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OPTIMAL THERAPY REPORT

COMPUS
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Optimal Therapy Recommendations for the Prescribing and Use of Blood Glucose Test Strips

Supporting Informed Decisions

À l'appui des décisions éclairées

This report is 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 contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. 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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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 in clinical practice, then proposing evidence-based interventions to address these gaps, and 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) members are listed in Appendix A of this document.
- Stakeholder feedback.

1.1 COMPUS Expert Review Committee (CERC)

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 (Appendix A). 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. CERC develops recommendations and advice with the aim of contributing to optimal health outcomes and fostering a sustainable health care system for Canadians. CERC considers the practical needs of policy makers, health care providers, and consumers in implementing and using the

recommendations and advice toward the promotion of optimal practices. 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 the 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 uncertainty regarding the benefits of self-monitoring of blood glucose (SMBG), especially in patients with type 2 diabetes mellitus not using insulin.[1-4] Moreover, costs associated with self-monitoring of blood glucose are high[5] and rising steadily[5-7] due to the increasing prevalence of type 2 diabetes.[8] In some publicly funded drug plans in Canada, blood glucose test strips are among the top five classes in total expenditure,[5] and more money is often spent on blood glucose test strips than for all oral antidiabetes drugs.[9,10] In 2006, $250 million was spent on blood glucose test strips in eight publicly funded drug plans in Canada (Newfoundland, Nova Scotia, Quebec, Ontario, Manitoba, Saskatchewan, British Columbia, Non-Insured Health Benefits Program), while over $120 million was spent in privately funded drug plans.*[10] It is estimated that greater than 50% of the total cost of blood glucose test strips is expended on patients with type 2 diabetes who are not using insulin agents.**[10]

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]

* Extrapolated from data reported for 67% of privately funded drug plans in Canada.

The global prevalence of diabetes is estimated to be 246 million and is projected to increase to 380 million by 2025.[15] In 2005/2006, approximately 1.9 million (5.9%) 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,[17] and the true prevalence of diabetes may approach 2.0 million.[18]

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 in order 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 antidiabetic drugs), and SMBG are recommended approaches in improving glycemic control.[17] 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

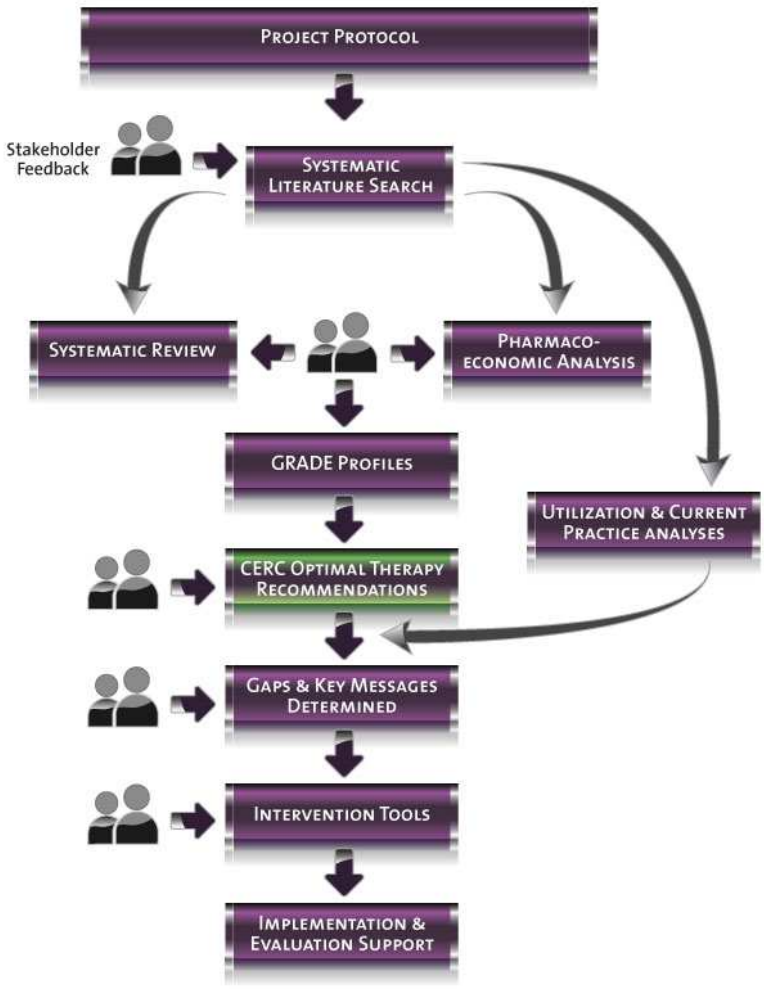
The purpose of SMBG is to collect detailed information about glucose levels across various time points each day and take appropriate action should those levels be outside the desired range.[19,20] SMBG requires that patients prick their finger with a lancet device to obtain a small blood sample (0.3 µL to 5 µL).[19,20] 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.[19] Results, based on an automated reading, are available from the photometer within five to 30 seconds.[19] 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.[19,20]

3 OBJECTIVE

This report provides recommendations for the optimal prescribing and use of blood glucose test strips for policy decision makers, health care professionals, and patients.

4 PROJECT OVERVIEW

Once a topic is selected, COMPUS undertakes activities related to key areas in the COMPUS procedure. The CAC provides advice and guidance throughout the process, from topic identification through to supporting intervention 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 medications. A broad range of stakeholders are invited to provide feedback at key stages in the COMPUS process.



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

This report represents the final optimal therapy recommendations for the prescribing and use of blood glucose test strips (green box).

5 RESULTS

5.1 Optimal Therapy Recommendations

Through careful evaluation of the evidence (Section 6) and significant deliberation of the issues (Section 7), CERC produced seven recommendations and suggestions on the use of blood glucose test strips for SMBG in children with type 1 diabetes and adults with type 1, type 2, and gestational diabetes. CERC applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (for developing recommendations (Section 7). As stipulated by the GRADE method, the strength of a recommendation is reflected by the use of the words "suggests" or "recommends,"(i.e., for a weak recommendation, "CERC **suggests** that...", and for a strong recommendation, "CERC **recommends** that...").

A summary of CERC's recommendations and suggestions is presented in Table 1. In addition to the recommendations, CERC specified that SMBG should not be applied in isolation; rather, it should be a component of a broader diabetes self-management strategy. Patients for whom SMBG is recommended require education and regular feedback so that blood glucose results are interpreted and applied appropriately.

Table 1: Summary of CERC Recommendations and Suggestions

- For adults and children with type 1 diabetes, CERC **recommends** that the optimal daily frequency of SMBG be **individualized**.
- For adults with type 2 diabetes using insulin with or without oral antidiabetes drugs, CERC **recommends** that the optimal daily frequency of SMBG be **individualized**. CERC **suggests** that the maximum weekly frequency of SMBG is **14 tests per week** for most of these patients.
- For most adults with type 2 diabetes using oral antidiabetes drugs (without insulin) or no antidiabetes drugs, the routine use of blood glucose test strips for SMBG is **not recommended** by CERC.
- For women with gestational diabetes not using antidiabetes drugs, CERC **recommends** that the optimal daily frequency of SMBG be **individualized**.

Detailed information around individual CERC recommendations/suggestions (i.e., vote results, the rating of overall quality of clinical evidence, underlying values and preferences related to the recommendations/suggestions, clinical notes, and context) are provided in Appendix B.

5.2 Research Gaps

An important aspect of COMPUS's mandate includes the identification and dissemination of research gaps; that is, areas in which there is insufficient evidence to guide optimal prescribing and use. The following sections outline gaps in research related to blood glucose test strips for

SMBG. Identification of these gaps will assist researchers and research funding organizations in planning future clinical research. The knowledge that results from such research will lead to improved clinical practice and better outcomes for patients with diabetes.

5.2.1 Populations and comparisons with insufficient evidence

Populations and comparisons for which evidence from randomized controlled trials and/or observational studies was absent are shown in Table 2. First Nations populations were of special interest given the high prevalence of diabetes.[8] Additional special populations identified by CERC included those for whom hypoglycemia may pose occupational risks (e.g., professional drivers, airline pilots, and construction workers). There were no studies identified comparing the use of SMBG versus no SMBG, or different frequencies of SMBG, in these populations.

Additional populations of interest for which there was no evidence include patients with any of the following characteristics: newly initiated on insulin; with a history of hypoglycemia; experiencing acute illness; undergoing changes in insulin dose/regimen or significant changes in routine; poorly controlled or unstable blood glucose levels; and pregnant or planning a pregnancy.

Table 2: Populations and Comparisons for Which No Evidence Was Found in the Systematic Review of Blood Glucose Test Strips

Population	SMBG Versus no SMBG	SMBG Frequency Comparisons
Pediatric		
Children with type 1 diabetes	Research question not addressed*	No RCTs
Children with type 2 diabetes	No RCTs, No OBS	No RCTs, No OBS
Children with monogenic diabetes	No RCTs, No OBS	No RCTs, No OBS
Adult		
Type 1 diabetes	Research question not addressed†	No RCTs
Patients treated with insulin secretagogues	RCT evidence available	No RCTs
Pregnant women type 1 diabetes	Research question not addressed†	No RCTs, No OBS
Pregnant women type 2 diabetes	No RCTs, No OBS	No RCTs, No OBS
Patients with gestational diabetes not using diabetes pharmacotherapy	RCT evidence available	No RCTs, No OBS
Patients with gestational diabetes using diabetes pharmacotherapy	No RCTs, No OBS	No RCTs, No OBS
Patients with monogenic diabetes	No RCTs, No OBS	No RCTs, No OBS

*SMBG is a standard of care in these populations
OBS=observational studies; RCTs=randomized controlled trials; SMBG=self-monitoring of blood glucose

5.2.2 Outcomes with limited evidence

There was insufficient evidence for a number of outcomes considered important for making recommendations on the use of blood glucose test strips for SMBG. Specifically, there were no studies reporting evidence for the following outcomes: hyperglycemic diabetic ketoacidosis, patient self-management, macrovascular complications, micovascular complications, and mortality. In addition, glycosylated hemoglobin (A1C) was the only outcome available for adults and children with type 1 diabetes, and for adults with type 2 diabetes who do not use antidiabetes drugs.

6 THE EVIDENCE

The clinical evidence for the use of blood glucose test strips for SMBG was derived from the COMPUS Optimal Therapy Report: *Systematic Review of Use of Blood Glucose Test Strips for the Management of Diabetes Mellitus*. Cost-effectiveness data for the use of blood glucose test strips for the self-monitoring of blood glucose (SMBG) were derived from a pharmacoeconomic analysis conducted by CADTH using the United Kingdom Prospective Diabetes Study (UKPDS) model. The results of those analyses are presented in the Optimal Therapy Report: *Cost-effectiveness of Blood Glucose Test Strips in the Management of Adult Patients With Diabetes Mellitus*. Stakeholder feedback was requested and incorporated into both the systematic review and the cost-effectiveness analyses, as directed by CERC.

7 CONSIDERATION OF THE EVIDENCE

7.1 CERC Process and Perspective

CERC members consider both clinical-effectiveness (i.e., benefits, harms, and burdens), and cost and cost-effectiveness data, when formulating recommendations. Committee members bring their individual expertise and experience to bear (as experts, general practitioners, interventionists, consumers, members of the public), and draw upon their own values and preferences to discuss the evidence and reach conclusions.

The process by which recommendations are formulated by CERC consists of two main stages. First, CERC considers the clinical evidence regarding safety and effectiveness and draws clinical findings regarding clinically important differences (if any) among the therapies in question. Second, CERC reviews and considers the cost and cost-effectiveness evidence. The sequential consideration of the clinical evidence, followed by the economic evidence, allows for clear delineation of the impact of cost-effectiveness on recommendations, thus increasing transparency of the deliberative process. Optimal therapy recommendations are then formulated based on the efficacy, safety, and pharmacoeconomic data.

CERC develops recommendations and advice with the aim of contributing to optimal health outcomes and fostering a sustainable health care system for Canadians. CERC considers the practical needs of policy-makers, health care providers, and consumers in implementing and using

the recommendations and advice toward the promotion of optimal practices. When possible, guidance is provided for management of specific subgroups of the identified population that may benefit from an alternate approach. To assist in knowledge transfer to intended audiences, CERC also develops clinical notes to provide guidance based on clinical judgment where there is insufficient evidence. Context statements also accompany the recommendations to provide commentary relating to the evidence.

COMPUS applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the available evidence and facilitate the generation of optimal therapy recommendations by CERC.[21] The GRADE methodology was developed by the GRADE Working Group, an international collaboration of methodologists, to provide committees charged with formulating recommendations with a framework for evaluating evidence. GRADE provides a systematic and transparent approach to appraise quality of evidence, weigh the balance of benefits versus harms, identify underlying values and preferences, and rate the overall strength of recommendations.[22] The GRADE methodology is used by a number of organizations world-wide, including the World Health Organization[23] and the American Thoracic Society.[24]

The process by which CERC used the GRADE evidence profiles and economic data to generate optimal therapy recommendations for blood glucose test strips consisted of eight steps. Each of these steps is described in further detail in Appendix C.

1. Individual review of GRADE evidence profiles and provision of feedback.
2. Discussion of clinical-effectiveness evidence and collated feedback from members.
3. Identification of clinical findings based on clinical evidence of effectiveness and safety.
4. Identification of draft optimal therapy recommendations based on clinical conclusions and cost and cost-effectiveness information.
5. Identification of underlying values and preferences for each recommendation.
6. Appraisal of overall quality of evidence.
7. Grading strength of recommendations.
8. Identification of research gaps.

7.2 Specific Considerations

Prior to initiation of the systematic review by CADTH, members of CERC identified the outcomes for which evidence was required to make recommendations for the use of blood glucose test strips for SMBG. These included:

- long-term complications of diabetes (e.g., mortality, cardiovascular disease, nephropathy, retinopathy)
- surrogate outcomes related to glycemic control (i.e., A1C, fasting plasma glucose, two-hour post-prandial plasma glucose)
- hypoglycemia
- body weight and body mass index
- quality of life and patient satisfaction
- resource use and costs.

For surrogate outcomes related to glycemic control, a published schema designed by Lassere *et al.* that assessed the validity of surrogate outcomes[25] was employed to guide CERC's deliberations.

7.2.1 A1C

A1C was the most frequently reported measure of glycemic control in the studies included in the CADTH systematic review of blood glucose test strips. During the formulation process for the *Optimal Therapy Recommendations for the Prescribing and Use of Insulin Analogues;*[26] (the previous COMPUS topic under diabetes management), CERC deliberated extensively on the evidence available to support the validity of A1C as a surrogate outcome for clinically relevant complications of diabetes,[13,14,25,27-48] and the minimal difference in this outcome that could be considered clinically relevant.[49-51] All the CERC members believed there were important limitations associated with the use of A1C as a surrogate outcome. Most felt that A1C was a valid surrogate in trials of type 1 diabetes, especially for microvascular complications. There was less certainty regarding its validity in type 2 diabetes, especially with respect to cardiovascular outcomes due to the importance of numerous other risk factors, such as blood pressure and lipid profile. A minority felt that A1C was an invalid surrogate outcome for both type 1 and type 2 diabetes given the low scores achieved for both conditions according to the surrogate validation schema.[25]

CERC recognized that the widespread implementation in clinical practice of A1C as a parameter to monitor treatment efficacy in patients with either type 1 or type 2 diabetes has revolutionized diabetes care by allowing for the measurement of long-term glycemic control. Furthermore, diabetes treatment guidelines define optimum glycemic control based on A1C targets. CERC agreed to use a minimal clinically important difference in A1C between 0.7% to 1% during the committee's deliberations.

7.2.2 Fasting and post-prandial glycemia

Both fasting and post-prandial glucose scored low, according to the validation schema for surrogate outcomes by Lassere et al.[25] However, CERC recognized that post-prandial blood glucose is increasingly seen as an important target in the treatment of type 2 diabetes due to its potential association with cardiovascular outcomes.

7.2.3 Hypoglycemia

CERC recognized that hypoglycemia, particularly severe and nocturnal episodes, pose a substantial barrier to achieving optimal glycemic control in patients with diabetes. CERC noted that the risk of hypoglycemia varied across patients, as well as within an individual patient over time, depending upon the type of antidiabetes therapies used and a number of other circumstances.

CERC deliberated extensively upon the potential benefits of SMBG in reducing the risk of hypoglycemia in patients at higher risk, particularly those treated with insulin or insulin secretagogues. Within the analysis of evidence related to the effects of SMBG on patients with type 2 diabetes, separate results were presented to CERC for patients treated with insulin or insulin secretagogues to allow for a clearer assessment of the effect of SMBG on the risk of hypoglycemia. In the absence of sufficient evidence for this outcome, CERC issued clinical notes to

identify patients and situations in which SMBG may be beneficial to reduce the risk of hypoglycemia. CERC also recognized that patients using SMBG must be properly educated in order to take appropriate actions when SMBG readings are lower than normal.

7.2.4 Education provided with SMBG

CERC recognizes that performing SMBG is more likely to have a positive impact on diabetes-related outcomes if patients and health care providers take appropriate actions based upon blood glucose readings. Patient education regarding self-interpretation and application was seen by CERC as a key component of SMBG as the available evidence was assessd and recommendations were developed. Because studies varied in the degree to which such education was provided, there was concern that any benefits of SMBG prescribed in combination with patient education may be negated by studies providing insufficient education. To avoid this possibility, subgroup analyses were performed in an attempt to isolate the effect of SMBG prescribed with adequate patient education. The results did not provide enough information for CERC to isolate an effect of education on the available outcomes.

7.2.5 SMBG as a component of self-management

CERC discussed possible benefits of SMBG beyond those measured in clinical trials. For example, SMBG may help assess the need for medication or lifestyle changes more quickly than periodic A1C testing. It may also assist in the timely assessment of the safety and efficacy of such changes, and provide tangible evidence for patients regarding benefits of treatment.

CERC further acknowledged that SMBG is widely held by health care providers and patients with diabetes to be an integral component of diabetes self-management strategies. The overall contribution of SMBG as a component of broader self-management strategies is difficult to isolate given the complex and varying nature of the different approaches. In the CADTH Systematic Review of Blood Glucose Test Strips for SMBG, studies in which the patient management strategy was substantially different between comparator arms in aspects not related to SMBG were excluded in the selection process to isolate the effects of SMBG. This included well-known, randomized controlled trials such as the Diabetes Control and Complications Trial (DCCT) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD). SMBG was only one of many components of the overall strategy used to achieve optimal blood glucose control in these trials, hence the specific contribution of SMBG could not be isolated. At the request of CERC, a literature search was performed to identify reviews investigating the effectiveness of diabetes self-management strategies, and the role of SMBG within such programs.[52-56] Although no specific evidence relating to the benefits of SMBG within self-management programs was identified, the results of these studies helped consolidate the CERC's view that SMBG should be practiced in conjunction with education and other self-management strategies.

7.2.6 Consideration of non-randomized studies

CERC considered the strengths and weaknesses of the various study designs included in the CADTH systematic review (i.e., randomized controlled trials, non-randomized trials, time series analysis, retrospective cohort studies, and prospective cohort studies). Non-randomized studies

can be defined as any quantitative study estimating the effectiveness of an intervention that does not use randomization to allocate participants to comparator groups.[57] In comparison with randomized controlled trials, the potential for selection bias and confounding (i.e., distortion in the degree of association between performing SMBG and the outcome of interest) is greater in non-randomized studies. When evaluating the available evidence, CERC identified confounding and selection bias as major limitations of evidence obtained from non-randomized studies.

7.2.7 Consideration of stakeholder feedback

Stakeholder feedback on the draft *Optimal Therapy Recommendations for the Prescribing and Use of Blood Glucose Test Strips* report was solicited for a period of 20 business days. Feedback was received from a variety of sources, including manufacturers of blood glucose test strips, associations and groups linked to diabetes care, and individuals from academic institutions. All stakeholder feedback was collated and brought to CERC for consideration. In several instances, CERC's deliberation of stakeholder feedback resulted in modifications to the report; specifically, the clinical notes accompanying the recommendations and the specific considerations described in this section. Feedback from stakeholders generally focused on limitations of the available evidence, and additional clinical scenarios in which increased testing was felt to be beneficial (e.g., safety concerns for patients on insulin or insulin secretagogues).

8 NEXT STEPS

These recommendations will be widely disseminated to encourage uptake and implementation by decision-makers at various levels (e.g., policy decision-makers, health care professionals, and patients). Gaps in practice/knowledge related to the use of blood glucose test strips for SMBG will be identified by comparing the final recommendations to information on current practice (*Current Practice Analysis of Health Care Providers and Patients on Self-Monitoring of Blood Glucose*) and utilization (*Current Utilization of Blood Glucose Test Strips in Canada*)[10] of these products in Canada.

Key messages to promote the optimal prescribing and use of blood glucose test strips for SMBG will be developed to address identified gaps in practice and knowledge. Intervention tools will be populated with the key messages and related evidence for implementation across Canada.

APPENDIX A: EXPERT COMMITTEE AND CONTRIBUTORS

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Conflicts of Interest

Dr. Lisa Dolovich was co-investigator in studies on behaviour change interventions funded by Merck Frosst Canada Ltd., GlaxoSmithKline Inc., Aventis Pharma Ltd., Eli Lilly Canada Inc., and Crystaal Corporation.

Dr. Michael Evans has received grant support from AstraZeneca Canada Inc. to offset the cost of Mini-Med School, an educational program for the public.

Dr. Scott Klarenbach is a member of a research group funded by an unrestricted grant from Amgen Canada Inc. and Merck Frosst Canada Ltd. to the Alberta Kidney Disease Network.

Dr. Ann Colbourne has received honoraria for educational lectures for Novo Nordisk Canada Inc., LifeScan Inc., Sanofi-Aventis Canada Inc., AstraZeneca Canada Inc., Pfizer Canada Inc., and Merck Frosst Canada Ltd. of $5,000 or less. She was involved in a community-based interprofessional collaborative chronic disease management program, funded by AstraZeneca Canada Inc., Pfizer Canada Inc., and Merck Frosst Canada Ltd.

Dr. Marshall Dahl has received an honorarium for less than $5,000 from Eli Lilly for his work related to workshops. He has also received an arms-length grant for a diabetes study in coronary artery patients from GlaxoSmithKline Inc. In addition, Dr. Dahl has received an honorarium for less than $5,000 from Sanofi-Aventis Canada Inc. for a lecture.

Dr. Heather Dean has received financial support from Eli Lilly Canada Inc. to attend an investigators' meeting on growth hormones in 2005.

Dr. Ehud Ur has received honoraria for educational lectures, honoraria for organizing conferences, or other honoraria for $5,000 or less from GlaxoSmithKline Inc., Novo Nordisk Canada Inc., Sanofi-Aventis Canada Inc., Merck Frosst Canada Ltd., and Novartis Pharmaceuticals Canada Inc. He has received funding for consultant or advisory services from GlaxoSmithKline Inc. and Novo Nordisk Canada Inc., and has received research grants through the Queen Elizabeth II Foundation (Halifax) from GlaxoSmithKline Inc., Novo Nordisk Canada Inc., and LifeScan, Inc.

None of the other CERC members declared any conflicts of interest. Conflict of Interest Guidelines are posted on the CADTH website.

APPENDIX B: DETAILED RECOMMENDATIONS WITH SUPPORTING EVIDENCE

BACKGROUND

The detailed recommendation tables offer the following information:

- **Vote results —** Indicates the number of CERC members voting in favour of the proposed recommendation statement.

- **CERC rating of overall quality of clinical evidence —** Indicates results of the vote by CERC on the overall quality of the evidence available for a recommendation. Possible ratings of quality were "low", "moderate", or "high", and were based on criteria developed by the GRADE working group.

- **Strength of recommendation —** Indicates the results of the vote by CERC on the strength of the recommendation, based on criteria developed by the GRADE working group. Possible ratings are "strong" or "weak".

- **Underlying values and preferences —** Indicates the values and preferences that CERC members identified as most important in guiding the recommendation.

- **Clinical note —** Provides guidance from CERC regarding specific, clinical considerations that may assist policy decision-makers, clinicians, and patients in selecting optimal therapy.

- **Context —** Lists key points arising from CERC's deliberation of the clinical and economic evidence, as well as clinical issues, pertaining to the recommendation. This information is provided to assist clinicians, patients, and policy decision-makers with the interpretation and application of the recommendation.

- **Evidence –** The most pertinent evidence used in generating the recommendations is presented following each recommendation table. The detailed evidence profiles for each condition and outcome are presented in the COMPUS Optimal Therapy Reports: *Systematic Review of Use of Blood Glucose Test Strips for the Management of Diabetes Mellitus*[58] and *Cost-Effectiveness of Blood Glucose Test Strips in the Management of Adult Patients With Diabetes Mellitus.*[59]

1. ADULTS AND CHILDREN WITH TYPE 1 DIABETES

CERC **recommends** that the optimal daily frequency of SMBG be individualized for adults and children with type 1 diabetes *(voting: agree 12, disagree 0; strong recommendation; low-quality evidence)*.

Clinical Notes: Given a lack of evidence, the following reflects CERC clinical opinion and accepted standards of practice: SMBG is an essential component of diabetes management for adults and children with type 1 diabetes.

Underlying Values and Preferences

- Primary considerations were: improved glycemic control, avoidance of clinically important complications of diabetes, and improved patient safety.
- Other values and preferences: patient empowerment and self-management, individualization of therapy, recognition of standard of care, and improved quality of life.

Context

Adults

- There was insufficient evidence to make a recommendation regarding optimal or maximum SMBG frequency for this population; however, low-quality evidence suggested that performing SMBG a minimum of three times daily was associated with better A1C in comparison with less than three times daily.[60]
- The only RCT data identified[61] were of limited relevance because the SMBG frequencies tested would not be considered acceptable in current clinical practice.
- Observational studies are more likely to overestimate the effect of SMBG on A1C despite controlling for potential confounding factors, since individuals who test more frequently may also be more likely to engage in behaviours that improve glycemic control other than SMBG. The effect of different SMBG frequencies on glycemic control cannot be accurately determined under such study conditions.
- A1C was the only outcome for which evidence was available.
- No cost-effectiveness data were available; only cost per blood glucose test strip was provided.

Children

- There was insufficient evidence to make a recommendation regarding optimal or maximum SMBG frequency for this population.
- A1C was the only outcome for which evidence was available.
- No cost-effectiveness data were available; only cost per blood glucose test strip was provided.

Summary of Findings Table for A1c From Comparisons of Various SMBG Frequencies in Adults and Children With Type 1 Diabetes Mellitus

Outcome	Number of Studies (Total Sample Size)	Effect Estimate MD% (95% CI)	Quality of Evidence
Adults			
Two per day on seven days per week versus four per day once per week	1 RCT[61] (n = 25)	0.10% (-1.04, 1.24)	Low
Two per day for seven days per week versus four per day on two non-consecutive days per week	1 RCT[61] (n = 25)	0.10% (-1.01, 1.21)	Low
At least three per day versus one per day	1 R. cohort[60] (n = 780)	-0.78% (-1.01, -0.55)	Very Low
Regression coefficient for an average of one additional strip per day	1 R. cohort[62] (n = 258*)	-0.661% (P<0.001)[†]	Very Low
Children[‡]			
Three to four per day versus less than three per day (after three months of SMBG)	1 nRT[63] (n = 60)	-0.6%[§] (-1.13, -0.02)	Very Low
Three to four per day versus less than three per day (after six months of SMBG)[¶]	1 nRT[63] (n = 40)	-0.5%[e] (-1.35, 0.34)	Very Low
Economic Evidence			
Unit cost: C$0.73 per test strip**			

A1C=hemoglobin A1C; CI=confidence interval; MD=mean difference; nRT=non-randomized trial; R. cohort=retrospective cohort; RCT=randomized controlled trial; SMBG=self-monitoring of blood glucose

* Children may have been included in this study.

[†] Adjusted for age, sex, duration of diabetes, and socioeconomic status. P-value is presented because confidence intervals were not provided.

[‡] Eight of 60 patients were over 18-years-old.

[§] The mean difference in A1C (95% CI; SMBG three to four times per day versus SMBG less than three times per day), adjusted for baseline A1C.

[¶] After six months of SMBG; post diabetes self-management education camp, excluding patients who changed SMBG frequency. The number of adult patients was not reported among 40 patients included in the analysis at six months.

** Due to the low quality of the clinical data, economic evaluations were not performed for adults or children with type 1 diabetes.

2. ADULTS WITH TYPE 2 DIABETES USING INSULIN

CERC **recommends** that SMBG be used and that the optimal daily frequency of SMBG be individualized for **most** adults with type 2 diabetes using insulin with or without oral antidiabetes drugs *(voting: agree 12, disagree 0; strong recommendation; low-quality evidence)*.

CERC **suggests** that the maximum average weekly frequency of SMBG for **most** adults with type 2 diabetes using insulin with or without oral antidiabetes drugs is 14 tests per week *(voting: agree 8, disagree 4; weak recommendation; low quality evidence).*

Clinical Notes:
This population is heterogeneous regarding the dose and frequency of insulin administration. Given a lack of evidence, the following reflects CERC clinical opinion and accepted standards of practice:

- Patients at increased risk of hypoglycemia or its consequences may benefit from performing SMBG more than 14 times per week. These include individuals:
  - using multiple daily insulin injections (i.e., three or more per day)
  - with a history of hypoglycemia
  - working in an occupation where hypoglycemia poses safety concerns or where testing is mandated by an employer (e.g., pilots, air-traffic controllers, critical positions in railways)[64,65]
  - private and commercial drivers who should abide by jurisdictional regulations concerning SMBG, hypoglycemia, and operation of motor vehicles. [66-69]
- Other populations which may benefit from performing SMBG more than 14 times per week include those:
  - newly initiated on insulin
  - experiencing acute illness
  - undergoing changes in insulin dose/regimen or significant changes in routine
  - with poorly controlled or unstable blood glucose levels
  - who are pregnant or planning a pregnancy.
- Patients who are not identified in the populations above may benefit from performing SMBG less than 14 times per week.

Underlying Values and Preferences

- When recommending that most patients perform SMBG, the primary consideration was improved glycemic control and avoidance of the clinically important complications of diabetes.
- For assigning an optimal frequency, the primary considerations were patient empowerment and self-management; and individualization of therapy.
- For assigning a maximal frequency, the primary consideration was cost-effectiveness.
- Other values and preferences: improved patient safety, patient choice, and recognition of standard of care; recognition of standard of care, validity of available evidence, improved quality of life, and lack of strong evidence of clinical benefit

Context

- Evidence for this population was limited to A1C and hypoglycemia data obtained from one non-randomized trial[70] and two observational studies.[60,71] As a result of such limited evidence, CERC concluded that there was insufficient evidence to make a recommendation regarding optimal SMBG frequency for this population; however, the cost-effectiveness evidence was sufficient to make a recommendation regarding maximal SMBG frequency for this population.
- In the cost-effectiveness analysis, there is a clear relationship between the number of blood glucose test strips used per week, modelled benefit in A1C, and incremental cost-utility ratio (ICUR). Thus, while inputs (i.e., benefits of SMBG) are uncertain due to the lack of adequate clinical evidence**,** relative cost-effectiveness can be elucidated over a plausible range of A1C differences.
- The results of the non-randomized trial[70] may not be generalizable to Canada since the study was conducted in Turkey and the authors studied unusual testing frequencies. As well, results may have been biased as the comparator groups differed from one another at baseline.
- Observational studies are likely to overestimate the effect of SMBG on A1C despite controlling for potential confounding factors, as individuals who test more frequently may also be more likely to engage in behaviours that improve glycemic control other than SMBG. Such studies cannot therefore establish that more frequent testing is beneficial.
- A1C and hypoglycemia were the only outcomes for which evidence was available.

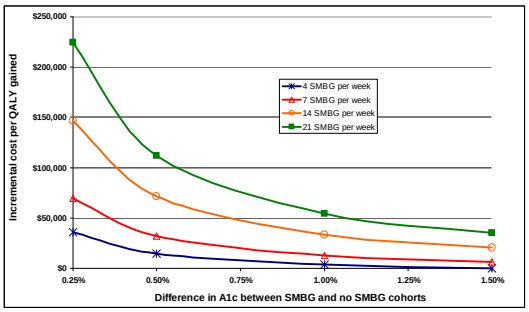
Summary of Findings Table for Adults With Type 2 Diabetes Using Insulin

Outcome	Number of Studies (Sample Size)	Effect Estimate (95% CI or P value)	Quality of Evidence
A1C (%)			
Four SMBG per day x one day per week versus no SMBG	1 nRT[70] (n = 71)	MD: -1.00%* (-1.68,-0.32)	Very Low
Four SMBG per day x once every two weeks versus no SMBG	1 nRT[70] (n = 55)	MD: -0.70%* (-1.41, 0.01)	Very Low
Four SMBG per day x one day per month versus no SMBG	1 nRT[70] (n = 36)	MD: -0.20%* (-1.08, 0.68)	Very Low
Four SMBG per day x one day per week versus four SMBG per day x one day every two weeks	1 nRT[70] (n = 82)	MD: -0.30%* (-0.82, 0.22)	Very Low
SMBG at least once per day versus no SMBG	1 R. cohort[60] (n = 4,061)	MD: -0.69%† (-0.84,-0.54)	Very Low
SMBG less than once per day versus no SMBG	1 R. cohort[60] (n = 2,541)	MD: -0.13%† (-0.30, 0.04)	Very Low
SMBG increased by one strip per day	1 R. cohort[62] (n = 290)	-0.108% (P = 0.357)‡,§	Very Low
SMBG increased by one strip per day	1 R. cohort[72] (n = 245)	-0.65% (P = 0.0236)‡,¶	Very Low
Overall hypoglycemia			
Four SMBG per day x one day per week versus no SMBG	1 nRT[70] (n = 71)	RR: 0.45* (0.03, 6.86)	Very Low
		Rate ratio: 4.04* (0.94, 17.42)	Very Low
Four SMBG per day x once every two weeks versus no SMBG	1 nRT[70] (n = 55)	RR: 0.67* (0.04, 10.11)	Very Low
		Rate ratio: 2.67* (0.57, 12.56)	Very Low
Four SMBG per day x one day per month versus no SMBG	1 nRT[70] (n = 36)	RR: 0.51* (0.02, 11.74)	Very Low
Four SMBG per day x one day per week versus four SMBG per day x one day every two weeks	1 nRT[70] (n = 82)	RR: 0.67* (0.04, 10.39)	Very Low
		Rate ratio: 1.52* (0.66, 3.48)	Very Low
Mortality			
SMBG versus no SMBG	1 P. cohort[71] (n = 153)	HR: 0.73** (0.43, 1.26)	Very Low

Economic Evidence

Unit cost: C$0.73 per blood glucose test strip

Because of the low-quality clinical data, cost-effectiveness results were presented for SMBG frequencies of 4, 7, 14, or 21 times weekly, and over a range of plausible A1C effect sizes.



A1C=hemoglobin A1C; CI=confidence interval; HR=hazard ratio; MD=mean difference; nRT=non-randomized trial; OADs=oral antidiabetes drugs; P. cohort=prospective cohort; R. cohort=retrospective cohort; RR=relative risk; x=times.

* Baseline patient characteristics including age, sex, disease duration, duration of insulin treatment, hypoglycemia, 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, block group annual income; and occupational class, years since diabetes diagnosis, diabetes therapy refill adherence, number of daily insulin injections (insulin users only), 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 room visit during the baseline year.

‡ The decrease in A1C level attributable to one additional SMBG per day.

§ Unadjusted.

¶ Adjusted for age, sex, region, body mass index, number of months A1C was tested after insulin, and number of insulin preparations received.

** Adjusted for age, sex, duration of diabetes, prior myocardial infarction, angina, coronary revascularization, diabetes education, A1C, ethnicity (Australian aboriginal).

3. ADULTS WITH TYPE 2 DIABETES WHO USE ORAL ANTIDIABETES DRUGS

Routine use of blood glucose test strips for SMBG is **not recommended** by CERC for **most** adults with type 2 diabetes using oral antidiabetes drugs. *(voting: agree 8, disagree 4; strong recommendation; moderate quality evidence).*

Clinical Notes:
Given a lack of evidence, the following reflects CERC's clinical opinion and accepted standards of practice:

- **Patients treated with insulin secretagogues may benefit from routine use of SMBG to reduce the risk of hypoglycemia.**
- Other populations that may benefit from SMBG include those:
  - at increased risk of hypoglycemia (e.g., due to a history of severe hypoglycemia or hypoglycemia unawareness, instances of inadequate caloric intake, unforeseen or unplanned physical activity)
  - experiencing acute illness
  - undergoing changes in pharmacotherapy or significant changes in routine
  - with poorly controlled or unstable blood glucose levels
  - who are pregnant or planning a pregnancy.

Underlying Values and Preferences

- Primary consideration was cost-effectiveness
- Other values and preferences: validity of available evidence; improved glycemic control and avoidance of clinically important complications of diabetes; avoidance of potentially detrimental effects of SMBG; improved patient safety; patient choice; patient empowerment and self-management; accessibility of resources to manage diabetes; and lack of strong evidence of clinical benefit

Context

- The pooled A1C difference of -0.25% was statistically significant in favour of SMBG in this population, but was not considered clinically significant. The A1C difference between SMBG and no SMBG was similar regardless of whether or not patients were given instructions on the self-interpretation and application of SMBG results.
- In the cost-effectiveness analysis, based on a pooled A1C difference of -0.25% and the average SMBG frequency used in studies (1.29 tests per day), the ICUR for SMBG versus no SMBG was $113.6 thousand per QALY gained. CERC members felt that this information supported the clinical finding that SMBG did not provide sufficient benefits to warrant its use by most patients with type 2 diabetes using oral antidiabetes drugs.
- For patients who choose to perform SMBG, there is insufficient clinical evidence to recommend an optimal frequency.

Summary of Findings for A1C From Studies Comparing SMBG Versus No SMBG in Adults With Type 2 Diabetes Treated With Oral Antidiabetes Drugs or No Antidiabetes Drugs

Analysis	Number of Studies (Sample Size)	WMD (95% CI) in A1C (%)	I^2 (%)	Quality of Evidence
Evidence from RCTs				
Overall estimate of effect	7 RCTs[4,73-78] (n = 2,270)	-0.25% (-0.36, -0.15)	0	Moderate
Good quality RCTs only	3 RCTs[73,75,77] (n = 1,247)	-0.21% (-0.34, -0.08)	0	High
RCTs in which all subjects used OADs	3 RCTs[73,74,77] (n = 1,628)*	-0.24% (-0.36, -0.11)	0	Moderate
RCT in which all patients use sulfonylureas	1 RCT[73] (n = 610)	-0.24% (-0.43, -0.05)	N/A	High
More intensive education	3 RCT[75-77] (n = 710)	-0.28% (-0.47, -0.08)	17.8	Moderate
Less intensive or unspecified education	5 RCTs[4,73,74,77,78] (n = 1,712)	-0.22% (-0.34, -0.10)	0	Moderate
Evidence from retrospective cohort studies				
At least one strip per day versus no SMBG	1 R. cohort[60] (n = 8,735)	-0.68% (-0.77, -0.59)†	N/A	Very low
Less than one strip per day versus no SMBG	1 R. cohort[60] (n = 10,243)	-0.21% (-0.30, -0.12) †	N/A	Very low
Prescription of two to four strips per week versus no prescription of strips	1 R. cohort[79] (n = 115)	-0.20% (-0.77, 0.37)‡	N/A	Very low
Prescription of 0.56 strips per day versus no prescription of strips	1 R. cohort[80] (n = 299)	-0.13% (-0.28, 0.02)§	N/A	Very low

A1C=hemoglobin A1C; CI=confidence interval; N/A=not applicable; OADs=oral antidiabetes drugs; R. cohort= retrospective cohort; RCT=randomized controlled trial; SMBG=self-monitoring of blood glucose; WMD=weighted mean difference

*Farmer *et al.* (2007)[77] presented data for a subgroup of patients treated with oral antidiabetes drugs.

† Data were 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 (insulin users only), 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 room visits during the baseline year.

‡ Data were not adjusted for any confounder and baseline A1C was not reported; however, age, weight, dose of glyburide, serum creatinine, and proteinuria were similar between the two groups.

§ Data were not adjusted for any possible confounders, although baseline A1C, body mass index, chronic illness, and disability payment system and ethnicity were similar between the two groups.

Summary of Findings for Hypoglycemia From RCTs Comparing SMBG Versus No SMBG in Adults With Type 2 Diabetes Treated With Oral Antidiabetes Drugs or No Antidiabetes Drugs

Analysis	Number of Studies (Sample Size)	Effect Estimate (95% CI)	I^2 (%)	Quality of Evidence
Overall hypoglycemia	3 RCTs[73,74,77] (n = 1,752)	RR: 1.99 (1.37, 2.89)	33.8	Moderate
	2 RCTs[73,75] (n = 794)	Rate ratio: 0.73 (0.55, 0.98)	0	High
Severe hypoglycemia	3 RCTs[73,76,77] (n = 1,752)	RR: 0.17* (0.01, 4.12)	N/A	Moderate
Nocturnal hypoglycemia	1 RCT[73] (n = 610)	RR: 0.41 (0.11, 1.58)	N/A	Moderate

95% CI=95% confidence intervals; N/A=not applicable; RCT=randomized controlled trial; RR=relative risk; SMBG=self-monitoring of blood glucose

*Since no events occurred in Guerci *et al.* (2003) or Barnett *et a.* (2008), only the RR from Farmer *et al.* (2007) contributed to the pooled estimate.

Summary of Findings for Patient Reported Outcomes From RCTs Comparing SMBG Versus No SMBG in Adults With Type 2 Diabetes Treated With Oral Antidiabetes Drugs or No Antidiabetes Drugs

Analysis	Number of Studies (Sample Size)	WMD (95% CI)	I^2 (%)	Quality of Evidence
DTSQ	2 RCTs[74,81] (n = 562)	-0.26 (-1.38, 0.86)	0	Low
WBQ - 12	1 RCT[81] (n = 339)	-0.85 (-2.27, 0.56)*	N/A	Moderate
WBQ - 22	1 RCT[82] (n = 223)	1.83 (-0.05, 3.71) *	N/A	Moderate
EuroQol – 5D				
Overall	1 RCT[83] (n = 453)	-0.06 (-0.13, 0.02) *	N/A	High
Less intensive education	1 RCT[83] (n = 302)	-0.029 (-0.084, 0.025) *	N/A	High
More intensive education	1 RCT[83] (n = 301)	-0.072 (-0.127,-0.017)*	N/A	High

DTSQ=Diabetes Treatment Satisfaction Questionnaire; RCT=randomized controlled trial; SMBG=self-monitoring of blood glucose; WBQ=well-being questionnaire; WMD=weighted mean difference

*mean difference (95% confidence interval)

Summary of Findings for Long-Term Complications From Studies Comparing SMBG Versus No SMBG in Adults With Type 2 Diabetes Treated With Oral Antidiabetes Drugs or No Antidiabetes Drugs

Analysis	Number of Studies (Sample Size)	Effect Estimate (95% CI)	I^2 (%)	Quality of Evidence
All-cause mortality (newly diagnosed patients)	1 R. cohort[84] (n = 2,515)	HR: 0.58* (0.35, 0.96)	N/A	Very low
All-cause mortality (previously diagnosed patients)	1 P. cohort[71] (n = 1,127)	HR:1.20† (0.94, 1.52)	N/A	Very low
Non-fatal events‡	1 R. cohort[84] (n = 2,515)	HR: 0.72*(0.52, 0.999)	N/A	Very low

CI=confidence interval; HR=hazard ratio; RCT=randomized controlled trial; MD=mean difference; N/A=not applicable; P. cohort=prospective cohort; RR=relative risk; R. cohort=retrospective cohort; WMD=weighted mean difference

* Results adjusted for age, sex, concomitant disease at diabetes diagnosis (hypertension, coronary heart disease, history of stroke), laboratory values (fasting blood glucose, triglycerides), treatment, qualification of the treating physician (general practitioner, internist), centre size (number of newly diagnosed patients with type 2 diabetes during 1995 to 1999), centre location (small town, city), patient's habitation (small town, city,) and patient's health insurance (public, private).

† Results adjusted for age, sex, duration of diabetes, prior coronary heart disease, cardiovascular disease, peripheral arterial disease, neuropathy, retinopathy, albumin/creatinine ratio, abdominal obesity (negative), use of lipid-lowering medications (negative), Australian Aboriginal, and current smoker status.

‡ Myocardial infarction, stroke, foot amputation, blindness in one or both eyes, or end-stage renal disease requiring dialysis.

Summary of A1C Findings For Studies Comparing Different SMBG Frequencies in Adults With Type 2 Diabetes Treated With Oral Antidiabetes Drugs or No Antidiabetes Drugs

SMBG Frequency		Number of Studies (Sample Size)	Effect Size (95% CI or P value)	Quality of Evidence
Evidence from RCT				
SMBG once per week versus SMBG four times per week		1 RCT[85] (n = 178)	MD: -0.08% (-0.41, 0.25)	Moderate
Evidence from retrospective cohort studies				
Average daily SMBG: once per day versus less than once per day		1 R. cohort[60] (n = 6,594)	MD: -0.47% (-0.57, -0.37)*	Very low
SMBG increased by one strip per day	Patients using OADs	1 R. cohort[72] (n =1,795)	0.09% (P = 0.5392)†	Very low
	Patients using sulfonylureas	1 R. cohort[86] (n =216)	0.02% (P > 0.50)‡	Very low
	New users of SMBG	1 R. cohort[87] (n = 5,546)	-0.42% (P < 0.0001)§	Very low
	Prevalent users of SMBG	1 R. cohort[87] (n = 7,409)	-0.16% (P < 0.0001)¶	Very low
SMBG increased by 10 test strips per week		1 R. cohort[88] (n = 5962)	-0.06 (0.01) ** (P = 0.38)	Very low

95% CI=95% confidence interval; MD=mean difference; OADs=oral antidiabetes drugs; R. cohort= retrospective cohort; RCT=randomized controlled trial; SMBG=self-monitoring of blood glucose.

*Data adjusted for age, sex, ethnicity, educational attainment, block group attainment, block group annual income and occupation class, years since diabetes diagnosis, diabetes therapy refill adherence, clinic appointment "no show" rate, annual eye exam attendance, self-reported exercise and diet as diabetes therapy, smoking status, alcohol consumption, and hospitalization and emergency room visits during the baseline year.

†Adjusted for age, sex, region, body mass index, months since initiation of oral antidiabetes drugs and A1C test, number of oral medications received in six months prior to A1C test.

‡Adjusted for age, daily glyburide dose, serum creatinine concentration, urine protein content, hospital admissions, number of providers, number of ophthalmology visits, number of diabetes clinic visits.

§ Data adjusted for pre-baseline A1C (last A1C prior to baseline), sex, age, inpatient comorbidity score, diabetes refill medication adherence, diabetes therapies, appointment "no show" rate, performance of annual ophthalmology exams, prebaseline rates of hospital, emergency room, primary care and specialty visits, primary care provider type, smoking status, neighbourhood level, median family income, residence in a poorly educated neighbourhood, residence in a predominately working-class neighbourhood, and the length of time between pre- and post-A1C tests.

¶ Data adjusted as in footnote "§" , but also for: SMBG, daily insulin injection frequency, appointment "no show" rate, inpatient comorbidity score, and inpatient/outpatient utilization.

**Coefficient (standard error) represents change in A1c for every ten glucose test strips used each week. Coefficients are derived for each outcome stratum using separate multivariate linear regression models adjusting for initial doses of glyburide and metformin and the number of oral antidiabetes drugs.

Summary of Economic Findings for the Comparison of SMBG Versus No SMBG for Adults With Type 2 Diabetes in Adults Using Oral Antidiabetes Drugs or No Antidiabetes Drugs

All Patients on OAD(s) or No Diabetes Pharmacotherapy			
	∆cost (C$)	∆QALYs	ICUR (C$/QALY)
Reference case			
WMD in A1C of -0.25 (-0.36, -0.15) favouring SMBG. Effect estimate derived using overall estimate of effect from seven RCTs[4,73-78]	$2,711	0.02385	$113,643/QALY
Probability SMBG is cost-effective at willingness to pay of $50,000 per QALY = 2% Probability SMBG is cost-effective at willingness to pay of $100,000 per QALY = 40%			
One-way sensitivity analyses			
WMD in A1C of -0.21 (-0.34, -0.08) favouring SMBG. Effect estimate derived from three, good-quality RCTs[73,75,77]	$2,735	0.02043	$133,829/QALY
∆A1C estimate of -0.68 (-0.77, -0.59) favouring SMBG. Effect estimate derived from a poor-quality observational study[60]	$2,523	0.05311	$47,512/QALY
∆A1C estimate of -0.28 (-0.47, -0.08) favouring SMBG. Effect estimate derived from two good-quality RCTs[75,77] and one poor-quality RCT[76] where patients used more intensive education	$2,694	0.02696	$99,916/QALY

C$=Canadian dollars; ICUR=incremental cost-utility ratio; QALY=quality-adjusted life-years; RCT=randomized controlled trial; SMBG=self-monitoring of blood glucose;∆=change

4. ADULTS WITH TYPE 2 DIABETES WHO DO NOT USE ANTIDIABETES DRUGS

Routine use of blood glucose test strips for SMBG is **not recommended** by CERC for most adults with type 2 diabetes who do not use diabetes pharmacotherapy *(voting: agree 9, disagree 2; strong recommendation; low-quality evidence)*

Clinical Notes:
Given a lack of evidence, the following reflects CERC clinical opinion and accepted standards of practice:

- Women with type 2 diabetes who are not using insulin and are considering a planned pregnancy may benefit from SMBG testing.

Underlying Values and Preferences

- Primary consideration was cost for payers.
- Other values and preferences: validity of available evidence, patient choice, patient empowerment and self-management, avoidance of potentially detrimental effects of SMBG, improved quality of life, individualization of therapy, accessibility of resources to manage diabetes, lack of strong evidence of clinical benefit, and limited RCT evidence supporting the benefits of SMBG in this patient population.

Context

- In the cost-effectiveness analysis, based on the statistically non-significant A1C difference of -0.05% in favour of SMBG observed in the RCT[77] and the average SMBG testing frequency of 0.71 per day, the ICUR for SMBG versus no SMBG was $291.1 thousand per QALY gained. CERC members felt that this information supported the clinical finding that SMBG did not provide sufficient benefits to warrant its use by most patients with type 2 diabetes who do not use antidiabetes drugs.
- A1C was the only outcome for which evidence was available.

Summary of Findings for Outcomes From Studies Comparing of SMBG Versus No SMBG for Adults With Type 2 Diabetes in Adults Using No Antidiabetes Drugs

Outcome	Number of Studies (Sample Size)	Effect Estimate MD (95% CI)	Quality of Evidence
A1C (%) change from baseline	1 RCT[77] (n = 124)	-0.05 (-0.33, 0.23)	Moderate
A1C (%) at end			
SMBG at least once per day versus no SMBG	1 R. cohort[60] (n = 3445)	-0.64* (-0.81,-0.47)	Very Low
SMBG less than once per day versus no SMBG	1 R. cohort[60] (n = 4198)	-0.34† (-0.47, -0.21)	Very Low
Economic Information			
Unit cost: C$0.73 per test strip ICUR — diet only, RCT data‡: C$292,144 per QALY gained (ΔC = C$1,372; ΔQALYs = 0.00470)			

A1C=hemoglobin A1C; CI=confidence interval; ICUR=incremental cost-utility ratio; MD=mean difference; QALY=quality-adjusted life-year; RCT=randomized controlled trial; R. cohort = retrospective cohort; ΔC=difference in costs between strategies; ΔQALY=difference in QALYs gained between strategies

* Adjusted for age, sex, ethnicity, educational attainment, block group annual income, occupational class, years since diabetes diagnosis, diabetes therapy refill adherence, number of daily insulin injections (insulin users only), 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 room visit during the baseline year.

† Initiating once-daily monitoring resulted in lowering of A1C concentration by 0.35% (P < 0.0001). Models were adjusted for pre-baseline A1C, sex, age, inpatient comorbidity score, diabetes refill medication adherence, diabetes therapies (therapeutic class), appointment "no show" rate, performance of annual ophthalmology exams, prebaseline rates of hospital, emergency room, primary care and specialty visits, primary care provider type, smoking status, neighborhood level, median family income, residence in a poorly educated neighborhood, residence in a predominately working-class neighborhood, and the length of time between pre- and post-A1C tests.

‡ Baseline A1C=7.48%; mean age = 66 years; duration of diabetes = three years; frequency = 0.71 test strips per day; WMD= -0.05 (-0.33, 0.23); time horizon=40 years.

5. WOMEN WITH GESTATIONAL DIABETES

CERC **recommends** that the optimal daily frequency of SMBG be individualized for most women with gestational diabetes not using diabetes pharmacotherapy *(voting: agree 10, disagree 1; strong recommendation; low-quality evidence)*.

Clinical Notes:
Given a lack of evidence, the following reflects CERC clinical opinion and accepted standards of practice:

- SMBG should be performed by women with gestational diabetes using insulin or oral antidiabetes drugs.
- SMBG should be performed by women with impaired glucose tolerance of pregnancy.

Underlying Values and Preferences

- Primary considerations were reduced fetal/neonatal complications, improved glycemic control, and avoidance of clinically important complications of diabetes
- Other values and preferences: patient empowerment and self-management; individualization of therapy; improved patient safety; recognition of standard of care

Context

- There was insufficient evidence to make a recommendation regarding optimal or maximum SMBG frequency for this population.
- The only statistically significant results in favour of SMBG in the RCT[89] were reduced risks for birth weight greater than 90th percentile (RR [95% CI] = 0.43 [0.20, 0.92]) and hyperbilirubinemia (RR [95% CI] = 0.51 [0.26, 0.99]) in the subgroup of women who had a one-hour, post-breakfast blood glucose of ≥7.8 mmol/L. Then, 25% of patients in both arms started using insulin during the trial because their glycemic target was not achieved.
- No cost-effectiveness data were available; only cost per strip was provided.

Summary of Findings From RCTs Comparing SMBG Versus No SMBG in Women With Gestational Diabetes

Outcome	Number of Studies (Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
Fasting blood glucose (mmol/L)	1 RCT[89] (n = 58)	MD: -0.22 (-0.55, 0.11)	Low
One-hour post-prandial blood glucose (mmol/L)	1 RCT[89] (n = 58)	MD: 0.47 (-0.12, 1.06)	Low
Weight gain (kg)	1 RCT[89] (n = 58)	MD: -2.50 (-6.16, 1.16)	Low
Self-efficacy at 37 weeks (Diabetes Empowerment Scale)*	1 RCT[89] (n = 58)	MD: 3.70 (-1.56, 8.96)	Low
Caesarean section	2 RCTs[89,90] (n = 400)	RR: 1.18 (0.61, 2.27)	Low
Birth trauma	1 RCT[89] (n = 58)	RR: 0.87 (0.06, 13.27)	Low
All-cause fetal mortality	2 RCTs[89,90] (n = 400)	RR: 1.46 (0.18, 11.59)	Low
Gestational age at delivery (weeks)	2 RCTs[89,90] (n = 400)	WMD: -0.05 (-0.35, 0.25)	Low
Hypoglycemia (not classified)	2 RCTs[89,90] (n = 391)	RR: 0.64 (0.39, 1.06)	Low
Macrosomia (birth weight > four kg)	1 RCT[90] (n = 342)	RR: 0.94 (0.53, 1.67)	Moderate
Birth weight > 90th percentile	2 RCTs[89,90] (n = 400)	RR: 0.82 (0.50, 1.37)	Low
Birth weight < 10th percentile	1[90] (n = 342)	RR: 1.19 (0.53, 2.67)	Moderate
Respiratory complications	1 RCT[89] (n = 58)	RR: 0.87 (0.06, 13.27)	Low
Hospitalization (neonatal intensive care)	1 RCT[89] (n = 58)	RR: 0.87 (0.13, 5.77)	Low
Apgar score — one minute	1 RCT[89] (n = 58)	MD: -0.40 (-1.51, 0.71)	Low
Apgar score — five minutes	1 RCT[89] (n = 58)	MD: -0.20 (-1.13, 0.73)	Low
Hyperbilirubinemia	2 RCTs[89,90] (n = 369)	RR: 0.64 (0.39, 1.04)	Low
Economic Information			
Unit Cost: C$0.73 per test strip			

95% CI=95% confidence interval; MD=mean difference; PBBG=post-breakfast blood glucose; RCT=randomized controlled trial; RR=relative risk; WMD=weighted mean difference

* Lower scores indicate greater self-efficacy.

CLINICAL FINDINGS OF BLOOD GLUCOSE TEST STRIPS

The following clinical findings, which represent an **intermediate step in the CERC deliberative process,** are derived solely from CERC's considerations of clinical evidence regarding blood glucose test strips. Economic evidence was not considered at this stage. Therefore, they **do not represent CERC's recommendations and suggestions** for the optimal prescribing and use of blood glucose test strips. CERC's optimal therapy recommendations for blood glucose test strips are presented in summary form (Section 5.1) and detailed form (Appendix B).

Patients who use insulin
For adults with type 1 diabetes: • The optimal daily frequency of SMBG should be individualized for most adults with type 1 diabetes.
For children with type 1 diabetes: • The optimal daily frequency of SMBG should be individualized for most children with type 1 diabetes.
For adults with type 2 diabetes: • Blood glucose test strips for SMBG should be used by most adults with type 2 diabetes using insulin. • The optimal daily frequency of SMBG should be individualized with adults with type 2 diabetes using insulin.

Patients who do not use insulin
For adults with type 2 diabetes: • Routine SMBG by most adults with type 2 diabetes using oral anti-diabetes drugs is not recommended/suggested by CERC. • Routine SMBG by most adults with type 2 diabetes not using diabetes pharmacotherapy is not recommended/suggested by CERC.

Gestational diabetes
For women with gestational diabetes who do not use phamacotherapy: • Most women with gestational diabetes should use blood glucose test strips for SMBG. The Canadian Diabetes Association 2008 guidelines recommend that SMBG should be conducted four or more times daily, both pre- and post-prandially. • The management of gestational diabetes differs significantly from that of diabetes that exists prior to conception.

APPENDIX C: DETAILED CERC PROCESS

The steps that CERC followed for generating optimal therapy recommendations are presented here.

1. Individual review of GRADE evidence profiles and provision of feedback

CERC members were provided with the GRADE evidence profiles and a graphical summary of the results presented in the profiles. The members completed a feedback form for each GRADE evidence profile. Feedback was collated and provided to CERC members in advance of the committee meeting.

2. Discussion of clinical-effectiveness evidence and collated feedback from members

CERC members discussed the evidence presented in the GRADE evidence profiles, and the associated feedback. Context and clinical issues raised during the discussion were recorded for each evidence profile. GRADE Summary of Findings tables, which were created to reflect the body of generated information, contained:

- results from the GRADE evidence profiles
- draft clinical findings
- summary of values and preferences expressed by CERC members
- summary of feedback on the criteria used to assess strength of recommendations.

3. Identification of clinical findings based on clinical-evidence of effectiveness and safety

Each member of CERC participating in the meeting voted for one clinical finding statement, the two most important values or preferences that guided their choice, and the overall quality of the available evidence. Points of discussion relating to the clinical finding statement were documented as context. A summary of the clinical findings is provided in Appendix B.

4. Identification of draft optimal therapy recommendations based on clinical conclusions and cost/cost-effectiveness information

CERC reviewed and discussed the results from the pharmacoeconomic analyses conducted by CADTH. Where one treatment strategy appeared to be more effective than the alternative, CERC assessed whether or not the increase in cost associated with the increase in effectiveness represented reasonable "value for money". There is no empirical basis for assigning a value (or values) to the cut-off between cost-effectiveness and cost-ineffectiveness.

Conclusions from the pharmacoeconomic analyses were added to the GRADE Summary of Findings tables. Costing data were supplied where cost-effectiveness results were not available. Draft optimal therapy recommendations, reflecting both clinical and cost/cost-effectiveness results, were prepared as a starting point for CERC's deliberation and voting. Voting was conducted by secret ballot and web voting. Quorum consisted of a minimum of five core CERC members, and 50% of members appointed as clinical experts in the management of diabetes. A majority vote was sufficient for a draft recommendation to be accepted. Each vote concluded with a committee discussion on the vote results in which members were given an opportunity to

discuss factors behind their individual votes. Draft recommendations could be modified by CERC during their deliberations.

Which treatment strategy to use?
If there is strong evidence that one treatment strategy dominates the alternative strategies (that is, it is both more effective and less costly), clearly this strategy would be chosen. However, if one treatment strategy is more effective but also more costly, then the choice is less clear and a pharmacoeconomic analysis can be undertaken to determine and compare the cost-effectiveness of the alternatives.

Pharmacoeconomic evaluations are the systematic assessment and comparative analysis of the costs and consequences of competing alternative treatment strategies. The results of a pharmacoeconomic evaluation are expressed as the difference in costs of the alternative strategies (incremental costs) divided by the difference in health outcomes of the alternative strategies (incremental health outcomes). Evaluations can be conducted in the form of a cost-effectiveness analysis (CEA) or a cost-utility analysis (CUA). In a CEA, the costs are measured in monetary units and the health outcome is measured in a natural or clinical unit. In a CUA, the costs are measured in monetary units and the health outcome is expressed in quality-adjusted life-years (QALYs). A QALY is a measurement of health outcome that considers both quantity and quality of life.

5. Identification of underlying values and preferences for each recommendation

An important component of each draft optimal therapy recommendation is a clear statement underlying values and preferences that supported CERC's choice of one alternative over another. These statements reflect the values expressed by CERC during their assessment of the clinical- and cost-effectiveness evidence. Where the clinical-effectiveness and cost-effectiveness evidence was deemed insufficient to evaluate differences between treatments, recommendations were formulated to reflect clinical opinion and standard of care. The values and preferences statements for each treatment option are provided as a guide for patients, clinicians, and decision-makers in selecting the most appropriate treatment alternative.

6. Appraisal of overall quality of evidence

CERC voted on the overall quality of clinical evidence available for each recommendation. Possible ratings were "high", "moderate", and "low". This rating was based on an assessment of evidence quality across all outcomes considered "important" or "critical" by CERC. Where evidence was lacking for such outcomes, an overall rating of "low" was more likely, regardless of the quality of evidence for outcomes reported in studies. For example, the overall quality of evidence could be rated "low" due to the lack of data on long-term complications of diabetes, even if there was high-quality evidence available regarding surrogate outcomes such as A1C.

7. Grading strength of recommendations

The final step in the GRADE methodology is assigning the strength of each recommendation as either "strong" or "weak". This rating is intended to convey the degree of confidence the

committee has that adherence to the recommendation will result in the desired outcome.[24] As stipulated by the GRADE process, strength of recommendations is reflected by the use of the words "suggests" or "recommends" (i.e., for weak recommendations, "CERC suggests that...." and for strong recommendations, "CERC recommends that...").

According to the GRADE Working Group, the rating of strength has implications for how users interpret a recommendation.[24]

A "strong" recommendation:

- is likely to be followed by most well-informed patients.
- is unlikely to require decision aids to elicit patient values and preferences.
- can often be implemented as policy.

A "weak" recommendation:

- is likely to be followed by the majority of well-informed patients; however, a significant minority would choose not to follow the recommendation.
- requires careful consideration of patient values and preferences. Decision aids may be helpful in determining the course of action.
- is likely to require debate and involvement of multiple stakeholders before policy can be determined.

A proposed rating of strength (i.e., either "strong" or "weak") was assigned to each recommendation, and feedback was provided by CERC members regarding the level of their agreement with the ratings. To facilitate this process, a summary of all prior CERC deliberations for each recommendation was distributed to members. This summary contained: the recommendation (with vote results), rating of overall quality of evidence (with vote results), listing of values and preferences (with vote results), a statement regarding the weight given by the committee to the economic evidence, a summary of contextual information, and proposed strength of recommendation. The proposed strength for each recommendation was based on answering four questions put forward by the GRADE Working Group as points of consideration when evaluating recommendation strength:

1. Is the available evidence of lower quality?
2. Is there uncertainty regarding the balance of benefits versus harms and burdens?
3. Is there uncertainty or are there differences in values and preferences?
4. Is there uncertainty about whether or not the net benefits are worth the costs?

An affirmative answer to one or more of these questions resulted in downgrading of a recommendation to "weak". Where recommendations were graded as weak, the rationale supporting CERC's decision is provided with the recommendation.

8. Identification of research gaps

Where there was insufficient information upon which to produce optimal therapy recommendations, CERC identified "gaps" in research/knowledge. These primarily consisted of

treatment comparisons and populations for which no peer-reviewed reports of randomized controlled trials or observational studies were identified. Research gaps were also identified when there was a paucity of comparative data on outcomes of interest for particular treatment comparisons or populations.

9. Consideration of stakeholder feedback and drafting of final optimal therapy recommendations

Stakeholder feedback was elicited through a web-based process on a report containing draft optimal therapy recommendations, summaries of the available evidence, and research gaps. This feedback will be collated and provided to CERC for consideration prior to drafting of the final optimal therapy recommendations for blood glucose test strips (Appendix B).

APPENDIX D: ABBREVIATIONS

A1C	glycosylated hemoglobin
CERC	COMPUS Expert Review Committee
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICUR	incremental cost-utility ratio
OAD	oral antidiabetes drug
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
SMBG	self-monitoring of blood glucose
WMD	weighted mean difference

APPENDIX E: 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.

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 conference interval is the 95% confidence interval.

Cost-effectiveness analysis: A form of economic evaluation that compares the costs and effects of two or more alternative treatments.

Crossover trial: A type of randomized controlled trial in which the intervention is applied at different times to each subject; that is, after a specified period of time, the original experiment group becomes the control group, and the original control group becomes the experimental group.

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.

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).

Fasting plasma glucose: Plasma glucose level measured when there has been no caloric intake for at least eight hours.

Gestational diabetes mellitus: Defined as glucose intolerance with first onset during pregnancy. It is 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 in relation 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).

Incremental cost-utility ratio: Ratio of the difference in costs between an intervention and comparator, to the difference in effects measured in quality-adjusted life-years.

Large for gestational age: Birth weights equal to or greater than the 90th percentile for a given gestational age.

Macrosomia: Usually defined as a birth weight greater than 4.0 kg or 4.5 kg

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

Monogenic diabetes: Rare forms of diabetes that result from mutations in a single gene. Most such mutations reduce the body's ability to produce insulin. Neonatal diabetes mellitus and maturity-onset diabetes of the young are the two main forms of monogenic diabetes.

Nocturnal hypoglycemia: Hypoglycemic events that occur at night, usually from midnight to 6:00 a.m.

Overall hypoglycemia: Overall hypoglycemia is defined by either symptoms or signs of hypoglycemia and/or blood glucose less than 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.

Rate ratio: The ratio of the person-time incidence rate in the exposed group to the person-time incidence rate in the unexposed group in an epidemiological study.

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.

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

Small for gestational age: Generally defined as the birth weight less than the 90th percentile for a given gestational age.

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

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. It may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance.

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

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