per week (1.29/day)			
1 SMBG/week (0.14/day)[68]	$151	0.02385	$6,322/QALY
4 SMBG/week (0.57/day)[68]	$1,096	0.02385	$46,445/QALY
5 SMBG/week (0.72/day)[38]	$1,418	0.02385	$59,449/QALY
7 SMBG/week (1/day)[69]	$2,055	0.02385	$86,168/QALY
12 SMBG/week (1.71/day)[5,37]	$3,628	0.02385	$152,095/QALY
c) Price of blood glucose test strips; reference case (C$0.72/strip)			
Price reduced by 25% (C$0.55/strip)	$2,054	0.02385	$86,129/QALY
Price reduced by 50% (C$0.36/strip)	$1,398	0.02385	$58,615/QALY
Price reduced by 75% (C$0.18/strip)	$742	0.02385	$31,101/QALY
Cheapest price in Ontario Drug Benefits Program (C$0.40/strip)	$1,524	0.02385	$63,892/QALY

Table 7: Results from Sensitivity Analyses and Variability Analyses			
	• Cost (C$)	• QALYs	ICUR (C$/QALY)
Alternative formulary list price (C$0.81/strip)	$2,937	0.02385	$123,143/QALY
d) Time horizon; reference case, 40 years			
Time horizon, 1 year	$340	0.00030	$1,144,674/QALY
Time horizon, 5 years	$1,363	0.00449	$303,339/QALY
Time horizon, 10 years	$2,090	0.01173	$178,184/QALY
Time horizon, 15 years	$2,176	0.01740	$125,057/QALY
Time horizon, 25 years	$2,675	0.02228	$120,054/QALY
e) Discount rate; reference case, 5% for both costs and effects			
0% discount rate for both costs and effects	$3,815	0.04229	$90,225/QALY
3% discount rate for both costs and effects	$3,067	0.02948	$104,020/QALY
f) Management costs for diabetes-related complications; reference case, Ontario Diabetes Study			
15% increase in management costs for all diabetes-related complications	$2,674	0.02385	$112,901/QALY
Costs of stroke and end-stage renal disease doubled	$2,609	0.02385	$109,378/QALY
g) Variation in other parameters			
History of diabetes-related complications reflective of patients in DICE study and Canadian diabetes atlases[40-43]	$2,077	0.02316	$89,656/QALY
A1C treatment effect converges after 5 years[43,50,70]	$2,828	0.01754	$161,262/QALY
HRQoL preferences for health states obtained from patients with diabetes[60]	$2,711	0.02714	$99,868/QALY
Assume patients are 87%[38] adherent to study protocol when actual testing frequency is not reported in RCTs	$2,514	0.02385	$105,401/QALY
Assume patients are 66%[36] adherent to study protocol when actual testing frequency is not reported in RCTs	$2,204	0.02385	$92,378/QALY
Mean utility of patients with type 2 diabetes mellitus and no history of diabetes-related complications = 0.844[56,57]	$2,711	0.02638	$102,767/QALY
Adequately controlled diabetes (baseline A1C = 7.5%)[35]	$2,793	0.02146	$130,153/QALY
Poorly controlled diabetes (baseline A1C = 9.5%)	$2,586	0.02609	$99,114/QALY
Newly diagnosed type 2 diabetes mellitus, duration of diabetes = 0 to 1 years	$3,189	0.02143	$148,834/QALY
Duration of diabetes = 7.8 years[35]	$2,391	0.02414	$99,026/QALY
Initial decrement in HRQoL of 0.008 QALYs applied in SMBG arm (discounted 39 year model plus costs and effects for year 1) [50]	$2,576	0.01424	$180,935/QALY
Weight loss of 0.26 kg (-0.60, 0.08) applied in SMBG arm	$2,670	0.02481	$108,395/QALY
h) Two-way sensitivity analyses			
SMBG < 1/day, (• A1C = -0.20%; frequency = 0.77 SMBG/day)[5,35,38]	$1,569	0.01921	$81,654/QALY

Table 7: Results from Sensitivity Analyses and Variability Analyses			
	• Cost (C$)	• QALYs	ICUR (C$/QALY)
SMBG 1 to 2/day, (• A1C = -0.26%; frequency = 1.46 SMBG/day) [34,36]	$3,070	0.02508	$122,416/QALY
SMBG > 2/day, (• A1C = -0.47%; frequency = 3.5 SMBG/day) [37,39]	$7,503	0.04437	$169,120/QALY
Baseline A1C < 8.0% (WMD in A1C% = 0.16%, baseline A1C = 7.5%)	$2,840	0.01328	$213,503/QALY
Baseline A1C, 8.0 to 10.5% (WMD in A1C% = 0.30%, baseline A1C = 8.7%)	$2,656	0.02812	$94,443/QALY
i) Multi-way sensitivity analyses (scenario analyses)			
Canadian-specific model[40-43], OAD(s) and/or diet*	$1,350	0.01478	$91,373/QALY
Multiple treatment effects applied, OAD(s) and/or diet †	$2,563	0.01537	$166,758/QALY
j) Subgroup analyses, by treatment group			
Patients using OAD(s), 3 RCTs[34,35,38] ‡	$2,217	0.02417	$91,724/QALY
Patients using insulin secretagogues, 1 RCT[34,35,38] ¶	$2,217	0.02418	$91,693/QALY
Patients using diet only therapy, 1 RCT[14] §	$1,372	0.00470	$292,144/QALY

• = change; A1C = glycosylated hemoglobin; CI = confidence interval; DICE = Diabetes in Canada Evaluation; HRQoL = health-related quality of life; ICUR = incremental cost-utility ratio; OAD = oral antidiabetic drug; QALY = quality-adjusted life-year; RCTs = randomized controlled trials; SMBG = self-monitoring of blood glucose; WMD = weighted mean difference.

*Model updated to reflect characteristics of patients in the Canadian clinical care setting. Baseline A1C = 7.5%; WMD in A1C%: -0.26 (-0.34, 0.03); mean age = 63 years; mean duration of diabetes = 7.8 years; proportion of patients with a history of complications is reflective of patients in DICE and Ontario and Alberta Diabetes Atlases (i.e., 1% of patients were assumed to have history of blindness,[40-42] end-stage renal disease,[40-42] amputation;[40-43] 4%[45,46] and 2%[43] of patients had history of atrial fibrillation and peripheral vascular disease on diagnosis of diabetes; 2% have history of stroke; 9% have history of myocardial infarction;[40-42] 4% have congestive heart failure;[40-42] and 10% had a history of ischemic heart disease[40-42]; average time since event is based on data from the Ontario Diabetes Economic Model[47], frequency = 0.96 test strips per day; cost of test strip = C$0.81 per strip; time horizon = 40 years; discount rate = 5%

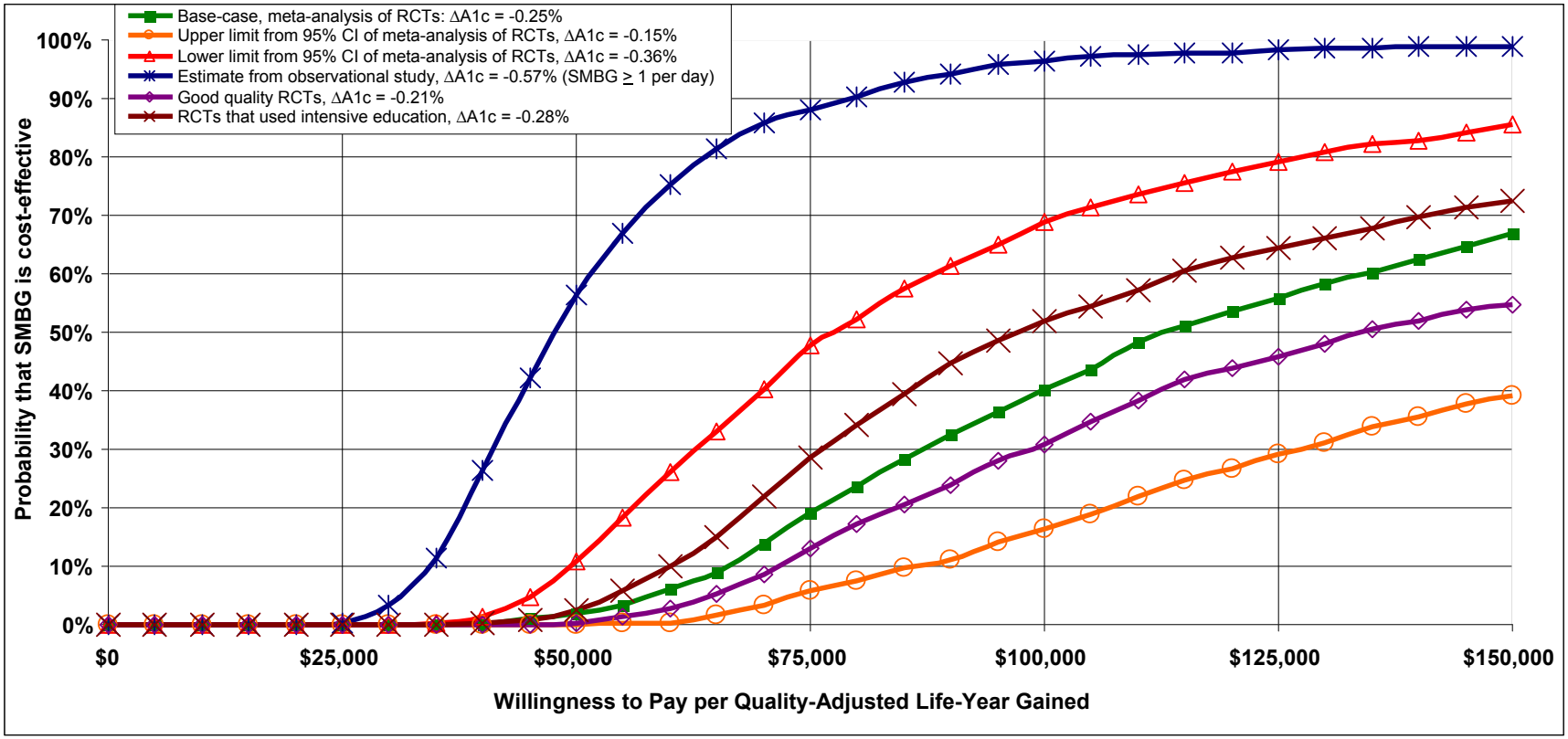
†Simulated cohort reflective of patients enrolled in seven RCTs;[5,34-39] however, other treatment effects reported to be critical or important outcomes by the COMPUS Expert Review Committee are also applied: • weight = -0.26 kg (-0.60, 0.08); initial decrement of 0.008 QALYs (-0.029, 0.012) applied in year one only.

‡Baseline A1C = 8.3%; WMD in A1C%: -0.24 (-0.36, -0.11); mean age = 61 years; mean duration of diabetes = 4.9 years; frequency = 1.08 test strips per day; cost of test strip = C$0.72 per strip; time horizon = 40 years; discount rate = 5%; assumed no history of diabetes-related complications, as data were not reported in three RCTs.[1,2,6]

¶Based on data from Barnett et al.,[34,35,38] it was assumed that 7% of patients would experience a symptomatic hypoglycemic episode with an excess of 2.38 episodes per year in the no SMBG arm. For each episode, it was assumed patients move to a health state characterized by moderate anxiety, with or without depression and some problems with performing usual activities.[71] Consequently, a disutility of 0.167[71] was applied for 15 minutes for each episode; Baseline A1C = 8.3%; WMD in A1C%: -0.24 (-0.36, -0.11); mean age = 61 years; mean duration of diabetes = 4.9 years; frequency = 1.08 test strips per day; cost of test strip = C$0.72 per strip; time horizon = 40 years; discount rate = 5%; assumed no history of diabetes-related complications, as data were not reported in three RCTs where patients used oral antidiabetes drugs.[34,35,38]

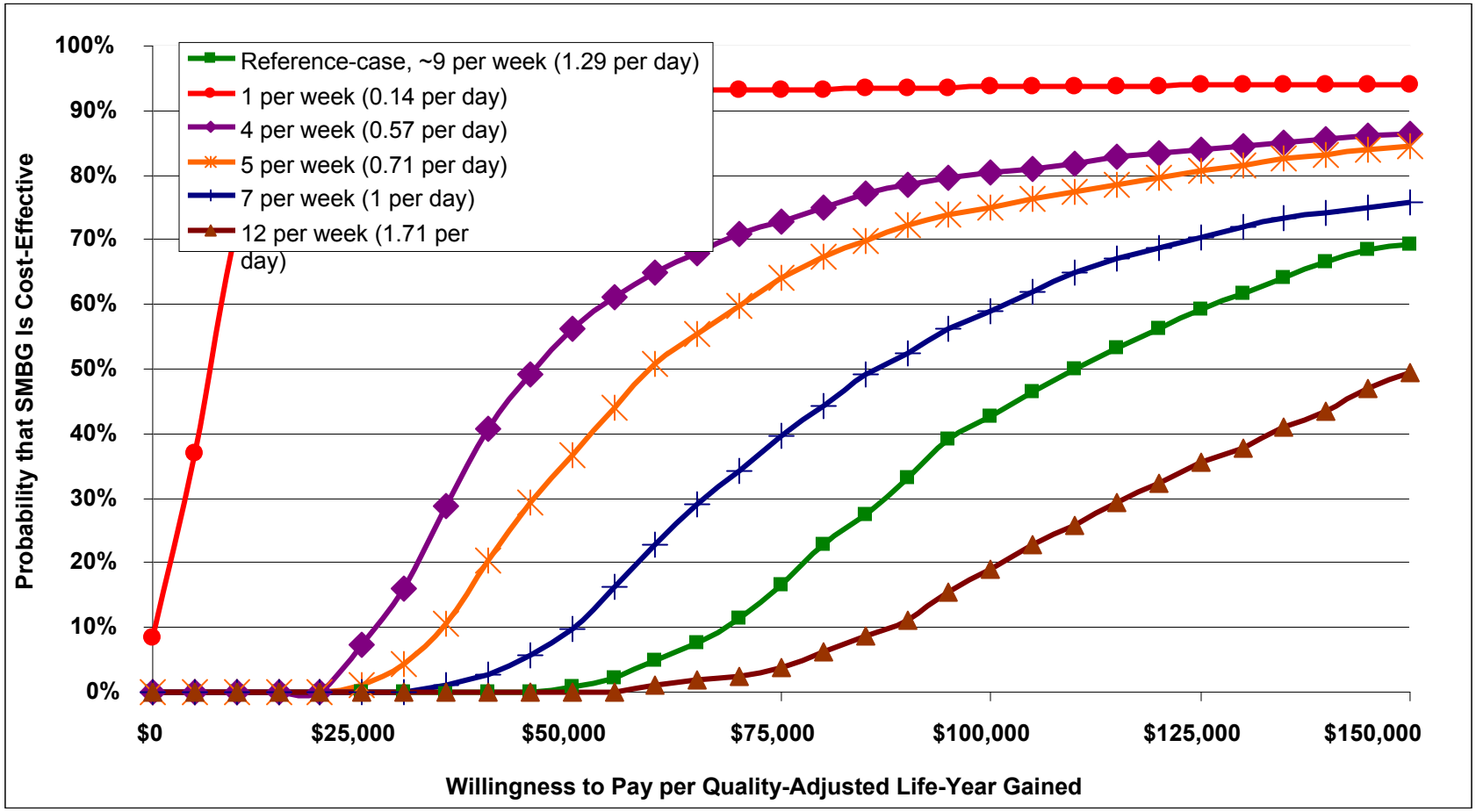
§Baseline A1C = 7.5%; WMD in A1C%: -0.05 (-0.33, 0.23); mean age = 66 years; mean duration of diabetes = 3 years; frequency = 0.71 test strips per day; cost of test strip = C$0.72 per strip; time horizon = 40 years; discount rate = 5%; assumed no history of diabetes-related complications, as data were not reported in three RCTs.[1,2,6]

Figure 4: Cost-Effectiveness Acceptability Curves for Different Glycosylated Hemoglobin Estimates of Effect While Holding Self-Monitoring of Blood Glucose Frequency Constant



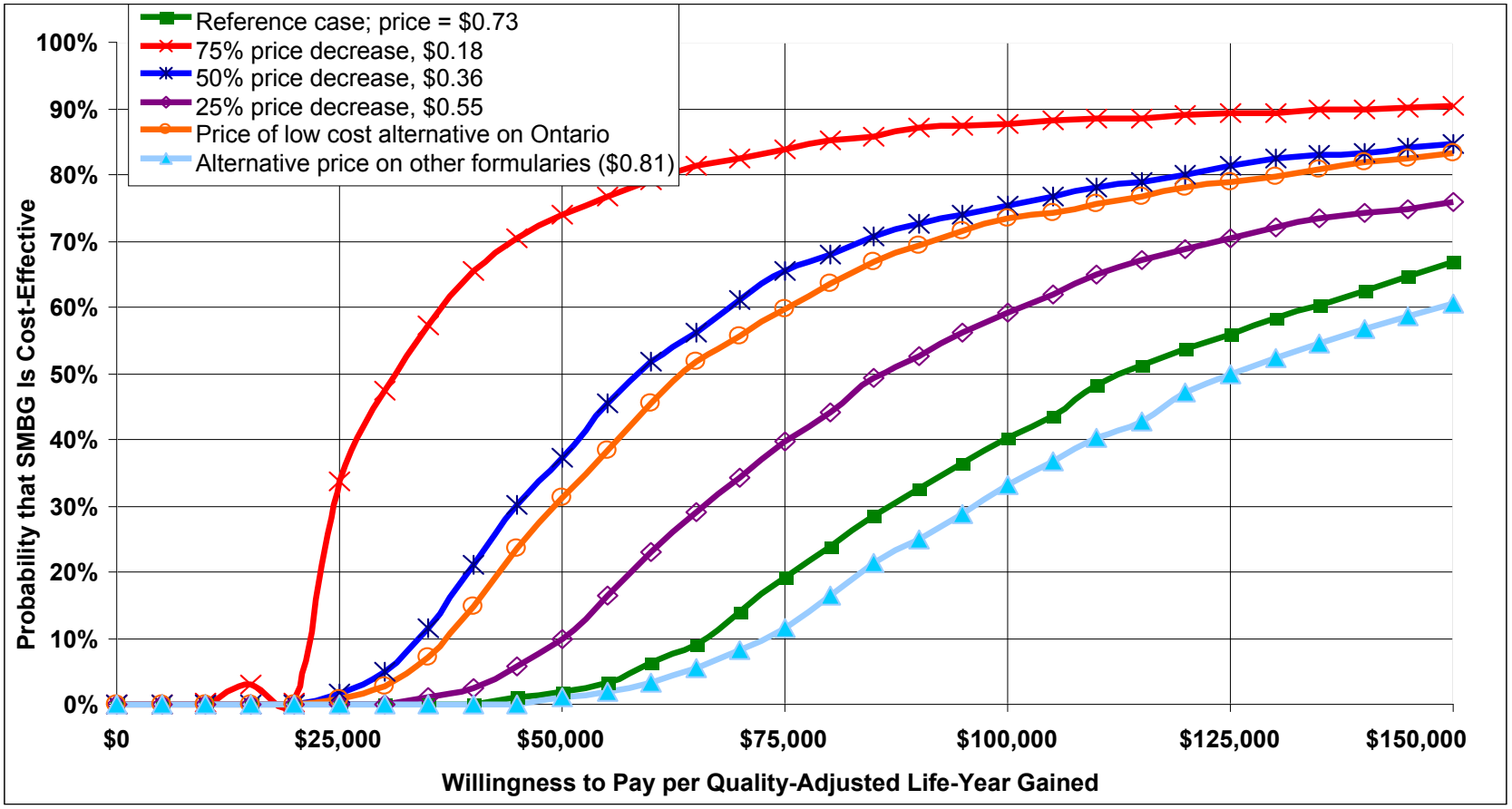
A1C = glycosylated hemoglobin; CI = confidence interval; RCTs = randomized controlled trials; SMBG = self-monitoring of blood glucose.
The cost-effectiveness acceptability curves show the probability that performing self-monitoring of blood glucose is cost-effective in patients with type 2 diabetes mellitus who are not using insulin, relative to not performing self-monitoring of blood glucose, across various decision-makers' willingness-to-pay thresholds.

Figure 5: Cost-Effectiveness Acceptability Curves for Different Self-Monitoring of Blood Glucose Testing Frequencies While Holding the Glycosylated Hemoglobin Estimate of Effect Constant (change in glycosylated hemoglobin of -0.25%, favouring self-monitoring of blood glucose)



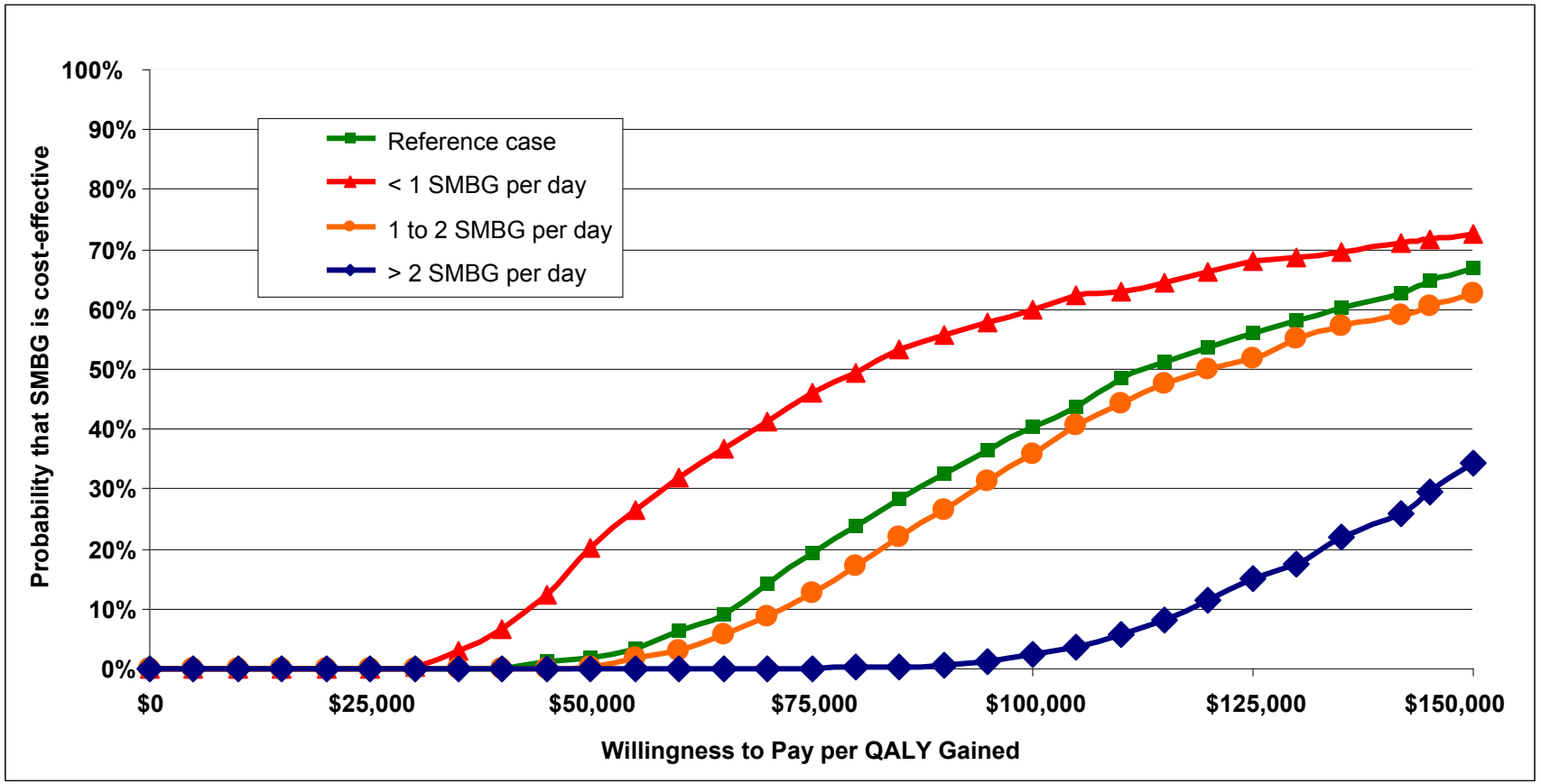
SMBG = self-monitoring of blood glucose.
The cost-effectiveness acceptability curves show the probability that performing SMBG is cost-effective in patients with type 2 diabetes mellitus who are not using insulin, relative to not performing SMBG, across various decision-makers' willingness-to-pay thresholds.

Figure 6: Cost-Effectiveness Acceptability Curves for Variation in Cost of Blood Glucose Test Strips



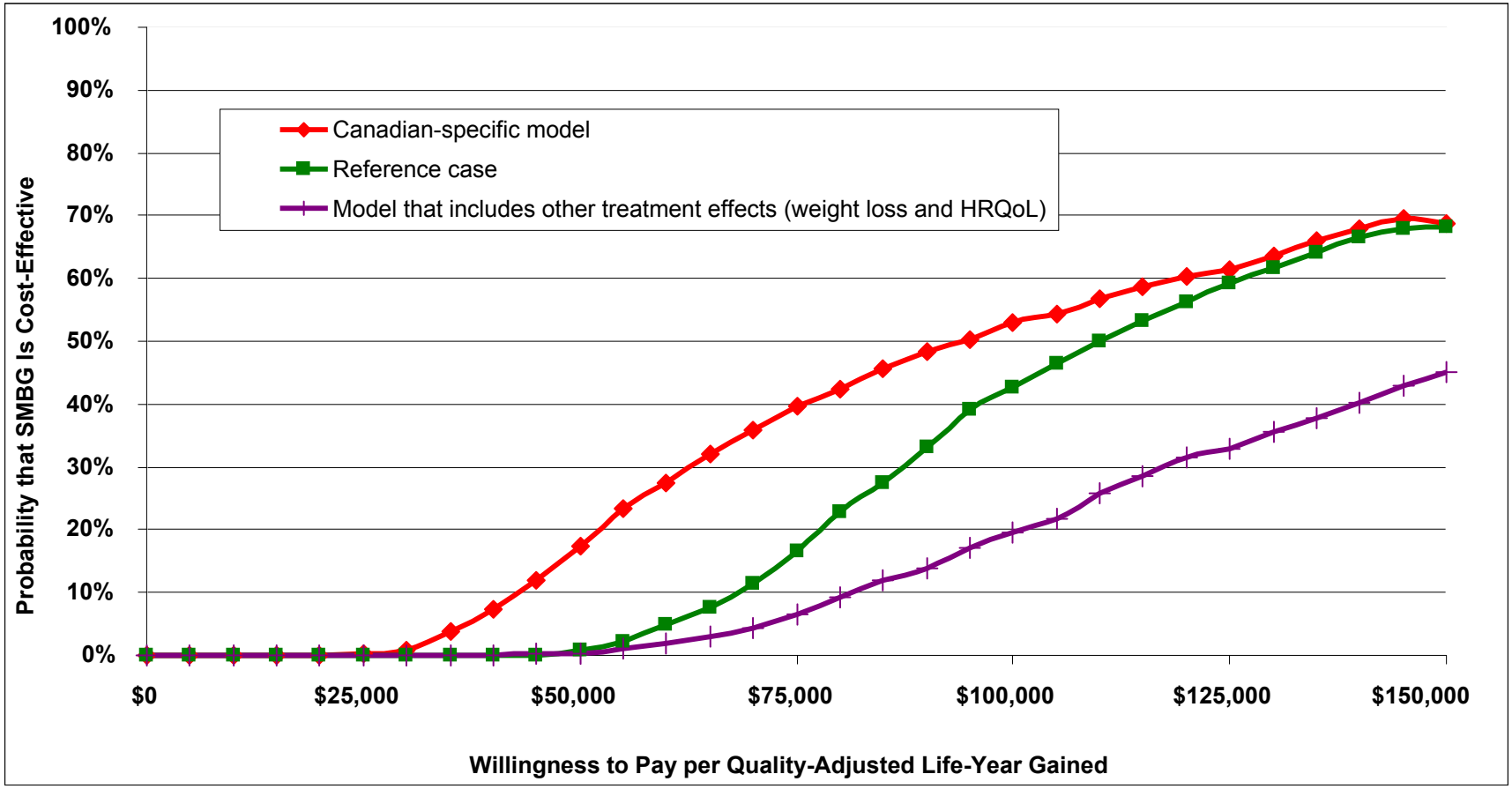
SMBG = self-monitoring of blood glucose.
The cost-effectiveness acceptability curves show the probability that performing SMBG is cost-effective in patients with type 2 diabetes mellitus who are not using insulin, relative to not performing SMBG, across various decision-makers' willingness-to-pay thresholds.

Figure 7: Cost-Effectiveness Acceptability Curve for Two-Way Sensitivity Analyses (variation in self-monitoring of blood glucose frequency and glycosylated hemoglobin treatment effect)



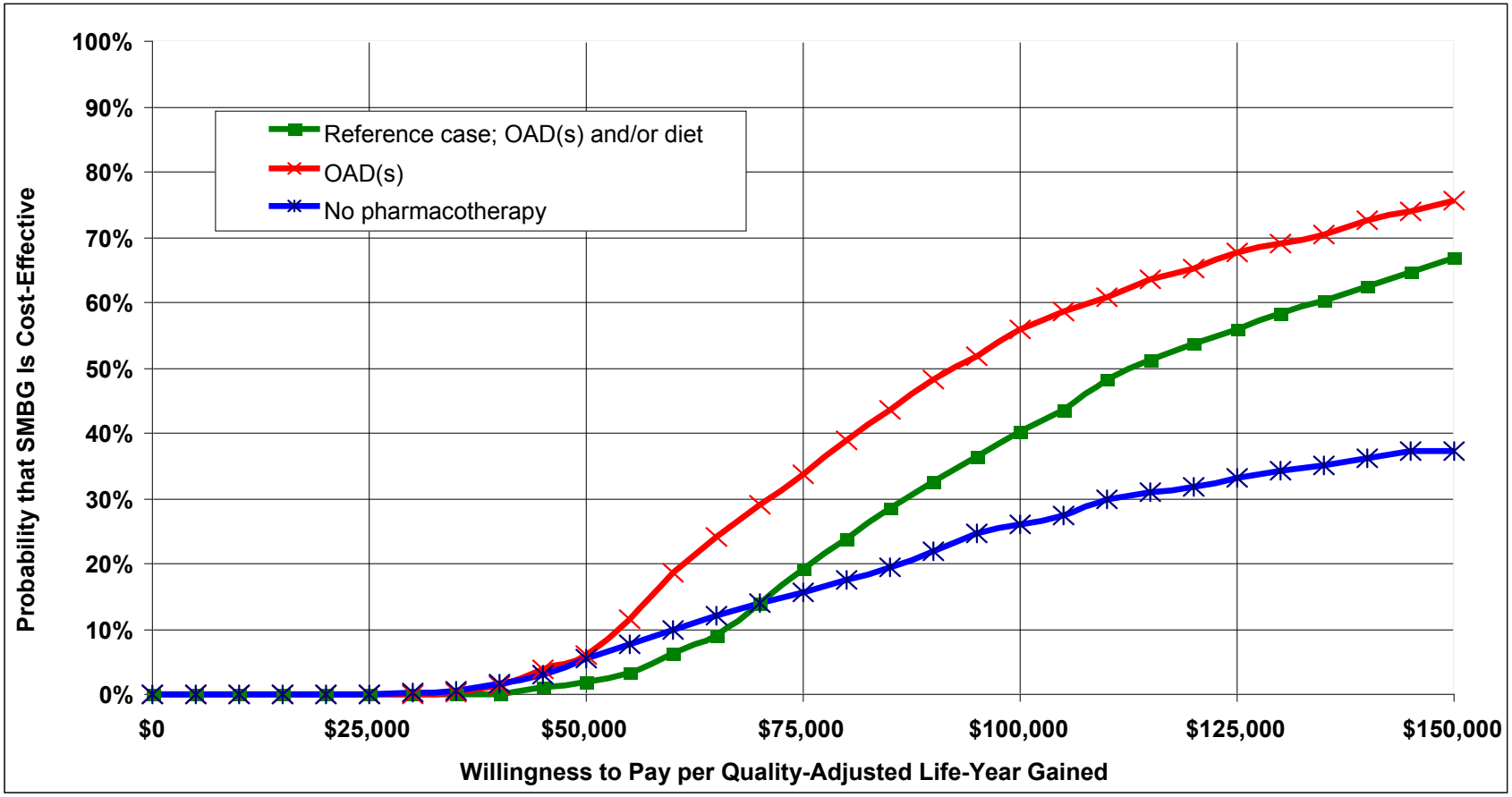
QALY = quality-adjusted life-year; SMBG = self-monitoring of blood glucose.
The figure presents the probability that performing SMBG in the management of patients with type 2 diabetes mellitus who are not using insulin therapy is cost-effective, relative to not performing SMBG, across various decision-makers' willingness to pay-thresholds.

Figure 8: Cost-Effectiveness Acceptability Curve for Multi-way Sensitivity (scenario analyses)



HRQoL= health-related quality of life; SMBG = self-monitoring of blood glucose.
The figure presents the probability that performing SMBG in the management of patients with type 2 diabetes mellitus who are not using insulin therapy is cost-effective, relative to not performing SMBG, across various decision-makers' willingness-to-pay thresholds.

Figure 9: Cost-Effectiveness Acceptability Curve, by Treatment Type



OAD = oral antidiabetes drug; SMBG = self-monitoring of blood glucose.
The figure presents the probability that performing SMBG in the management of patients with type 2 diabetes mellitus who are not using insulin therapy is cost-effective, relative to not performing SMBG, across various decision-makers' willingness-to-pay thresholds.

5.2 Patients with Insulin-Treated Type 2 Diabetes Mellitus

5.2.1 Incremental cost per quality-adjusted life-year gained

Given the heterogeneity in clinical information, cost-effectiveness estimates for several plausible scenarios are reported (Table 8 and Figure 10). Results in Table 8 range from almost cost neutral to an incremental cost of $224,169 per QALY gained. Figure 10 demonstrates that patients who perform more SMBG must attain higher A1C estimates of effect to have achieved more favourable cost-effectiveness estimates.

Table 8: Incremental Cost per Quality-Adjusted Life-Year Gained* (incremental cost; incremental quality-adjusted life-years) for Self-Monitoring of Blood Glucose versus No Self-Monitoring of Blood Glucose in Patients with Type 2 Diabetes Mellitus Who Require Insulin Therapy

	4 SMBG per Week	7 SMBG per Week	14 SMBG per Week	21 SMBG per Week
• A1C = -0.25%	**ICUR = $36,084/QALY** • QALYs = 0.01998 • Costs = $721	**ICUR = $69,488/QALY** • QALYs = 0.01998 • Costs = $1,388	**ICUR = $146,722/QALY** • QALYs = 0.01998 • Costs = $2,932	**ICUR = $224,169/QALY** • QALYs = 0.01998 • Costs = $4,479
• A1C = -0.5%	**ICUR = $14,566/QALY** • QALYs = 0.03887 • Costs = $566	**ICUR = $31,877/QALY** • QALYs = 0.03887 • Costs = $1,239	**ICUR = $71,901/QALY** • QALYs = 0.03887 • Costs = $2,931	**ICUR = $112,036/QALY** • QALYs = 0.03887 • Costs = $4,355
• A1C = -1.00%	**ICUR = $3,636/QALY** • QALYs = 0.07602 • Costs = $276	**ICUR = $12,626/QALY** • QALYs = 0.07602 • Costs = $960	**ICUR = $33,412/QALY** • QALYs = 0.07602 • Costs = $2,540	**ICUR = $54,255/QALY** • QALYs = 0.07602 • Costs = $4,142
• A1C = -1.50%	**ICUR = $0.17/QALY** • QALYs = 0.11073 • Costs = $0.02	**ICUR = $6,264/QALY** • QALYs = 0.11073 • Costs = $694	**ICUR = $20,746/QALY** • QALYs = 0.11073 • Costs = $2,297	**ICUR = $35,268/QALY** • QALYs = 0.11073 • Costs = $3,905

• = difference; A1C = glycosylated hemoglobin; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SMBG = self-monitoring of blood glucose.

*Discounted at 5% per year.

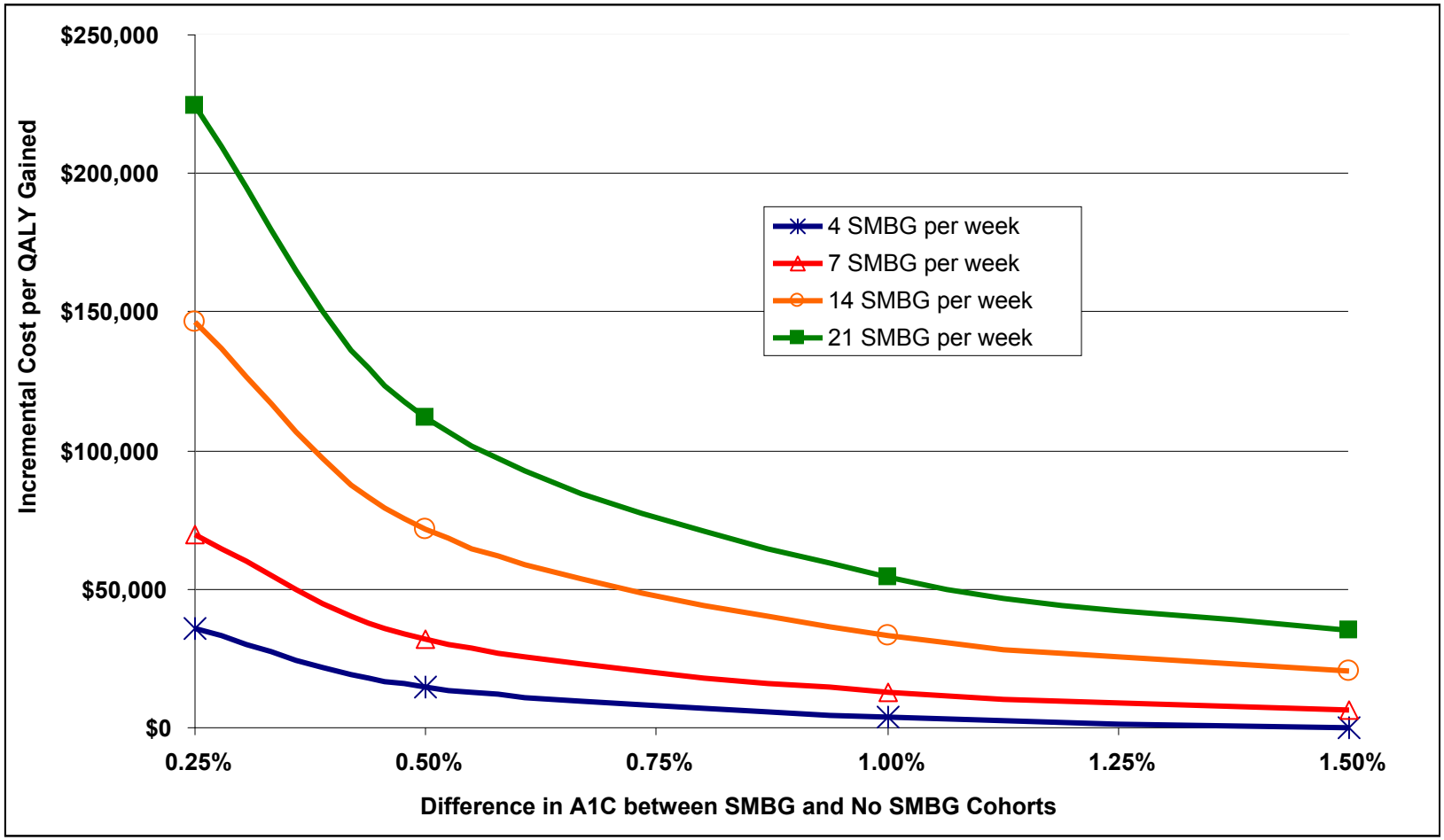
5.2.2 Cost-effectiveness acceptability curves

Figures 11 to 14 present cost-effectiveness acceptability curves for alternative SMBG frequencies, versus no SMBG, for:

- A1C difference = 0.25% favouring SMBG
- A1C difference = 0.50% favouring SMBG
- A1C difference = 1.00% favouring SMBG
- A1C difference = 1.50% favouring SMBG.

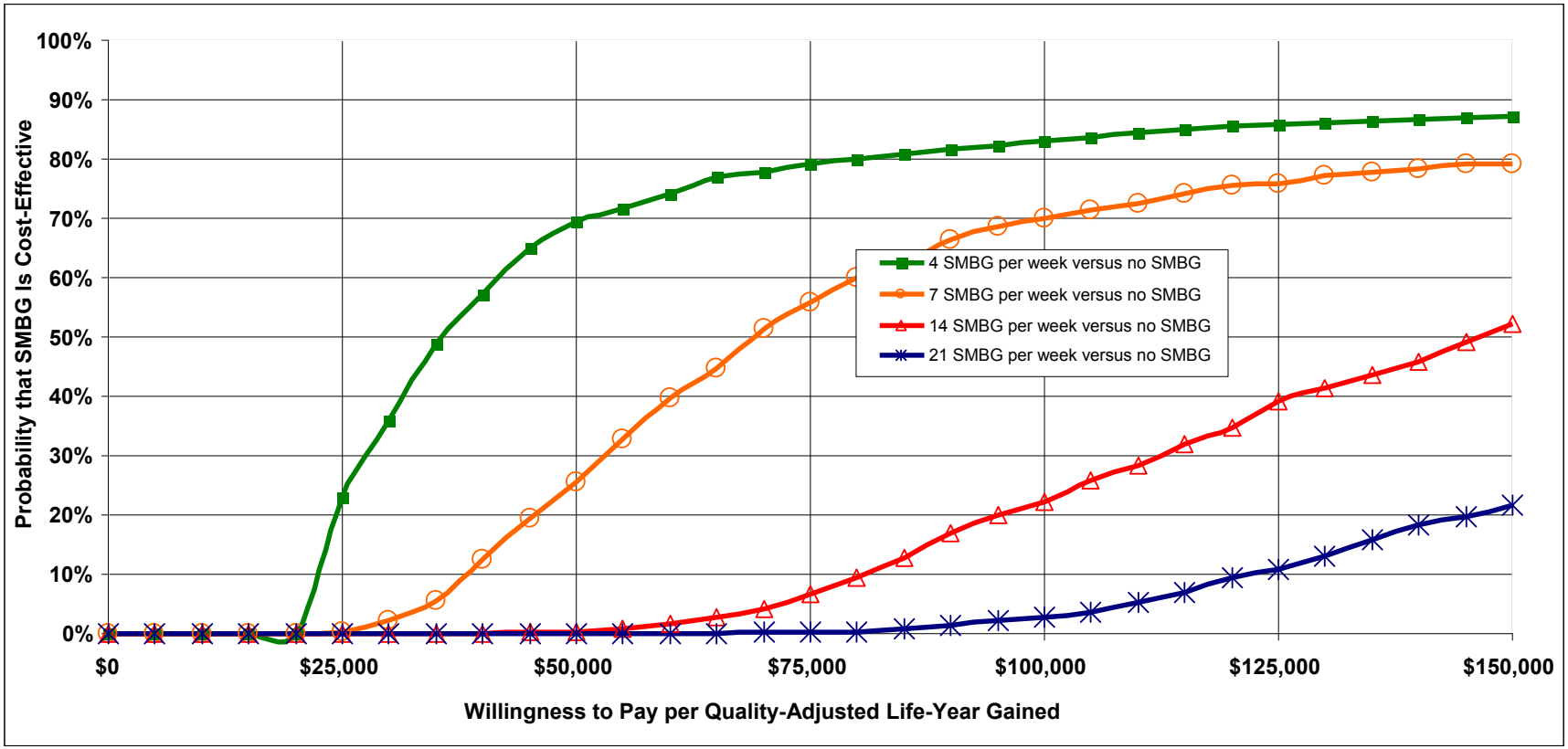
For example, if an A1C difference of 0.25% favouring SMBG (Figure 11) is assumed, there is a low probability that a testing frequency of 21 SMBG tests per week is cost-effective across the range of decision-makers' willingness-to-pay thresholds. The probability that SMBG is cost-effective increases, however, at lower SMBG testing frequencies.

Figure 10: Incremental Cost per Quality-Adjusted Life-Year Gained Across Glycosylated Hemoglobin Treatment Effects and Self-Monitoring of Blood Glucose Testing Frequencies in Patients with Insulin-Treated Type 2 Diabetes Mellitus



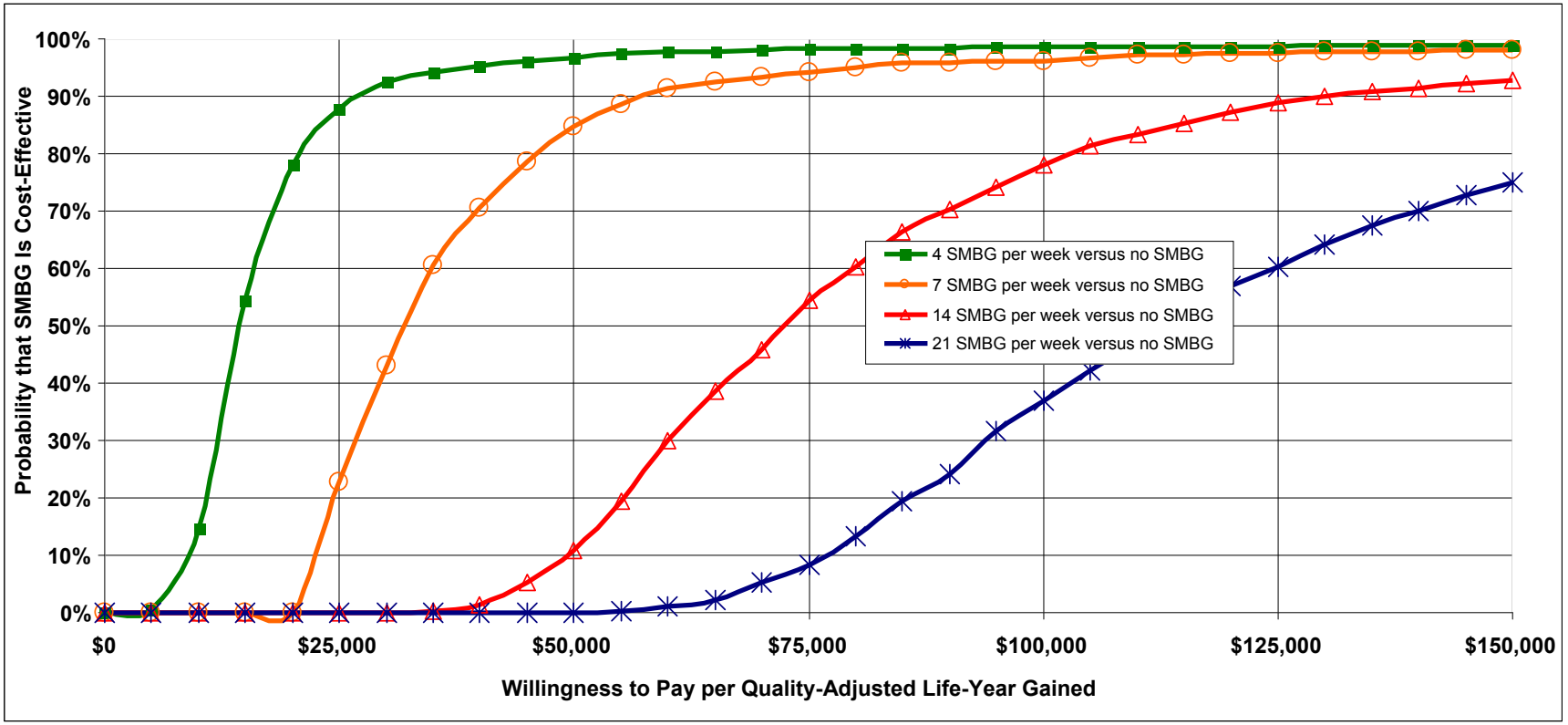
A1C = glycosylated hemoglobin; QALY = quality-adjusted life-year; SMBG = self-monitoring of blood glucose.

Figure 11: Probability that Different Self-Monitoring of Blood Glucose Testing Frequencies Are Cost-Effective in Patients Who Are Using Insulin, Relative to Not Performing Self-Monitoring of Blood Glucose, if a Glycosylated Hemoglobin Estimate of Effect of 0.25% Is Achieved in the Self-Monitoring of Blood Glucose Arm



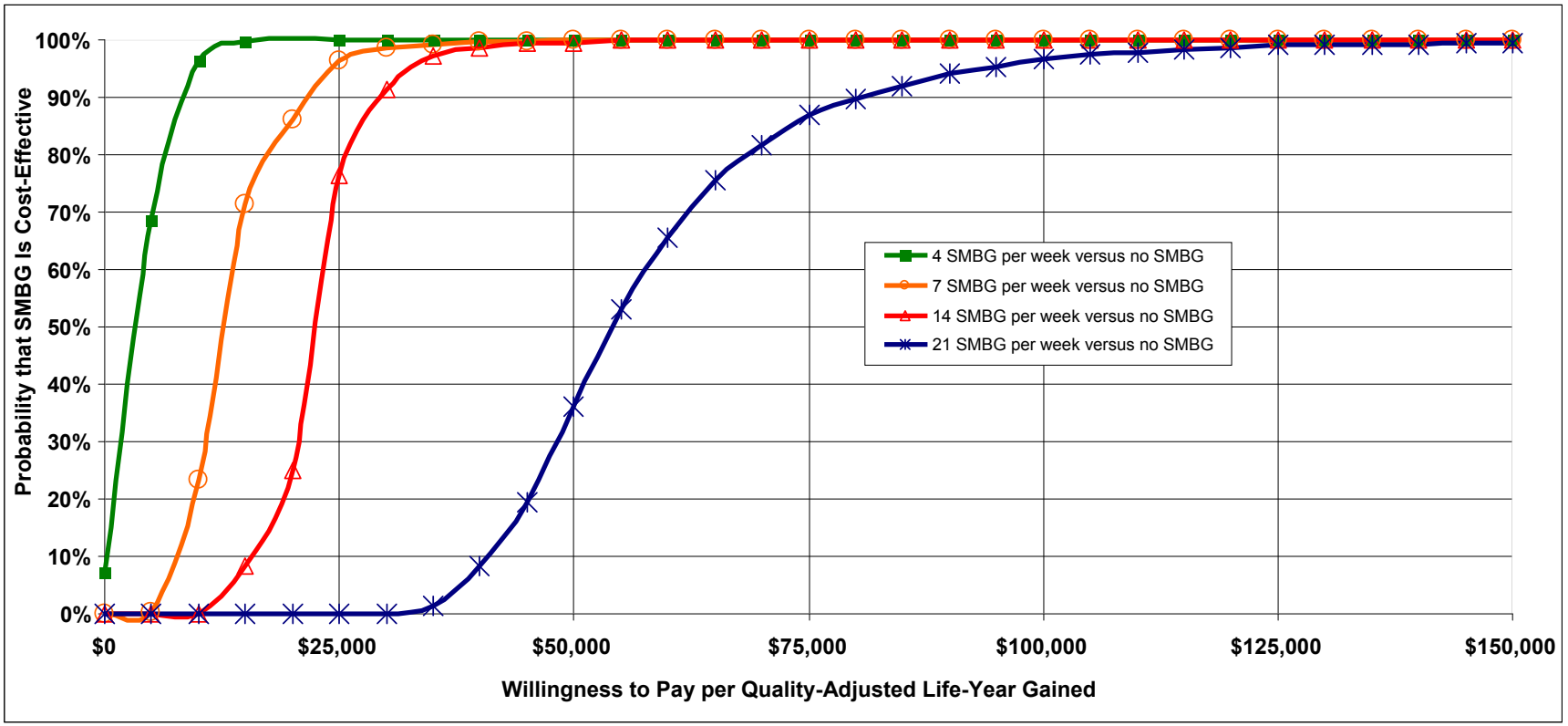
SMBG = self-monitoring of blood glucose.

Figure 12: Probability that Different Self-Monitoring of Blood Glucose Testing Frequencies Are Cost-Effective in Patients Who Are Using Insulin, Relative to Not Performing Self-Monitoring of Blood Glucose, if a Glycosylated Hemoglobin Estimate of Effect of 0.50% Is Achieved in the Self-Monitoring of Blood Glucose Arm



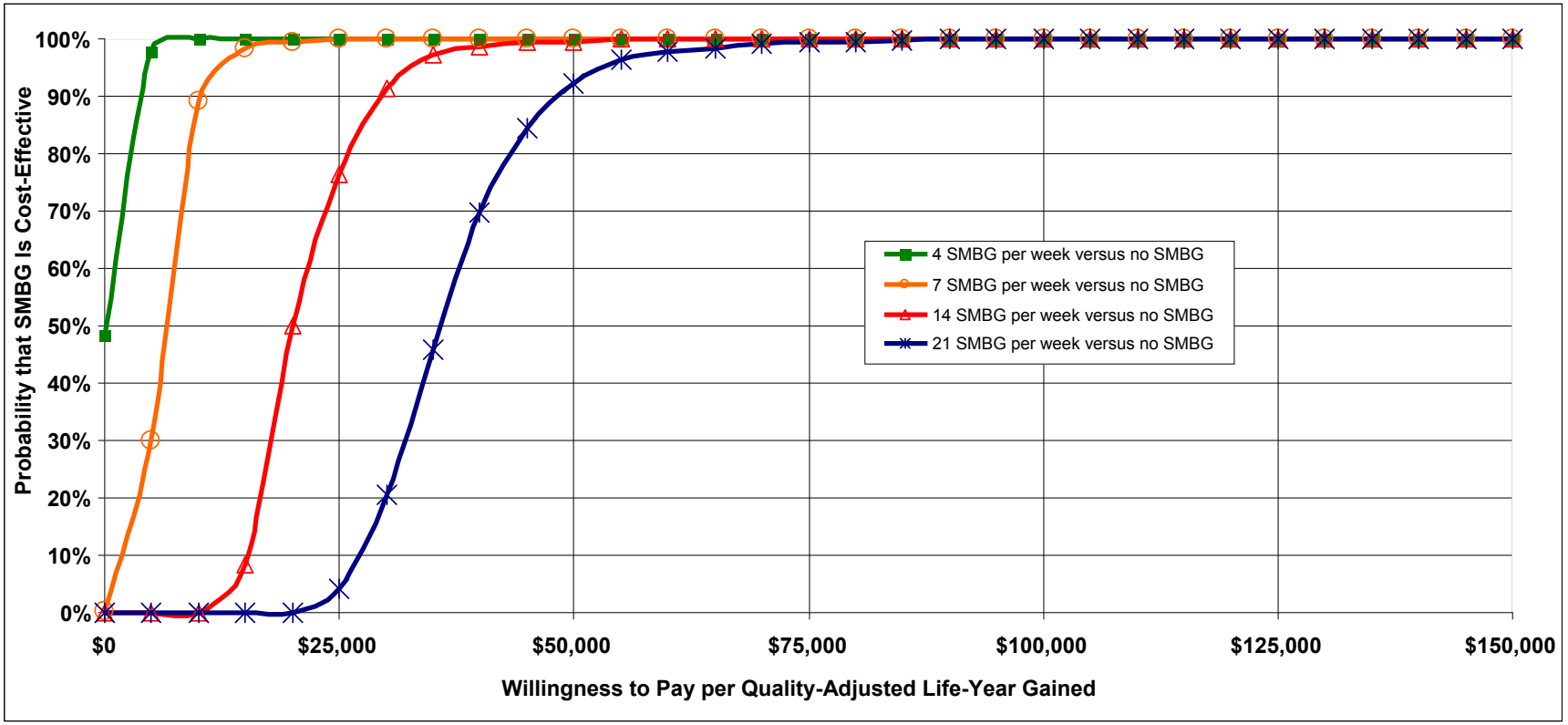
SMBG = self-monitoring of blood glucose.

Figure 13: Probability that Different Self-Monitoring of Blood Glucose Testing Frequencies Are Cost-Effective in Patients Who Are Using Insulin, Relative to Not Performing Self-Monitoring of Blood Glucose, if a Glycosylated Hemoglobin Estimate of Effect of 1.00% Is Achieved in the Self-Monitoring of Blood Glucose Arm



SMBG = self-monitoring of blood glucose.

Figure 14: Probability that Different Self-Monitoring of Blood Glucose Testing Frequencies Are Cost-Effective in Patients Who Are Using Insulin, Relative to Not Performing Self-Monitoring of Blood Glucose, if a Glycosylated Hemoglobin Estimate of Effect of 1.50% is Achieved in the Self-Monitoring of Blood Glucose Arm



SMBG = self-monitoring of blood glucose.

6 DISCUSSION

6.1 Summary of Main Findings

6.1.1 Patients with non–insulin-treated type 2 diabetes mellitus

The cost-effectiveness analysis uses clinical data derived from a methodologically sound systematic review,[19] which reports robust results. The systematic review[19] demonstrates that use of SMBG in patients with type 2 diabetes mellitus who are not using insulin is associated with statistically significant, albeit clinically modest,[72] improvement in glycemic control (WMD in A1C = -0.25%; 95% CI -0.36 to -0.15).

This analysis suggests that the clinically modest reduction in A1C resulting from SMBG translates into a small reduction in downstream diabetes-related complications. It was found that SMBG at a frequency of approximately nine tests per week was associated with an incremental cost of $113,643 per QALY gained, relative to no self-monitoring. Thus, clinical benefits and the associated cost-savings do not offset the cost associated with routine self-monitoring. Consequently, decision-makers will have to determine whether use of SMBG represents good value for money. In light of the increasing prevalence of type 2 diabetes mellitus, consideration of budget implications, along with cost-effectiveness, is necessary.

Through sensitivity analyses, conditions under which use of SMBG may be more cost-effective were explored. When the price of blood glucose test strips was decreased, cost-effectiveness estimates become more favourable. When the lowest price per test strip ($0.40 per strip) listed in the ODBP was applied in the model, the incremental cost of SMBG, relative to no self-monitoring, decreased from $113,643 to $63,892 per QALY gained. Similarly, when price per blood glucose test strip was reduced by 50% or 75%, ICURs fell to $58,615 and $31,101 per QALY gained, respectively. To the best of CADTH's knowledge, this is the first economic analysis[43,73] to explore the impact of test strip price on cost-effectiveness of SMBG.

Results from two-way sensitivity analyses suggest that more frequent SMBG (e.g., > 2 SMBG tests per day versus < 1 SMBG test per day) is associated with less favourable cost-effectiveness estimates. This finding is likely attributable to diminishing returns, as each additional SMBG test is likely to yield less benefit for each subsequent test. However, each test strip costs the same price per unit. Based on consideration of one-way and two-way sensitivity analyses, it appears that lower testing frequencies (e.g., one to two SMBG tests per week) are more likely to yield the most favourable cost-effectiveness estimates, whereas higher testing frequencies (e.g., > 12 to 14 SMBG tests per week) are likely to yield unfavourable cost-effectiveness estimates. In one-way sensitivity analysis of testing frequency, the benefit in A1C was assumed to remain constant; however, it is likely that the A1C benefit would diminish with test strip use (as in the two-way sensitivity analysis). As such, these results may underestimate the true cost-effectiveness ratio.

Results did not change substantially when considering patients with greater baseline A1C, or those treated with oral antidiabetes drugs alone. When the analysis was restricted to studies with baseline A1C > 8.0%, the incremental cost associated with SMBG decreased to $94,443 per QALY.

Similarly, when an A1C estimate of effect was used from studies where all patients enrolled used oral antidiabetes drugs, the incremental cost associated with SMBG decreases to $91,724 per QALY.

Most clinical guidelines suggest an SMBG frequency ≥ 7 test strips per week,[28] or that SMBG be individualized in patients with type 2 diabetes mellitus who are not using insulin.[6,74] Differences between this work and others are likely attributable to differences in consideration of costs and cost-effectiveness. The current analysis factors in costs and clinical effects. Clinical Practice Guidelines — including the 2008 Canadian Diabetes Association Clinical Practice Guidelines[6] — often do not consider costs or cost-effectiveness information.

6.1.2 Patients with insulin-treated type 2 diabetes mellitus

Studies identified in the review[19] are of low quality. Moreover, studies differed with respect to SMBG frequencies used and A1C estimates of effect reported. Because of this, the current analysis reports cost-effectiveness estimates for a range of plausible SMBG frequencies and A1C estimates of effect, as reported in the systematic review.[19]

Results demonstrate that patients who perform a higher frequency of SMBG must attain higher A1C estimates of effect to achieve more favourable cost-effectiveness estimates. As such, SMBG testing frequencies beyond 21 test strips per week required large A1C estimates of effect to achieve favourable incremental cost per QALY estimates. Available clinical evidence suggests that most patients are unlikely to achieve A1C estimates > 1.0%.[19] An SMBG testing frequency • 21 test strips per week is at odds with recommendations from clinical practice guidelines.[6,28] Some clinical guidelines suggest an SMBG frequency ≥ 2 or 3 test strips per day in patients with type 2 diabetes mellitus who are using insulin.[6,28] Differences in results are likely attributable to differences in consideration of costs and cost-effectiveness. Clinical practice guidelines — including the 2008 Canadian Diabetes Association Clinical Practice Guidelines[6] — may not consider costs or cost-effectiveness information.

6.2 Results in Relation to Other Economic Studies

Results reported in this economic report differ from those reported in earlier incremental cost-utility analyses.[43,50,73] Palmer et al.[43] found that routine use of SMBG was associated with incremental costs of £4,509 (2004 C$10,750[75]), £4,593 (2004 C$10,950[75]), and £15,515 (2004 C$36,991[75]) per QALY gained, for patients with type 2 diabetes mellitus using oral antidiabetes drugs, insulin, and diet and exercise, respectively. Palmer et al.[43] assumed that patients using diet and exercise, oral antidiabetes drugs, and insulin used one, two, and three test strips per day, respectively. Similarly, Tunis and Minshall[73] found that SMBG once daily in patients with type 2 diabetes mellitus taking oral antidiabetic drugs was associated with an incremental cost of US$7,856 per QALY gained (2006 C$8,909[76]). Simon et al.[50] found that SMBG was more costly and less effective than usual care in patients with type 2 diabetes mellitus who are not using insulin, a result which was based on findings from the Diabetes Glycaemic Education and Monitoring (DiGEM) trial.[38 50]

Differences in results are likely attributable to differences in model inputs and assumptions. For patients with non–insulin-treated type 2 diabetes mellitus, the CADTH economic analysis obtains clinical inputs from a CADTH systematic review of randomized controlled trials[35,36,38,48,50] that produced an A1C effect estimate of 0.25% favouring SMBG. In contrast, Tunis and Minshall[73] used a higher A1C effect estimate (A1C difference of 0.45% favouring SMBG) derived from an observational study,[21] whereas Palmer et al.[43] used estimates (A1C difference of 0.40% favouring SMBG in patients using oral antidiabetic drugs) heavily influenced by results from the same observational study.[21] Unlike RCTs, observational studies do not control for unknown confounding variables, and estimates are likely to be biased in favour of SMBG. Simon et al.[50] used data based solely on the DiGEM trial,[50] which was included in the CADTH systematic review. The A1C estimate of effect, however, in the DiGEM trial[50] was smaller (A1C difference of 0.14% favouring SMBG) than that reported in the CADTH systematic review, which included seven RCTs.[35,36,38,48,50] Moreover, Simon et al.[50] applied a decrement in HRQoL in patients who perform SMBG, due to increased anxiety and depression, which CADTH did not. Although a decrement for HRQoL was not applied in the reference case, it is included in the CADTH sensitivity analyses.

For patients with insulin-treated type 2 diabetes mellitus, Palmer et al.[43] used an A1C estimate of effect (A1C difference of 0.6% favouring SMBG), based on results from an observational study.[21] In contrast, the CADTH economic analysis takes a very cautious approach in presenting cost-effectiveness information. Rather than present one cost-effectiveness estimate, CADTH presents results for a variety of plausible scenarios. The rationale behind this decision is based on:

- paucity and quality of clinical evidence
- large variation in A1C estimates of effect across studies
- different SMBG testing frequencies used in studies.

Differences in utility decrements may also explain some of the differences in results between studies. HRQoL scores in earlier analyses[43,73] are based on data from patients with type 2 diabetes mellitus.[60] The study[60] for which these estimates are based, albeit rigorous, did not control for non–diabetes-related complications and other confounding variables (e.g., income, education, ethnicity, number of comorbidities), all of which impact HRQoL. The CADTH economic analysis, in contrast, uses estimates obtained from the general population, as recommended in CADTH Economic Guidelines.[54] Estimates are obtained from a community-based EQ-5D Catalogue from the US,[56,57] which has been described as "as good as it gets"[77] given the level of detail in controlling for chronic conditions and other determinants of health (e.g., age, gender, income, education).

Palmer et al.[43] and Tunis and Minshall[73] also used the Center for Outcomes Research (CORE) Diabetes Model[78] as opposed to the UKPDS Outcomes Model.[30] The CORE Diabetes Model[78] includes a number of morbidities and intermediate states that are not included in the UKPDS Outcomes Model.[43] However, the impact of this difference should not be overstated. First, outcomes that were excluded were not major endpoints in the UKPDS Outcomes Model.[43] Second, Tunis and Minshall[73] reported very small absolute risk differences for morbidities and intermediate states that are not included in the UKPDS Outcomes Model.[43] Finally, for many sub-models, the CORE Diabetes Model[78] uses regression equations derived from the older UKPDS 56 Risk Engine,[79] as opposed to equations presented in the more recent UKPDS 68 Outcomes Model.[43] The UKPDS Outcomes Model[43] should provide a more accurate estimate of events because it uses a wider

variety of input data, including knowledge of previous events, and incorporates updated risk factor data over time.[43]

Differences in cumulative incidence rates of events between the UKPDS Outcomes Model[43] and the CORE Diabetes Model[78] have been observed, particularly in end-stage renal disease.[73] The UKPDS Outcomes Model[43] forecasts end-stage renal disease using data based on sophisticated regression equations derived from UKPDS 68, in which a wide variety of input data were incorporated, including knowledge of previous events.[30] Cumulative incidence rates of end-stage renal disease as projected by the UKPDS Outcomes Model[43] coincide with those reported in recent Canadian diabetes studies.[40-43,47] The incidence of end-stage renal disease for patients in the CORE Diabetes Model[78]was derived using data from several smaller and less credible studies.[30] Findings from validation analyses for the end-stage renal disease sub-model within the CORE Diabetes Model[78] have been mixed.[80] In one validation analysis, the CORE Diabetes Model[78] overestimated the 30-year cumulative incidence of end-stage renal disease by fourfold, whereas in another analysis, it slightly underestimated the cumulative incidence of end-stage renal disease.[80]

6.3 Strengths and Limitations of the Approach

There are a number of strengths in the CADTH approach. First, this economic analysis follows a transparent and accepted methodology. It adheres to the Guidelines for the Economic Evaluation of Health Technologies in Canada.[54] Second, CERC, which is comprised of endocrinologists, family physicians, pharmacists, and health economists, provides advice throughout the development of this current economic analysis. Third, this economic evaluation uses the well-validated UKPDS Outcomes Model.[30] The ability of the UKPDS Outcome Model[30] to forecast long-term diabetes-related complications in patients with type 2 diabetes mellitus has been validated against published clinical and epidemiological studies.[80] Fourth, as recommended by economic guidelines,[56,57] disutility estimates used in the current economic analyses were obtained from a community-based US EQ-5D catalogue.[56,57] Fifth, clinical inputs, when available, are derived from a recent systematic review.[19] Finally, detailed sensitivity and variability analyses were performed to examine robustness of results to variation in model parameters and assumptions. Other economic evaluations[43,73] have not explored uncertainty and variability of results in this level of detail.

Nevertheless, CADTH results and the strength of the conclusions are limited by available clinical evidence. The paucity of good-quality clinical evidence, particularly in patients with insulin-treated type 2 diabetes mellitus, necessitated the use of low-quality clinical evidence to form economic conclusions. Consequently, results for these populations should be interpreted with caution.

Another limitation is that the model used A1C, a surrogate endpoint, to project the occurrence of long-term diabetes related complications. The validity of surrogate outcomes is, and continues to be, debated in the literature.[81-84] Nevertheless, A1C is routinely used in clinical practice as an indicator of treatment success[69] and, thus, is likely to provide an acceptable estimate of efficacy for these analyses.

A number of morbidities and intermediate states are not included in the UKPDS Outcomes Model.[43] However, as noted above, this limitation should not be overstated, as Tunis and Minshall[73] reported very small absolute risk differences for morbidities, and intermediate states are not included in the UKPDS Outcomes Model.[43] Post-monitoring of data from the UKPDS Outcomes Model[43], in time, will provide additional data for these states. When data become available, a reassessment of the economic evaluation of SMBG in patients with type 2 diabetes mellitus may be warranted.

There is a lack of clinical data demonstrating that SMBG decreases the incidence of hypoglycemia, and in particular severe episodes. Moreover, the UKPDS Outcomes Model[43] cannot accommodate hypoglycemia. Consequently, the CADTH economic analyses do not incorporate benefits that may be incurred, resulting from decreased hypoglycemia. Hypoglycemic episodes, however, are rare in patients with type 2 diabetes mellitus not using insulin;[85] consequently, this inherent limitation should not significantly alter cost-effectiveness estimates for this population. For patients with insulin-treated type 2 diabetes mellitus, the incidence of severe hypoglycemia is greater, albeit less frequent than in patients with type 1 diabetes mellitus.[25-27] Finally, for the reference case analyses, CADTH assumed that SMBG was not associated with a decrement in HRQoL, despite evidence from the DiGEM trial suggesting the contrary.[38,50] Thus, current estimates may be biased in favour of SMBG. Future investigators should include methodologically rigorous HRQoL assessments in their study protocols. If additional data become available and clearly demonstrate that SMBG decreases HRQoL, then a reassessment of the economic evaluation of SMBG may be warranted.

6.4 Generalizability

CADTH derived A1C estimates of effect from a meta-analysis of seven RCTs. Overall, findings in the CADTH systematic review are consistent with those reported in other published systematic reviews.[86-90] Estimates of A1C effect, however, differ from those reported in observational studies. Consequently, when an A1C estimate of effect from an observational study was used, cost-effectiveness estimates for SMBG improved. However, it should be noted that observational studies do not control for confounding variables and have a greater likelihood of selection bias, making it difficult to isolate the effect of SMBG on glycemic control.[91] Earlier industry-sponsored studies[43,50,73] have used estimates from observational studies in their economic analyses, an assumption that will likely bias results in favour of SMBG.

Studies that are most generalizable to the overall population are of relevance to decision-makers. Consequently, the DiGEM study[38], which does not restrict patients by baseline A1C is of particular interest to population-level decisions. The baseline A1C of patients in the DiGEM trial[38] closely coincides with that reported in the DICE study.[42] This base-case analysis used an baseline A1C derived from seven RCTs (i.e., 8.5%) despite being much higher than that reported in the DICE study.[42] This assumption may bias the reference case analysis in favour of SMBG. CADTH performed detailed one- and two-way sensitivity analyses to explore how baseline A1C may impact cost-effectiveness results. When both A1C estimate of effect and baseline A1C were varied simultaneously, patients with A1C < 8.0% yielded an ICUR of $213,503/QALY, whereas those with baseline A1C between 8.0% and 10.5% yielded an ICUR of $94,443 per QALY.

The CADTH reference case analysis uses the most "internally valid" cohort. That is, CADTH attempted to derive patient characteristics from the same population that was used to generate A1C estimates of effect. However, because RCTs did not report history of diabetes-related complications and excluded patients with impending diabetes-related complications or history of serious disease, CADTH assumed that patients had no history of serious diabetes-related complications. This assumption could inhibit the generalizability of findings. CADTH performed sensitivity analyses to examine the potential impact that this assumption may have on the results. When the cohort was modified to reflect the history of diabetes-related complications as reported in Canadian observational studies, the incremental cost-effectiveness of SMBG, relative to no SMBG, decreased from $113,643 per QALY to $86,656 per QALY.

CADTH is the first to conduct sensitivity analyses related to "internal" validity versus "generalizability." In contrast, other studies[73] have obtained baseline characteristics and A1C estimates of effect from disparate sources and did not conduct sensitivity analyses on their assumptions. For example, Tunis and Minshall[73] obtained A1C effect estimates from an observational study of "new SMBG users" and obtained patient characteristics from a separate group of patients that had more severe diabetes (e.g., illness duration of 12 years).[73,92] Consequently, estimates by Tunis and Minshall[73] are likely to overestimate the benefit of SMBG.

6.5 Knowledge Gaps

The lack of high-quality studies in patients with insulin-treated type 2 diabetes mellitus limits CADTH's ability to draw conclusions about relative benefits and costs of SMBG in this population. Given the increasing prevalence of type 2 diabetes mellitus, RCTs evaluating the effect of alternative SMBG testing frequencies in patients in this population should be a high priority for researchers and funders.

Given the paucity and quality of evidence, an economic evaluation was not conducted for patients with type 1 diabetes mellitus. This is a key research gap; future well-designed RCTs are needed to assess the impact of alternative SMBG frequencies on glycemic control and prevention of hypoglycemic episodes in patients with type 1 diabetes mellitus. The development of more robust equations for models, specific to patients with type 1 diabetes mellitus and based on the most recent data from the Diabetes Control and Complications Trial, would also be of value. Collectively, more robust clinical data and equations will enable analysts to more accurately forecast the occurrence of diabetes-related complications and, in-turn, generate more robust cost-effectiveness estimates.

For patients with type 2 diabetes mellitus who were not using insulin, the clinical evidence was more robust. CADTH identified seven RCTs,[5,34-39] some of which were reported to be of high quality.[34,36,38] Although these studies[5,34-39] reported consistent results for A1C estimates of effect, in general, there was a lack of data regarding the effect of SMBG on HRQoL and hypoglycemia (specifically, for patients using sulphonylureas). Only the DiGEM trial[38,50] reported findings for both HRQoL and incidence of hypoglycemia. This is a key knowledge gap, and future investigators should include appropriate HRQoL and hypoglycemia assessments in their study protocols. Stratification of results by type of oral antidiabetes drug may also be beneficial.

7 CONCLUSION

The strength of CADTH's economic conclusions are limited by available clinical evidence. Overall, the quality of evidence for patients with insulin-treated diabetes (either type 1 or type 2 diabetes mellitus) is poor. For patients with non–insulin-treated diabetes, the clinical evidence is more robust. Within the limitations of modelling and available data, CADTH concludes:

- Routine use of SMBG (≥ 1 test strip per day) in all patients with non–insulin-treated type 2 diabetes mellitus is associated with incremental cost of $113,643 per QALY gained, relative to no SMBG.
- A reduction in the price of blood glucose test strips would improve the cost-effectiveness of SMBG. To the best of CADTH's knowledge, this represents the first Canadian economic analysis that explores the impact of price of test strips on cost-effectiveness of SMBG.
- For patients with insulin-treated type 2 diabetes mellitus, results suggest that SMBG testing frequencies beyond 21 test strips per week require large A1C estimates of effect to achieve favourable incremental cost per QALY estimates.

The COMPUS model does not incorporate HRQoL due to conflicting evidence. Potential benefits associated with a reduction in hypoglycemia were also not incorporated in the model due to lack of evidence. Further well-designed RCTs are needed to explore the impact of SMBG on HRQoL and incidence of hypoglycemia among patients with either insulin- or non–insulin-treated type 2 diabetes mellitus.

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