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OPTIMAL THERAPY REPORT

COMPUS
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Optimal Therapy Recommendations for the Prescribing and Use of Insulin Analogues

Supporting Informed Decisions

À l'appui des décisions éclairées

This report is based on comprehensive meta-analyses — *Long-Acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta-analyses of Clinical Outcomes*, Update of CADTH Technology Report No. 92; and *Rapid-Acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta-analyses of Clinical Outcomes*, Update of CADTH Technology Report No. 87; and economic reporting on the topic: *An Economic Evaluation of Insulin Analogues for the Treatment of Patients with Type 1 and Type 2 Diabetes Mellitus in Canada*, as well as evidence profiling: *GRADE Evidence Profiles on Long- and Rapid-Acting Insulin Analogues for the Treatment of Diabetes Mellitus* prepared by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) of the Canadian Agency for Drugs and Technologies in Health (CADTH).

This report is a comprehensive review of the existing public literature available to CADTH at the time it was prepared and it was guided by expert input and advice throughout its preparation. The recommendations were provided by experts. The authors have also considered input from other stakeholders.

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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ABBREVIATIONS

A1C	glycosylated hemoglobin
CAC	COMPUS Advisory Committee
CERC	COMPUS Expert Review Committee
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CSII	continuous subcutaneous insulin infusion
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICUR	incremental cost-utility ratio
MDI	multiple daily injection
NPH	neutral protamine Hagedorn
QALY	quality-adjusted life-year
RCT	randomized controlled trials

GLOSSARY

Basal insulin: Intermediate- or long-acting insulin or insulin analogue preparations designed to mimic the action of basally secreted endogenous insulin.

Biphasic insulin preparation: Pre-mixed insulin containing both a bolus and basal insulin in the same vial or cartridge (e.g., regular human insulin and insulin NPH).

Body mass index: Body weight in kilograms divided by the square of height in metres.

Bolus insulin: Short- or rapid-acting insulin or insulin analogue preparations designed to mimic the endogenous secretion of insulin in response to food intake.

Carry-over effect: Occurs in a crossover trial when the treatment given prior to crossover has residual effects that confound the interpretation of results after crossover.

Confidence interval: The probable range 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.

Congestive heart failure: A condition in which an abnormality of cardiac structure or function results in an inability of the heart to fill with, or eject, sufficient blood to fulfill tissue requirements.

Continuous subcutaneous insulin infusion: A method of insulin administration designed to mimic endogenous insulin secretion through continuous subcutaneous delivery of basal doses of short- or rapid-acting insulin via an insulin pump, and user-controlled bolus doses prior to food intake.

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 experimental clinical study in which both intervention and control treatments are applied to each subject at different times. Subjects are initially assigned (usually through randomization) to either the intervention or control treatment and, after a specified time, are switched to the alternative treatment.

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.

Diabetic ketoacidosis: An acute complication of marked hyperglycemia (due to uncontrolled diabetes) characterized by increased fatty acid metabolism, accumulation of ketone bodies, and acidosis.

Effectiveness: The extent to which a specific intervention, procedure, regimen, or service produces beneficial outcomes when deployed under routine circumstances.

Efficacy: The degree to which a specific intervention, procedure, regimen, or service produces a beneficial outcome under ideal circumstances.

Fasting plasma glucose: Plasma glucose level measured at least eight hours after caloric intake.

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.

Hemoglobin A1C: A glycated form of hemoglobin. Hemoglobin A1C levels reflect average glycemia over the course of 90 to 120 days, and are, therefore, commonly used as a measure of long-term glycemic control in diabetics.

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 both 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 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.

Insulin analogue: Pharmaceutical agents produced through alterations of the amino acid sequence of regular human insulin with the intent to alter the pharmacokinetic properties of regular human insulin while maintaining its pharmacological effects.

Ischemic heart disease: Heart disease caused by inadequate blood perfusion of the myocardium, which results in an imbalance between oxygen supply and demand.

Long-acting insulin analogues: A class of insulin analogues — produced by introducing alterations in the amino acid sequence and/or molecular structure of regular human insulin — which mimics the action of basal endogenous insulin secretion by providing a prolonged, non-fluctuating level of insulin activity.

Meta-analysis: Statistical synthesis of the results of individual studies for the purpose of integrating findings and producing a single estimate of effect.

Monophasic insulin preparation: An insulin preparation containing a single type of insulin (i.e., not biphasic).

Multiple daily injection: A method of insulin administration involving three or more daily subcutaneous injections of insulin (i.e., both basal and bolus insulins, in various combinations) designed to mimic endogenous insulin secretion.

Neutral protamine Hagedorn: An insulin preparation with an intermediate duration of action produced through combination of regular human insulin with protamine.

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

Observational study: A type of epidemiological study in which the investigator does not determine exposure of subjects to the risk factor or treatment under study.

Oral antidiabetic drug: One of several oral agents used to reduce hyperglycemia in patients with type 2 diabetes.

Overall hypoglycemia: Defined in most studies by signs or symptoms of hypoglycemia, and/or blood glucose below a certain threshold (e.g., < 4 mmol/L).

Quality-adjusted life-year: A health outcome measure that combines both quantity and quality of life.

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

Rapid-acting insulin analogue: A class of insulin analogues — produced through alterations of the amino acid sequence of regular human insulin — designed to closely mimic the short duration of action of meal-induced endogenous insulin secretion.

Rate ratio: The ratio of the person-time incidence rate in the exposed or experimental group to the person-time incidence rate in the control group.

Regular human insulin: Unmodified, short-acting human insulin.

Relative risk: The ratio of the absolute risk of an outcome of interest in the exposed or experimental group to the absolute risk of the outcome in the control group.

Severe hypoglycemia: Severe hypoglycemia is defined as an event with characteristic hypoglycemic symptoms requiring assistance of another person. Some studies also require the presence of blood glucose values below a certain threshold (e.g., < 4 mmol/L).

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.

Transient ischemic attack: Episodes of stroke symptoms that last only briefly; the current definition of duration is < 24 hours, but the average duration of a transient ischemic attack is about 12 minutes.

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 disease progresses.

Weighted mean difference: A method of meta-analysis used to pool continuous measures (e.g., body weight) where the mean, standard deviation and sample size in each group are known. The relative weight given to each study is proportional to the inverse of the variance of the reported mean.

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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 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

CERC (Appendix A) 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 on one or more specific topics. For the insulin analogues, 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, health economists or other relevant qualifications, with expertise in 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 CAC has identified the management of diabetes mellitus as a priority area for optimal practice initiatives, based on the following criteria:

- large deviations from optimal utilization (over- or under-use)
- 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 the insulin analogues was identified by CAC as a priority topic. Given the high prevalence and rising incidence of diabetes in Canada, the optimal prescribing and use of insulin and insulin analogues has the potential to positively impact health outcomes for a large number of patients. Although the insulin analogues may have certain clinical advantages as compared to conventional insulins, acquisition costs of insulin analogues (i.e., insulin aspart, insulin lispro, insulin detemir, and insulin glargine) are greater than those for conventional insulin products (e.g., insulin neutral protamine Hagedorn [NPH] and regular human insulin). Given the increasing number of people diagnosed with diabetes mellitus each year, health care providers, consumers, and policy makers require evidence-based information on the optimal use of these agents.

3 OBJECTIVE

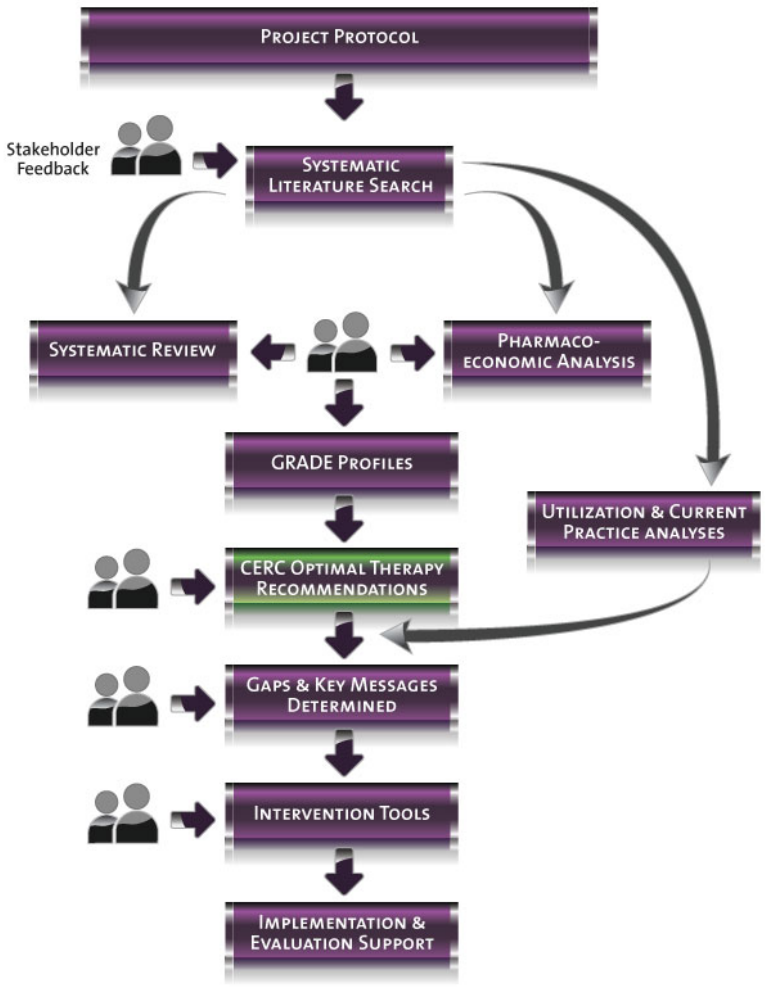
This report provides recommendations for the optimal prescribing and use of long- and rapid-acting insulin analogues for policy decision makers, health care professionals, and patients.

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 feedback and approval of recommendations and supporting interventions. 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 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 long- and rapid-acting insulin analogues, COMPUS follows the process outlined in the flow chart to the right.

This report represents the final optimal therapy recommendations by CERC (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 16 recommendations/suggestions on the use of insulin analogues in various populations (i.e., pre-adolescents, adolescents, adults, pregnant women, with type 1 and type 2 diabetes, and pregnant women with gestational diabetes). CERC applied the GRADE methodology for developing recommendations (Section 6). 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/suggestions is presented in Table 1; individual recommendations/suggestions are presented in Table 2.

Table 1: Summary of CERC Recommendations/Suggestions

When a basal insulin* is required, insulin NPH is **recommended**† over the long-acting insulin analogues (i.e., insulin glargine and insulin detemir) in most patients with type 1 and type 2 diabetes. If a long-acting insulin analogue is used, CERC **recommends** that either insulin glargine or insulin detemir can be used. When a bolus insulin‡ is required, either regular human insulin or the rapid-acting insulin analogues (i.e. insulin aspart and insulin lispro) are **recommended**§ in most patients with type 1 diabetes, with the exception of adolescents. In adolescents with type 1 diabetes, a rapid-acting insulin analogue is **suggested** over regular human insulin. When a bolus insulin is required for patients with type 2 diabetes, regular human insulin is **suggested** over the rapid-acting insulin analogues. If a rapid-acting insulin analogue is used, CERC **recommends** that either insulin aspart or insulin lispro be used.

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

* Longer-acting insulin that controls blood glucose levels between meals and overnight.
† For most children with type 1 diabetes, CERC suggests that insulin NPH be used in preference to long-acting insulin analogues.
‡ Faster-acting insulin that provides the boost of insulin needed to stop the rise in blood glucose levels that occurs after meals.
§ For most preadolescents and pregnant women with type 1 diabetes and women with gestational diabetes, CERC suggests that either regular human insulin or the rapid-acting insulin analogues can be used.

Table 2: Individual CERC Recommendations/Suggestions by Comparator/Populations

Comparators and Populations			Recommendation/Suggestion
Long-acting Insulin Analogues	Insulin NPH versus long-acting insulin analogues	Type 1 diabetes mellitus in adults	CERC recommends that insulin NPH be used in preference to either of the long-acting insulin analogues (i.e., insulin glargine or insulin detemir) in most adults with type 1 diabetes.
		Type 1 diabetes mellitus in children	CERC suggests that insulin NPH be used in preference to either of the long-acting insulin analogues (i.e., insulin glargine or insulin detemir) in most children with type 1 diabetes.
		Type 2 diabetes mellitus in adults taking oral antidiabetic agents	CERC recommends that insulin NPH be used in preference to either of the long-acting insulin analogues (i.e., insulin glargine or insulin detemir) in most adults with type 2 diabetes taking oral anti-diabetic agents and who require a basal insulin.
		Type 2 diabetes mellitus in adults using pre-meal bolus insulin	CERC recommends that insulin NPH be used in preference to either of the long-acting insulin analogues (i.e., insulin glargine or insulin detemir) in most adults with type 2 diabetes using pre-meal bolus insulin and who require a basal insulin.
	Insulin glargine versus insulin detemir	Type 1 diabetes mellitus in adults	CERC recommends that either insulin glargine or insulin detemir be used in adults with type 1 diabetes if treatment with a long-acting insulin analogue is chosen.
		Type 2 diabetes mellitus in adults	CERC recommends that either insulin glargine or insulin detemir be used in adults with type 2 diabetes taking oral antidiabetic agents if treatment with a long-acting insulin analogue is chosen.
Rapid-acting Insulin Analogues	Regular human insulin versus rapid-acting insulin analogues	Type 1 diabetes mellitus in pre-adolescents	CERC suggests that either regular human insulin or a rapid-acting insulin analogue (i.e., insulin lispro or insulin aspart) be used in most pre-adolescents with type 1 diabetes (CSII or MDI).
		Type 1 diabetes mellitus in adults using CSII	CERC recommends that either regular human insulin or a rapid-acting insulin analogue (i.e., insulin aspart or insulin lispro) be used in most adults with type 1 diabetes using CSII.
		Type 1 diabetes mellitus in adults using MDI	CERC recommends that either regular human insulin or a rapid-acting insulin analogue (i.e., insulin aspart or insulin lispro) be used in most adults with type 1 diabetes using MDI.
		Type 1 diabetes mellitus in pregnant women	CERC suggests that either regular human insulin or a rapid-acting insulin analogue (i.e., insulin aspart or insulin lispro) be used in most pregnant women who have type 1 diabetes.
		Gestational diabetes mellitus	CERC suggests that either regular human insulin or a rapid-acting insulin analogue (i.e., insulin lispro or insulin aspart) be used in most women who develop gestational diabetes.
		Type 1 diabetes mellitus in adolescents using MDI	CERC suggests that insulin lispro be used in preference to regular human insulin in most adolescents with type 1 diabetes using MDI.
		Type 2 diabetes mellitus in adults	CERC suggests that regular human insulin be used in preference to the rapid-acting insulin analogues (i.e., insulin lispro and insulin aspart) in most adults with type 2 diabetes who require bolus insulin therapy.
	Insulin lispro versus insulin aspart	Type 1 diabetes mellitus in children	CERC recommends that either insulin lispro or insulin aspart be used in children with type 1 diabetes using CSII if treatment with a rapid-acting insulin analogue is chosen.
		Type 1 diabetes mellitus in adults	CERC recommends that either insulin lispro or insulin aspart be used in adults with type 1 diabetes using CSII if treatment with a rapid-acting insulin analogue is chosen.
		Type 2 diabetes mellitus in adults	CERC recommends that either biphasic insulin lispro or biphasic insulin aspart be used in adults with type 2 diabetes using MDI if treatment with a biphasic rapid-acting insulin analogue preparation is chosen.

CERC=COMPUS Expert Review Committee; CSII=continuous subcutaneous insulin infusion; MDI=multiple daily injection; NPH=neutral protamine Hagedorn.

5.2 Research Gaps

An important aspect of COMPUS' 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 the use of insulin analogues. These gaps will benefit researchers and research funding organizations in their planning of future research in clinical practice. 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 (RCTs) was absent are shown in Table 3.

Two populations that have yet to be studied in a comparative trial of insulin analogues versus conventional insulins are children and pregnant women with type 2 diabetes. Furthermore, the long-acting insulin analogues have not been studied in pregnant women. One of the objectives of the systematic reviews upon which CERC's recommendations are based was to identify ethnic groups that may benefit from the use of insulin analogues. First Nations populations were of special interest given the high prevalence of diabetes.[1] No studies comparing insulin analogues to conventional insulins in this population were identified.

5.2.2 Outcomes with insufficient evidence

There was insufficient evidence for a number of outcomes considered important for making recommendations on the use of insulin analogues. There were no studies that were adequately powered and of sufficient duration to measure the effect of the insulin analogues on the long-term microvascular and macrovascular diabetes complications. Efficacy outcomes were restricted to intermediate outcomes such as A1C and plasma glucose. As well, the potential benefits of the insulin analogues regarding quality of life were infrequently reported. In particular, increased convenience and reduced fear of hypoglycemia are often cited as benefits of the insulin analogues, yet these benefits have not been adequately quantified in RCTs.

Table 3: Populations and Comparisons for which no RCT Evidence was found in the Systematic Reviews of Long-acting and Rapid-acting Insulin Analogues

Population	Long-acting Insulin Analogues			Rapid-acting Insulin Analogues		
	Insulin glargine versus insulin NPH	Insulin detemir versus insulin NPH	Insulin glargine versus insulin detemir	Insulin lispro versus regular human insulin	Insulin aspart versus regular human insulin	Insulin lispro versus insulin aspart
Pediatric						
Pre-adolescent type 1 diabetes			X	B	B*	B†
Adolescent type 1 diabetes				B*	B‡	B†
Pre-adolescent type 2 diabetes	X	X	X	X	X	X
Adolescent type 2 diabetes	X	X	X	X	X	X
Adult						
Type 1 diabetes				B	B	X‡
Type 2 diabetes						M
Pregnant women type 1 diabetes	X	X	X	B	B	X
Pregnant women type 2 diabetes	X	X	X	X	X	X
Gestational diabetes	X	X	X	B	B	X

B=trials have only compared monophasic preparations, biphasic preparations have not been studied; M=trials have only compared biphasic preparations, monophasic preparations have not been studied; X=no comparative trials were identified
* No studies in which insulins were administered as CSII were identified.
†The only peer-reviewed study identified[2] enrolled both pre-adolescents and adolescents and did not report data for each subgroup. Insulins were administered as CSII.
‡ The only study identified[3] (published as an abstract) enrolled both pre-adolescents and adolescents and did not report data for each subgroup. Insulins were administered as MDI.

6 THE EVIDENCE

The clinical evidence for the insulin analogues was derived from two systematic reviews: *Rapid-acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta-analyses of Clinical Outcomes*, and *Long-acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta-analyses of Clinical Outcomes*, both conducted by COMPUS.[4,5] These reviews were updates of existing systematic reviews on the rapid-acting insulin analogues (*Short-acting Insulin Analogues for Diabetes Mellitus: Meta-analysis of Clinical Outcomes and Assessment of Cost Effectiveness, March 2007)* and long-acting insulin analogues (*Long-acting Insulin Analogues for Diabetes*

Mellitus: Meta-analysis of Clinical Outcomes and Assessment of Cost Effectiveness, October 2007) from CADTH's Health Technology Assessment program.[6,7] A further update of the literature search was conducted for studies published between the search cut-off date of the COMPUS systematic reviews (April 2007) and September 2008 to identify any additional evidence that addressed existing recommendations or research gaps. Although the systematic reviews included all relevant data from peer-reviewed articles, as well as abstracts and grey literature, CERC based its recommendations only on evidence from peer-reviewed studies. Results from abstracts were assessed separately by the committee to determine their impact on the recommendations. Cost-effectiveness data for the insulin analogues were derived from pharmacoeconomic analyses conducted by COMPUS using the Center for Outcomes Research (CORE) Diabetes model. The results of those analyses are presented in an Economic Report: *An Economic Evaluation of Insulin Analogues for the Treatment of Patients with Type 1 and Type 2 Diabetes Mellitus in Canada*.[8] Stakeholder feedback was requested and incorporated into both systematic reviews and the economic 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 draft recommendations are formulated by CERC consists of two main stages. First, the committee considers the clinical evidence regarding safety and effectiveness and draws conclusions regarding clinically important differences (if any) among the therapies in question. Second, the committee 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 that cost-effectiveness considerations have on the recommendations, thus increasing transparency of the deliberative process. Optimal therapy recommendations are then formulated based on the efficacy, safety, and pharmacoeconomic data.

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. 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, the Committee also develops context statements related, but not limited to, safety, quality, and quantity of evidence, cost-effectiveness, and directness of 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.[9] 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.[10] The GRADE methodology is used by a number of organizations world-wide, including the World Health Organization[11] and the American Thoracic Society.[12] Details of the GRADE process as applied by COMPUS for the insulin analogues project, as well as the GRADE evidence profiles generated for this topic, have been reported previously.[13]

The process by which CERC used the GRADE evidence profiles and economic data to generate optimal therapy recommendations for insulin analogues consisted of nine 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.
9. Consideration of stakeholder feedback and drafting of final optimal therapy recommendations.

7.2 Specific Considerations

Prior to initiation of the systematic reviews by COMPUS, members of CERC identified the outcomes for which evidence was required to make recommendations for the insulin analogues. These included:

- long-term complications of diabetes (e.g., mortality, cardiovascular disease, nephropathy, retinopathy)
- surrogate outcomes related to glycemic control (i.e., hemoglobin A1C, fasting plasma glucose, two-hour post-prandial plasma glucose)
- other surrogate outcomes (e.g., lipids, blood pressure)
- hypoglycemia
- body weight
- 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[14] was employed to guide CERC's deliberations.

7.2.1 Hemoglobin A1C

Hemoglobin A1C is the most frequently reported measure of long-term glycemic control in studies of anti-diabetes agents, including insulin analogues. CERC deliberated extensively on the evidence available to support the validity of hemoglobin A1C as a surrogate outcome for clinically relevant complications of diabetes,[14-38] and the minimal difference in this outcome that could be considered clinically relevant.[39-41] All members of the committee 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.[14]

The committee 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 glucose control. Furthermore, diabetes treatment guidelines define optimum glycemic control based on A1C targets. CERC agreed on the use of a minimal clinically important difference in A1C between 0.7% and 1% for use during the Committee's deliberations. Differences in A1C for the various comparators and across the different populations of interest, as based on analyses of available evidence, failed to approach this range.

7.2.2 Fasting and post-prandial glycemia

CERC restricted its deliberations on potential benefits of insulin analogues regarding fasting and post-prandial glucose to laboratory-measured plasma values. Data from self-monitoring were excluded due to concerns regarding reliability. Both fasting and post-prandial glucose scored low according to the validation schema for surrogate outcomes by Lassere et al.[14] 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

Members of CERC recognize that hypoglycemia, particularly severe and nocturnal episodes, pose a substantial barrier to achieving optimal glycemic control in patients with diabetes. Evidence regarding the prevalence of nocturnal hypoglycemia, its clinical importance, its effects on quality of life, sleep, memory, and cardiovascular function were collected. The evidence was reviewed by CERC.[42-68]

Every effort was made to identify situations from the evidence profiles that demonstrated statistically significant differences in the incidences of hypoglycemia between comparator groups. These cases formed the basis for extensive deliberation by CERC prior to developing and voting on recommendations. The effect (i.e., direction and effect size) of insulin analogues related to traditional insulin products on hypoglycemia was inconsistent across the different comparators and study populations. Individual evidence profiles in Appendix B capture CERC's extensive discussion on the available evidence related to hypoglycemia in the management of diabetes mellitus.

Despite the lack of evidence, the Committee acknowledges the behavioural changes (e.g., purposefully running higher glycemic control) that may be associated with the fear of hypoglycemia. CERC also recognizes the relative importance placed on avoiding hypoglycemia in patients who manage their diabetes with insulin. These issues were discussed extensively by the Committee prior to developing and voting on recommendations.

7.2.4 Quality of life and patient satisfaction

CERC recognized that one of the potential benefits of the rapid-acting insulin analogues as compared to regular human insulin is increased flexibility in the timing and content of meals. This may result in improved quality of life and patient satisfaction. Convenience and flexibility were, therefore, identified as being important factors influencing the choice of insulin by patients and clinicians. As a result, the Committee carefully considered the available evidence on the insulin analogues pertaining to these outcomes. Evidence regarding the minimal clinically important difference for commonly used instruments to measure patient satisfaction (e.g., the Diabetes Treatment Satisfaction Questionnaire) was also reviewed,[69-72] although a minimal clinically important difference could not be identified from these studies. Every effort was made to identify situations from the evidence profiles that demonstrated a statistically significant difference in quality of life instrument scores between comparator groups. Individual evidence profiles in Appendix B capture CERC's extensive discussion on the available evidence related to quality of life and patient satisfaction issues in the management of diabetes mellitus.

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 insulin analogues will be identified by comparing the final recommendations to information on the current practice (*Current Practice Analysis: Insulin Analogues. A Qualitative Analysis of Canadian Physician Perceptions and Use of Insulin Analogues*) utilization (*Current Utilization of Insulin Products in Canada*) of these agents in Canada.[73,74]

Key messages to promote the optimal prescribing and utilization of insulin analogues 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 in Canada.

9 APPENDIX A: Expert Committee and Contributors

COMPUS Expert Review Committee

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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 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 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, 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, 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.

Dr. Heather Dean has received financial support from Eli Lilly 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.

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10 APPENDIX B: Detailed Recommendations with Supporting Evidence

1 Long-acting insulin analogues

1.1 Insulin NPH versus long-acting insulin analogues
- 1.1.1 Type 1 diabetes mellitus in adults
- 1.1.2 Type 1 diabetes mellitus in children
- 1.1.3 Type 2 diabetes mellitus in adults taking oral antidiabetic agents
- 1.1.4 Type 2 diabetes mellitus in adults using pre-meal bolus insulin

1.2 Insulin glargine versus insulin detemir
- 1.2.1 Type 1 diabetes mellitus in adults
- 1.2.2 Type 2 diabetes mellitus in adults

2 Rapid-acting insulin analogues

2.1 Regular human insulin versus rapid-acting insulin analogues
- 2.1.1 Type 1 diabetes mellitus in pre-adolescents
- 2.1.2 Type 1 diabetes mellitus in adults using continuous subcutaneous insulin infusion
- 2.1.3 Type 1 diabetes mellitus in adults using multiple daily injection
- 2.1.4 Type 1 diabetes mellitus in pregnant women
- 2.1.5 Gestational diabetes mellitus
- 2.1.6 Type 1 diabetes mellitus in adolescents using multiple daily injection
- 2.1.7 Type 2 diabetes mellitus in adults

2.2. Insulin lispro versus insulin aspart
- 2.2.1 Type 1 diabetes mellitus in children
- 2.2.2 Type 1 diabetes mellitus in adults
- 2.2.3 Type 2 diabetes mellitus in adults

3 Clinical findings of insulin analogues

The detailed recommendation tables offer the following information:

- **Vote results —** Indicates the number of CERC members voting in favour of the proposed draft 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 draft 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 draft 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 draft 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 draft recommendation. This information is provided to assist clinicians, patients, and policy decision makers with the interpretation and application of the recommendation.

1 Long-acting insulin analogues

1.1 Insulin NPH versus long-acting insulin analogues

1.1.1 Type 1 diabetes mellitus in adults

CERC recommends that insulin NPH be used in **preference to** either of the long-acting insulin analogues (i.e., insulin glargine or insulin detemir) in most **adults with type 1 diabetes**.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Glargine	Detemir
	8/11	7/11
CERC Rating of Overall Quality of Clinical Evidence	Low	Moderate
Strength of Recommendation	**Strong**	

Underlying values and preferences:

- Primary consideration: the incremental cost of long-acting insulin analogues over insulin NPH outweighs their modest clinical benefits.
- Other values and preferences:
  - patient convenience and lifestyle benefits associated with availability of premixed insulins, and the option of mixing basal and bolus insulin doses in the same syringe. Due to the onset of action of insulin NPH at 2 to 4 hours, a morning dose may also eliminate need for administration of bolus insulin at lunchtime — favours insulin NPH
  - there is greater clinical experience with insulin NPH — favours insulin NPH
  - reduced incidence of hypoglycemia (especially nocturnal) — favours long-acting insulin analogues.

Clinical notes:

- Based on CERC clinical opinion and limited evidence, long-acting insulin analogues can be tried in patients who experience significant hypoglycemia, particularly nocturnal and severe hypoglycemia, while using insulin NPH.
- Some comparative studies demonstrated a reduced risk or incidence of hypoglycemia with long-acting insulin analogues versus insulin NPH. This benefit, however, was not observed consistently across all studies, comparisons, and types of hypoglycemia (i.e., severe, nocturnal, overall). Methodological limitations (e.g., lack of clear definitions for hypoglycemia in studies, high degree of heterogeneity in meta-analyses) associated with the outcome of hypoglycemia were also identified in most cases.
- Of studies that reported data on hypoglycemia outcomes, subjects with a prior history of recurrent severe hypoglycemia were excluded in 7 of 9 trials comparing insulin detemir with insulin NPH and none of the trials comparing insulin glargine with insulin NPH.
- Some members of CERC felt strongly that hypoglycemia is an important concern for some patients, and a potentially significant barrier to achieving optimal glycemic control.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Glargine	Detemir
	8/11	7/11
CERC Rating of Overall Quality of Clinical Evidence	Low	Moderate
Strength of Recommendation	**Strong**	

Context:

- Overall quality of evidence was low to moderate.
- Studies primarily reported results regarding surrogate outcomes, and sparse data were available for long-acting insulin analogues concerning clinically important long-term outcomes.
- Results from abstracts were identified for the outcomes of A1C, weight gain, nocturnal hypoglycemia, and overall hypoglycemia in the comparison of insulin NPH and insulin glargine. Inclusion of the results from abstracts did not significantly affect the overall results derived from published peer-reviewed research (as determined by sensitivity analyses).
- An updated search of the literature from the cut-off date of the COMPUS meta-analysis (April 2007) to September 2008 yielded two additional RCTs[75,76] comparing insulin glargine with insulin NPH, and one additional RCT[77] comparing insulin detemir with insulin NPH, in adults with type 1 diabetes. In sensitivity analyses, these results did not have a significant impact on the existing pooled estimates of effect.
- Only insulin glargine demonstrated a small but statistically significant difference in A1C compared with insulin NPH (0.12%), which was not considered clinically significant.
- Mean differences in body weight as compared to insulin NPH were statistically significant in favour of both long-acting insulin analogues.
- Patient satisfaction favoured long-acting insulin analogues. However, the magnitude of the difference between treatments was of uncertain clinical significance.
- Incremental cost-utility ratios for long-acting insulin analogues relative to insulin NPH in adults ranged from approximately $90,000 (glargine) to $390,000 (detemir) per QALY gained.
  - The unit cost of insulin glargine cartridges (15 mL) was $109.87 at the time the economic analysis was conducted. This was recently reduced by approximately 23% to $85.17. As part of univariate sensitivity analyses considered by CERC, the average acquisition cost of insulin glargine (including both vials and cartridges) in the model was reduced by 15%. Since the cost of insulin glargine vials remains unchanged, a reduction in average cost of 15% adequately accounts for the reduced cost of insulin glargine vials, since cartridges were assumed to account for 65% of the insulin glargine market.
  - Results from a number of other univariate sensitivity analyses were also considered by CERC, including incorporation of a disutility for fear of hypoglycemia to the insulin NPH arm only, reduction of the cost of managing hypoglycemia, assumption of no A1C difference between long-acting insulin analogues and insulin NPH, and reduced discounting rates. For both insulin glargine and insulin detemir, only the scenario in which disutility for fear of hypoglycemia was incorporated in the model (for the insulin NPH arm alone) resulted in ICUR values that fell within a range normally considered cost-effective.
- Results from studies that compared a long-acting insulin analogue in combination with a rapid-acting insulin analogue versus a combination of insulin NPH and regular human insulin, in adults with type 1 diabetes, were generally similar to studies in which the same bolus insulin was used in both treatment arms.
- Long-acting insulin analogues potentially require more injections because they cannot be mixed with bolus insulins.
- Patients can have wide variation in insulin NPH absorption/distribution (i.e., differences in duration of effect). Insulin NPH variability is highly affected by shaking the vial before withdrawing the dose.

A1C=glycosylated hemoglobin; CERC=COMPUS Expert Review Committee; NPH=neutral protamine Hagedorn; QALY=quality-adjusted life-year; RCTs=randomized controlled trials

Summary of findings table for insulin glargine versus insulin NPH in adults with type 1 diabetes (common pre-meal bolus insulin in both arms):

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	8 (N = 2,406)[78-85]	-0.12 (-0.25 to -0.01)$_h$ *†	Very low
Severe hypoglycemia (relative risk)	6 (N = 2,113)[78-80,82,83,86]	0.81 (0.49 to 1.36)†	Very low
Severe hypoglycemia (rate ratio)	3 (N = 1,278)[79,80,84]	0.88 (0.54 to1.43)†‡	Moderate
Nocturnal hypoglycemia (relative risk)	5 (N = 1,943)[78,79,84,85,87]	0.97 (0.87 to 1.09)$_h$	Very low
Nocturnal hypoglycemia (rate ratio)	4 (N = 916)[79,82-84]	0.67(0.37 to 1.23)$_h$†	Low
Overall hypoglycemia (relative risk)	5 (N = 1,893)[79,81,84,85,87]	1.02 (0.97 to 1.07)$_h$†	Low
Overall hypoglycemia (rate ratio)	2 (N = 670)[79,82]	0.82(0.52 to 1.28)$_h$†	Low
Other surrogates	Mean difference in body weight favoured insulin glargine over NPH [3 RCTs,[79,84,87] (N = 1,138)[2], WMD (95% CI): -0.40 (-0.76 to -0.03), low quality]. No data for other surrogates.		
Long-term complications/mortality	No difference between treatments for retinopathy.[79] No data for other complications. All cause mortality not estimable.		
HRQoL and patient satisfaction	No difference between treatments for HRQoL.[88] Significantly higher patient satisfaction with insulin glargine as measured by the DTSQ [1 RCT,[88] N = 517, WMD = 1.83 (0.82, 2.84), moderate quality].		
Cost-effectiveness[8]	**Incremental cost-utility analysis — base case:** • C = $3,423; • QALYs = 0.039; ICUR = $87,932 per QALY gained **Sensitivity analyses:** 1. WMD for A1C = 0: ICUR increases to $916,401 per QALY gained. 2. Cost of managing severe hypoglycemic episode increased to C$440: ICUR decreases to $71,067 per QALY gained. 3. Discount rates = 0% and 3% (for both costs and QALYs): ICUR decreases to $45,645 and $66,828, respectively. 4. Incorporation of fear of hypoglycemia (disutility = 0.0052): ICUR decreases to $17,225 per QALY gained. 5. Price of insulin glargine decreased by 15%: ICUR decreases to $60,860 per QALY gained. 6. Variation of other parameters in SAs did not change results significantly.		

A1C=hemoglobin A1C; CI=confidence interval; DTSQ=Diabetes Treatment Satisfaction Questionnaire; h=significant heterogeneity (I^2 > 50%); HRQoL=health-related quality of life; ICUR= incremental cost-utility ratio; NPH=neutral protamine Hagedorn; QALY=quality-adjusted life-year; RCT=randomized controlled trial; SA=sensitivity analysis; WMD=weighted mean difference; ΔC=difference in costs between strategies; ΔQALY=difference in QALYs gained between strategies.

*Two additional abstracts[89,90] were identified; their inclusion in the meta-analysis did not significantly affect the overall estimate of effect on A1C.

† An updated search of the literature from the cut-off date of the COMPUS meta-analysis (April 2007) to September 2008 yielded two additional RCTs[75,76] comparing insulin glargine with insulin NPH. In sensitivity analyses, these results did not have a significant impact on the existing pooled estimates of effect.

‡ One additional abstract[89] was identified; its inclusion in the meta-analysis did not significantly affect the overall estimate of effect on hypoglycemia.

Summary of findings table for insulin detemir versus insulin NPH in adults with type 1 diabetes (common pre-meal bolus insulin in both arms):

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%)	7 (N = 2,558)[91-97]	WMD = -0.06 (-0.13 to 0.02)*	Moderate
Severe hypoglycemia (relative risk)	7 (N = 2,442)[91-96,98]	RR = 0.74 (0.58 to 0.96)*	Moderate
Severe hypoglycemia (rate ratio)	7 (N = 2,442)[91-94,96-98]	0.95 (0.65 to 1.38)$_h$*	Low
Nocturnal hypoglycemia (relative risk)	6 (N = 2,311)[91,93-97]	0.92 (0.85 to 0.98)*	Low
Nocturnal hypoglycemia (rate ratio)	8 (N = 2,695)[91-98]	0.66 (0.60 to 0.73)$_h$*	Low
Overall hypoglycemia (relative risk)	6 (N = 2,110)[91,93,94,96-98]	1.00 (0.96 to 1.04)*	Moderate
Overall hypoglycemia (rate ratio)	6 (N = 2,109)[91,93,94,96-98]	0.84 (0.74 to 0.97)$_h$*	Low
Other surrogates	Mean body weight difference favoured detemir group over NPH group [6 RCTs,[91-96] N =2,302, WMD –0.73 (-1.42 to –0.03)$_h$*, low quality]. No data for other surrogates.		
Long-term complications / mortality	No difference between treatments regarding ischemic heart disease, retinopathy, stroke/transient ischemic attack (TIA).[94,96,97] No difference between treatments regarding all cause mortality.[96,97]		
Cost-effectiveness[8]	**Incremental cost-utility analysis — base case:** • C = $4,344; • QALYs = 0.011; ICUR = $387,729 per QALY gained **Sensitivity analyses:** 1. WMD for A1C = 0: ICUR increases to $1,958,928 per QALY gained. 2. Incorporation of fear of hypoglycemia (disutility = 0.0052): ICUR decreases to $25,666 per QALY gained. 3. Other SAs yielded ICURs > $150,000 per QALY gained.		

A1C=hemoglobin A1C; CI=confidence interval; h=significant heterogeneity (I^2 > 50%); ICUR=incremental cost-utility ratio; NA=not available in Canada as a vial (i.e., 1x10mL, 100units/mL); NPH=neutral protamine Hagedorn; QALY=quality-adjusted life-year; RCT=randomized controlled trial; SA=sensitivity analysis; TIA=Transient Ischemic Attack; WMD=weighted mean difference;
• C=difference in costs between strategies; • QALY=difference in QALYs gained between strategies.
* An updated search of the literature from the cut-off date of the COMPUS meta-analysis (April 2007) to September 2008 yielded one additional RCT[77] comparing insulin detemir with insulin NPH. In sensitivity analyses, these results did not have a significant impact on the existing pooled estimates of effect.

1.1.2 Type 1 diabetes mellitus in children

CERC suggests that insulin NPH be used in **preference to** either of the long-acting insulin analogues (i.e., insulin glargine or insulin detemir) in most **children with type 1 diabetes**.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Glargine	Detemir
	12/12	12/12
CERC Rating of Overall Quality of Clinical Evidence	Low	Low
Strength of Recommendation	**Weak**	

Rationale for weak recommendation:

- CERC graded the recommendation as weak due to the lack of a cost-effectiveness analysis and the low overall quality of the evidence.

Underlying values and preferences:

- Primary consideration: Although cost-effectiveness data were lacking for children with type 1 diabetes, CERC assessed that for most patients, the incremental cost of long-acting insulin analogues over insulin NPH outweighs their modest clinical benefits.
- Other values and preferences:
  - patient convenience and lifestyle benefits associated with availability of premixed insulins, and the option of mixing basal and bolus insulin doses in the same syringe — favours insulin NPH
  - there is greater clinical experience with insulin NPH — favours insulin NPH
  - reduced incidence of hypoglycemia (especially nocturnal) — favours long-acting insulin analogues.

Clinical notes:

- Based on CERC clinical opinion and limited evidence, long-acting insulin analogues can be tried in patients who experience significant hypoglycemia, particularly nocturnal and severe hypoglycemia, while using insulin NPH.
- Some comparative studies demonstrated a reduced risk/incidence of hypoglycemia with long-acting insulin analogues versus insulin NPH. This benefit, however, was not observed consistently across all studies, comparisons, and types of hypoglycemia (i.e., severe, nocturnal, overall). Methodological limitations (e.g., lack of clear definitions for hypoglycemia in studies, high degree of heterogeneity in meta-analyses) associated with the outcome of hypoglycemia were also identified in most cases.
- Some members of CERC felt strongly that hypoglycemia is an important concern for some patients, and a potentially significant barrier to achieving optimal glycemic control.

CERC=COMPUS Expert Review Committee; NPH=neutral protamine Hagedorn.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Glargine	Detemir
	12/12	12/12
CERC Rating of Overall Quality of Clinical Evidence	Low	Low
Strength of Recommendation	**Weak**	

Context:

- Overall quality of evidence was low.
- Studies primarily reported results regarding surrogate outcomes and sparse data were available for long-acting insulin analogues concerning clinically important long-term outcomes.
- Results from abstracts were identified for the outcomes of A1C, severe hypoglycemia, and overall hypoglycemia for the comparison of insulin NPH and insulin glargine. Inclusion of the results from abstracts did not significantly affect the overall results derived from published peer-reviewed research (as determined by sensitivity analyses).
- An updated search of the literature from the cut-off date of the COMPUS meta-analysis (April 2007) to September 2008 yielded one additional RCT[99] comparing insulin glargine with insulin NPH in children with type 1 diabetes. In sensitivity analyses, these results did not have a significant impact on the existing pooled estimates of effect.
- Differences in A1C were not statistically significant for either insulin glargine or insulin detemir compared with insulin NPH.
- Long-acting insulin analogues potentially require more injections because they cannot be mixed with bolus insulins.
- Patients can have wide variation in insulin NPH absorption/distribution (i.e., differences in duration of effect). Insulin NPH variability is highly affected by shaking the vial before withdrawing the dose.
- Since insulin NPH has an onset of effect of between 2 and 4 hours, a dose administered in the morning may be sufficient to control post-lunch glucose levels, thereby eliminating the need to administer an injection of bolus insulin at lunchtime. In contrast, long-acting insulin analogues do not have a pronounced peak; therefore, an injection of bolus insulin is required before lunch. This may be impractical during school hours for young children (<14 years of age).

A1C=glycosylated hemoglobin; COMPUS=Canadian Optimal Medication Prescribing and Utilization Service; NPH=neutral protamine Hagedorn; RCT=randomized controlled trial

Summary of findings table for insulin glargine versus insulin NPH in children with type 1 diabetes (common premeal bolus insulin in both arms):

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 (N = 349)[100]	-0.22 (-0.53 to 0.09)*†	Low
Severe hypoglycemia (relative risk)	1 (N = 349)[100]	0.80 (0.56 to 1.15)*†	Low
Nocturnal hypoglycemia (relative risk)	1 (N = 349)[100]	0.71 (0.43 to 1.18)	Low
Overall hypoglycemia (relative risk)	1 (N = 349)[100]	1.01 (0.90 to 1.12)*†	Moderate
Other surrogates	No difference between treatments regarding BMI.[99] No data for other surrogates.		
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin glargine = $55.07 Insulin NPH (Humulin N) = $17.20 Insulin NPH (Novolin ge NPH) = 18.33 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin glargine = $109.87‡ Insulin NPH (Humulin N) = $35.68 Insulin NPH (Novolin ge NPH) = $35.97		
Average daily cost of drugs	Data regarding average weight or insulin dose for this population are not available.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin glargine versus insulin NPH are not available for this population.		

A1C=hemoglobin A1C; BMI= body mass index; CI=confidence interval; NPH=neutral protamine Hagedorn; RCT=randomized controlled trial; WMD=weighted mean difference.

*Two additional abstracts[101,102] were identified; their inclusion in the meta-analysis did not significantly affect the overall estimate of effect on A1C or hypoglycemia.

†An updated search of the literature from the cut-off date of the COMPUS meta-analysis (April 2007) to September 2008 yielded one additional RCT[99] comparing insulin glargine with insulin NPH in children with type 1 diabetes. In sensitivity analyses, these results did not have a significant impact on the existing pooled estimates of effect. This study also reported a statistically non-significant result for rate of overall hypoglycemia.

‡Unit cost was recently reduced to $85.17 by the manufacturer.

Summary of findings table for insulin detemir versus insulin NPH in children with type 1 diabetes (common premeal bolus insulin in both arms):

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 (N = 347)[103]	0.10 (-0.1 to 0.3)	High
Severe hypoglycemia (relative risk)	1 (N = 347)[103]	0.80 (0.5 to01.28)	High
Severe hypoglycemia (rate ratio)	1 (N = 347)[103]	0.94 (0.68 to 1.3)	High
Nocturnal hypoglycemia (relative risk)	1 (N = 347)[103]	0.85 (0.77 to 0.94)	High
Nocturnal hypoglycemia (rate ratio)	1 (N = 347)[103]	0.77 (0.7 to 0.84)	High
Overall hypoglycemia (relative risk)	1 (N = 347)[103]	0.98 (0.94 to 1.01)	High
Overall hypoglycemia (rate ratio)	1 (N = 347)[103]	0.89 (0.86 to 0.93)	High
Other surrogates	BMI: WMD in Z-score significantly favoured detemir (-0.18 (95% CI: -0.25 to -0.11)).[103] No data for other surrogates.		
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin detemir = not applicable Insulin NPH (Humulin N) = $17.20 Insulin NPH (Novolin ge NPH) = 18.33 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin detemir = $109.86 Insulin NPH (Humulin N) = $35.68 Insulin NPH (Novolin ge NPH) = $35.97		
Average daily cost of drugs	Data regarding average weight or insulin dose for this population are not available.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin detemir versus NPH are not available for this population.		

A1C=hemoglobin A1C; CI= confidence interval; NA=not available in Canada as a vial (i.e., 1 x 10 mL, 100 units/mL); NPH=neutral protamine Hagedorn; RCT randomized controlled trial; WMD = weighted mean difference.

1.1.3 Type 2 diabetes mellitus in adults taking oral antidiabetic agents

CERC recommends that insulin NPH be used in **preference to** either of the long-acting insulin analogues (i.e., insulin glargine or insulin detemir) in most **adults with type 2 diabetes** taking oral anti-diabetic agents who require a basal insulin.

Vote Results (Number of CERC members in favour/number participating in meeting)	Glargine	Detemir
	12/12	12/12
CERC Rating of Overall Quality of Clinical Evidence	Moderate	Low
Strength of recommendation	**Strong**	

Underlying values and preferences:

- Primary consideration: The incremental cost of long-acting insulin analogues over insulin NPH outweighs their modest clinical benefits.
- Other values and preferences:
  - there is greater clinical experience with insulin NPH — favours insulin NPH
  - reduced incidence of hypoglycemia (especially nocturnal) — favours long-acting insulin analogues.

Clinical notes:

- Based on CERC clinical opinion and limited evidence, long-acting insulin analogues can be tried in patients who experience significant hypoglycemia, particularly nocturnal and severe hypoglycemia, while using insulin NPH.
- Some studies demonstrated a reduced risk/incidence of hypoglycemia with long-acting insulin analogues versus insulin NPH. However, some effects were marginal and of uncertain clinical significance. Furthermore, statistically significant effects were not observed consistently across all studies, comparisons, and types of hypoglycemia (i.e., severe, nocturnal, overall). Methodological limitations (e.g., lack of clear definitions for hypoglycemia, failure to confirm hypoglycemia by blood glucose testing, high degree of heterogeneity in meta-analyses) associated with the outcome of hypoglycemia were also identified in most cases.
- Of studies that reported data on hypoglycemia outcomes, subjects with a history of recurrent severe hypoglycemia were excluded in 2 of 3 trials comparing insulin detemir with insulin NPH. Patients with a history of recurrent hypoglycemia were not excluded from trials comparing insulin glargine with insulin NPH.
  - Some members of CERC felt strongly that hypoglycemia is an important concern for some patients, and a potentially significant barrier to achieving optimal glycemic control.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Glargine	Detemir
	12/12	12/12
CERC Rating of Overall Quality of Clinical Evidence	Moderate	Low
Strength of Recommendation	**Strong**	

Context:

- Overall quality of evidence was low to moderate.
- Studies primarily reported results regarding surrogate outcomes and sparse data were available for long-acting insulin analogues concerning clinically important long-term outcomes.
- Results from abstracts were identified for the outcomes of A1C, fasting plasma glucose, body weight, nocturnal hypoglycemia, and overall hypoglycemia for the comparison of insulin NPH and insulin detemir. Inclusion of the results from abstracts did not significantly affect the overall results derived from published peer-reviewed research (as determined by sensitivity analyses), except that the A1C difference was rendered statistically significant in favour of insulin NPH.
- There were no significant differences in A1C.
- Insulin detemir was associated with significantly less weight gain than insulin NPH.
- The incremental cost-utility ratio for insulin detemir versus insulin NPH in patients using oral antidiabetic agents was approximately $640,000 per QALY gained, while insulin glargine was dominated by insulin NPH (i.e., it was less effective and more costly).
  - The unit cost of insulin glargine cartridges (15 mL) was $109.87 at the time the economic analysis was conducted. This was recently reduced by approximately 23% to $85.17. As part of univariate sensitivity analyses considered by CERC, the average acquisition cost of insulin glargine (including both vials and cartridges) in the model was reduced by 15%. Since the cost of insulin glargine vials remains unchanged, a reduction in average cost of 15% adequately accounts for the reduced cost of insulin glargine vials, since cartridges were assumed to account for 65% of the insulin glargine market.
  - A recent RCT[104] comparing the long-acting insulin analogues in patients with type 2 diabetes using oral antidiabetic agents reported higher mean daily doses of insulin detemir (0.78 IU/kg/day) were required as compared to insulin glargine (0.44 IU/kg/day). In the economic analysis considered by CERC, the mean daily dose for both agents was 0.53 IU/kg/day. For insulin detemir, this value is significantly lower than the mean daily dose reported in the RCT; therefore, the estimated base-case ICUR is likely conservative. In contrast, the results of the RCT suggest that the base-case ICUR may have been overestimated for insulin glargine. Although long-acting insulin analogue doses were not subjected to sensitivity analysis, the sensitivity analysis in which the average cost of insulin glargine was reduced by 15% corresponds to the scenario in which the average dose is reduced by 15% (i.e., 0.45 IU/kg) while acquisition cost remains the same as in the base case. The resulting ICUR ($450,000 per QALY gained) was still well above conventional thresholds of cost-effectiveness.
  - Results from a number of other univariate sensitivity analyses were also considered by CERC, including incorporation of a disutility for fear of hypoglycemia to the insulin NPH arm only, reduction of the cost of managing hypoglycaemia, assumption of no A1C differences between long-acting insulin analogues and insulin NPH, and reduced discounting rates. For both insulin glargine and insulin detemir, the scenario in which disutility for fear of hypoglycemia was incorporated in the model (for the insulin NPH arm alone) resulted in the lowest ICUR values (approximately $74,000 per QALY gained for insulin glargine, and $235,000 per QALY gained for insulin detemir).
- Patients can have wide variations in insulin NPH absorption/distribution (i.e., differences in duration of effect). Insulin NPH variability is highly affected by shaking the vial before withdrawing the dose.

A1C=glycosylated hemoglobin; CERC=COMPUS Expert Review Committee; ICUR-incremental cost-utility ratio; NPH=neutral protamine Hagedorn; QALY=quality-adjusted life-year; RCT=randomized controlled trial

Summary of findings table for insulin glargine versus insulin NPH in adults with type 2 diabetes (using oral antidiabetic agents):

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	9 (N = 3,397)[105-113]	-0.05 (-0.13 to 0.04)	Moderate
Fasting plasma glucose (mmol/L) (WMD)	6 (N = 2,406)[107-110,113,114]	-0.10 (-0.28 to 0.07)	Moderate
Severe hypoglycemia (relative risk)	7 (N = 2,866)[106-110,112,113]	0.66 (0.29 to 1.48)$_h$	Very low
Severe hypoglycemia (rate ratio)	3 (N = 1,681),[109,110,112]	0.51 (0.15 to 1.79)$_h$	Very low
Nocturnal hypoglycemia (relative risk)	7 (N = 2,532),[105-108,110,112,113]	0.56 (0.47 to 0.68)	Low
Nocturnal hypoglycemia (rate ratio)	4 (N = 1,705),[109,110,112,113]	0.41 (0.29 to 0.59)$_h$	Low
Overall hypoglycemia (relative risk)	8 (N = 2,642),[105-108,110-113]	0.87 (0.81 to 0.93)	Low
Overall hypoglycemia (rate ratio)	4 (N =1,705),[109,110,112,113]	0.82 (0.64 to 1.06)$_h$	Low
Other surrogates	No difference between treatments in terms of body weight gain, BMI, mean systolic and diastolic blood pressure, LDL-C, and the percentage of patients who reached target A1C (≤7%).[105-113]		
Long-term complications / mortality	No difference between treatments in terms of ischemic heart disease.[107,110] Insufficient data for other complications or mortality.		
HRQoL and Patient Satisfaction	Mean improvement in treatment satisfaction score significantly favoured insulin glargine over insulin NPH: 1 RCT,[110] N = 481, WMD (95%CI) = 0.60 (0.07 to 1.13), moderate quality.		
Cost-effectiveness[8]	**Incremental cost-utility analysis — base case:** • C=$4,945; • QALYs = 0.008; ICUR = $642,994 per QALY gained **Sensitivity analyses:** 1. WMD for A1C = 0: ICUR increases to $1,577,457 per QALY gained. 2. Incorporation of fear of hypoglycemia (disutility = 0.0052): ICUR decreases to $73,989 per QALY gained. 3. Other SAs yielded ICURs >$450,000 per QALY gained.		

A1C=hemoglobin A1C; BMI=body mass index; CI=confidence interval; h=significant heterogeneity (I^2 > 50%); HRQoL=health-related quality of life; ICUR= incremental cost-utility ratio; LDL-C=low-density lipoprotein cholesterol; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; QALY=quality-adjusted life-year; RCT=randomized controlled trial; SA=sensitivity analysis; WMD=weighted mean difference; • C=difference in costs between strategies; • QALY=difference in QALYs gained between strategies.

Summary of findings table for insulin detemir versus insulin NPH in adults with type 2 diabetes (using oral antidiabetic agents):

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	2 (N = 796)[115,116]	0.14 (-0.01 to 0.28)*	Moderate
Fasting plasma glucose (mmol/L) (WMD)	2 (N = 784)[115,116]	-0.14 (-1.02 to 0.74)$_h$†	Low
Severe hypoglycemia (relative risk)	2 (N = 808)[115,116]	0.75 (0.03 to 20.01)$_h$	Very low
Severe hypoglycemia (rate ratio)	1 (N = 463)[115]	0.13 (0.02 to 0.91)	Low
Nocturnal hypoglycemia (relative risk)	2 (N = 808)[115,116]	0.53 (0.31 to 0.91)$_h$	Moderate
Nocturnal hypoglycemia (rate ratio)	2 (N = 798)[115,116]	0.45 (0.38 to 0.54)†	Moderate
Overall hypoglycemia (relative risk)	2 (N = 808)[115,116]	0.65 (0.39 to 1.07)$_h$	Low
Overall hypoglycemia (rate ratio)	2 (N = 798)[115,116]	0.54 (0.50 to 0.58)†	Moderate
Other surrogates	Mean difference in body weight favoured insulin detemir over insulin NPH: 2 RCTs[115,116] (N = 782); WMD (95%CI) = -1.27 (-1.95 to -0.58)$_h$†, low quality. No difference between treatments in percentage of patients who reached target A1C (≤7%) (1 RCT,[115] N = 463). No data for other surrogate outcomes.		
Long-term complications/mortality	No data for long-term complications. No difference between treatments regarding all cause mortality (1 RCT,[116] N = 333, low quality)		
Cost-effectiveness[8]	**Incremental cost-utility analysis — base case:** • C = $6,521; • QALYs = -0.034; ICUR = Dominated **Sensitivity analyses:** 1. WMD for A1C = 0: ICUR decreases to $882,155 per QALY gained. 2. Incorporation of fear of hypoglycemia (disutility = 0.0052): ICUR decreases to $234,606 per QALY gained. 3. Changes to other parameters in the model did not significantly alter base case results.		

A1C = hemoglobin A1C; CI = confidence interval; h = significant heterogeneity (I^2 > 50%); ICUR= incremental cost-utility ratio; NPH = neutral protamine Hagedorn; OAD = oral antidiabetic agent; QALY= quality adjusted life-year; RCT = randomized controlled trial; WMD = weighted mean difference; • C= difference in costs between strategies; • QALY= difference in QALYs gained between strategies.

*One additional abstract[117] was identified; its inclusion in the meta-analysis resulted in an overall effect on A1C that was statistically significant in favour of insulin NPH.

†One additional abstract[117] was identified; its inclusion in the meta-analysis did not significantly affect the overall estimate of effect on fasting plasma glucose, hypoglycemia, or body weight.

1.1.4 Type 2 diabetes mellitus in adults using pre-meal bolus insulin

CERC recommends that insulin NPH be used in **preference to** either of the long-acting insulin analogues (i.e., insulin glargine or insulin detemir) in most **adults with type 2 diabetes** using pre-meal bolus insulin who require a basal insulin.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Glargine	Detemir
	12/12	12/12
CERC Rating of Overall Quality of Clinical Evidence	Moderate	Low
Strength of Recommendation	**Strong**	

Underlying values and preferences:

- Primary consideration: Although cost-effectiveness data were lacking for adults with type 2 diabetes treated with pre-meal bolus insulin, CERC assessed that for most patients, the incremental cost of long-acting insulin analogues over insulin NPH outweighs their modest clinical benefits.
- Other values and preferences:
  - there is greater clinical experience with insulin NPH — favours insulin NPH
  - reduced incidence of hypoglycemia (especially nocturnal) — favours long-acting insulin analogues.

Clinical notes:

- Based on CERC clinical opinion and limited evidence, long-acting insulin analogues can be tried in patients who experience significant hypoglycemia, particularly nocturnal and severe hypoglycemia, while using insulin NPH.
- Some studies demonstrated a reduced risk/incidence of hypoglycemia with long-acting insulin analogues versus insulin NPH. However, some effects were marginal and of uncertain clinical significance. Furthermore, statistically significant effects were not observed consistently across all studies, comparisons, and types of hypoglycemia (i.e., severe, nocturnal, overall). Methodological limitations (e.g., lack of clear definitions for hypoglycemia, failure to confirm hypoglycemia by blood glucose testing, high degree of heterogeneity in meta-analyses) associated with the outcome of hypoglycemia were also identified in most cases.
- Subjects with a history of recurrent severe hypoglycemia were excluded in the only trial comparing insulin detemir with insulin NPH. Patients with a history of hypoglycemia were not excluded from trials comparing insulin glargine with insulin NPH.
  - Some members of CERC felt strongly that hypoglycemia is an important concern for some patients, and a potentially significant barrier to achieving optimal glycemic control.

Context:

- Overall quality of evidence was low to moderate.
- Studies primarily reported results regarding surrogate outcomes. No data were available for long-acting insulin analogues concerning clinically important long-term outcomes.
- There were no significant benefits of long-acting insulin analogues regarding A1C.
- Insulin detemir was associated with significantly less weight gain than insulin NPH.
- Results from studies in which the combination of a long-acting insulin analogue and a rapid-acting insulin analogue was compared with the combination of insulin NPH and regular human insulin in adult type 2 diabetes were generally similar to those in which the same bolus insulin was used in both treatment arms.
- Patients can have wide variation in insulin NPH absorption/distribution (i.e., differences in duration of effect). Insulin NPH variability is highly affected by shaking the vial before withdrawing the dose.

A1C=glycosylated hemoglobin; CERC=COMPUS Expert Review Committee; NPH=neutral protamine Hagedorn.

Summary of findings table for insulin glargine versus insulin NPH in adults with type 2 diabetes using pre-meal bolus insulin (not using oral antidiabetic agents)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 (N = 518)[118]	0.28 (0.07 to 0.49)	Moderate
Nocturnal hypoglycemia (relative risk)	1 (N = 518)[118]	0.78 (0.62 to 0.98)	Moderate
Overall hypoglycemia (relative risk)	1 (N = 518)[118]	0.92 (0.81 to 1.05)	Moderate
Other surrogates	No difference in body weight (1 RCT,[118] N = 518) and percentage that reached target A1C (≤ 7%) (1 RCT,[119] N = 100). No data for other surrogates.		
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin glargine = $55.07 Insulin NPH (Humulin N) = $17.20 Insulin NPH (Novolin ge NPH) = 18.33 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin glargine = $109.87* Insulin NPH (Humulin N) = $35.68 Insulin NPH (Novolin ge NPH) = $35.97		
Average daily drug costs	Insulin glargine = $3.24 Insulin NPH = $1.49		
Cost-effectiveness	Data regarding cost-effectiveness of insulin glargine versus NPH are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; NPH=neutral protamine Hagedorn; RCT=randomized controlled trial; WMD=weighted mean difference.
*Unit cost was recently reduced to $85.17 by the manufacturer.

Summary of findings table for insulin detemir versus insulin NPH in adults with type 2 diabetes using pre-meal bolus insulin (not using oral antidiabetic agents)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 (N = 505)[120]	0.10 (-0.18 to 0.38)	Moderate
Fasting plasma glucose (mmol/L) (WMD)	1 (N = 461)[120]	0.10 (-0.61 to 0.81)	Moderate
Nocturnal hypoglycemia (relative risk)	1 (N = 505)[120]	0.66 (0.45 to 0.96)	Moderate
Overall hypoglycemia (relative risk)	1 (N = 505)[120]	0.91 (0.75 to 1.11)	Moderate
Other surrogates	Mean difference in body weight favoured insulin detemir over insulin NPH: 1 RCT,[120] N = 505, WMD -0.80 (-1.46 to -0.14), moderate quality. No data for other surrogates.		
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin detemir = not applicable Insulin NPH (Humulin N) = $17.20 Insulin NPH (Novolin ge NPH) = 18.33 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin detemir = $109.86 Insulin NPH (Humulin N) = $35.68 Insulin NPH (Novolin ge NPH) = $35.97		
Average daily prescription drug costs	Insulin detemir = $3.54 Insulin NPH = $1.49		
Cost-effectiveness	Data regarding cost-effectiveness of insulin detemir versus insulin NPH are not available for this population.		

A1C=hemoglobin A1C; RCT=randomized controlled trial; CI=confidence interval; WMD=weighted mean difference; NPH=neutral protamine Hagedorn.

1.2 Insulin glargine versus insulin detemir

1.2.1 Type 1 diabetes mellitus in adults

CERC recommends that either insulin glargine or insulin detemir be used in **adults with type 1 diabetes** if treatment with a long-acting insulin analogue is chosen.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	11/12
CERC Rating of Overall Quality of Clinical Evidence	Moderate
Strength of Recommendation	**Strong**

Underlying values and preferences:

- Primary consideration: the desirability of allowing patients and clinicians to choose between agents similar in cost and effectiveness.
- Some members expressed a preference for insulin detemir over glargine due to the reduced incidence of severe and nocturnal hypoglycemia observed with the former agent.

Context:

- Overall quality of evidence was moderate.
- The single study reporting this comparison primarily reported results regarding surrogate outcomes. No data were available for clinically important long-term outcomes.
- There were no significant differences in A1C.
- Although reduced incidence rates of severe and nocturnal hypoglycemia were observed in favour of insulin detemir, CERC concluded that there was insufficient evidence to recommend insulin detemir over insulin glargine for the following reasons:
  - Statistically significant differences in favour of insulin detemir were not observed for all hypoglycemia outcomes.
  - Patients with a history of recurrent severe hypoglycemia were excluded from the study.
  - Insulin detemir was dosed twice daily while insulin glargine was dosed once daily in the RCT. This may have contributed to the observed difference in hypoglycemia rates.
- The average daily bolus dose was slightly lower in the insulin detemir arm than in the insulin glargine arm, whereas the average daily insulin detemir dose was slightly higher than the average daily insulin glargine dose.

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee; RCT=randomized controlled trial.

Summary of findings table for insulin detemir versus insulin glargine in adults with type 1 diabetes (common pre-meal bolus insulin in both arms)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 (N = 320)[121]	-0.03 (-0.26 to 0.2)	High
Severe hypoglycemia (relative risk)	1 (N = 320)[121]	0.25 (0.07 to 0.86)	Moderate
Severe hypoglycemia (rate ratio)	1 (N = 320)[121]	0.41 (0.2 to 0.86)	High
Nocturnal hypoglycemia (relative risk)	1 (N = 320)[121]	0.94 (0.75 to 1.17)	High
Nocturnal hypoglycemia (rate ratio)	1 (N = 320)[121]	0.66 (0.58 to 0.76)	High
Overall hypoglycemia (relative risk)	1 (N = 320)[121]	1.05 (0.93 to 1.19)	High
Overall hypoglycemia (rate ratio)	1 (N = 320)[121]	0.96 (0.92 to 1.02)	High
Other surrogates	No difference between treatments in terms of body weight.[121] No data for other surrogates.		
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin detemir = NA Insulin glargine = $55.07 **Cartridge, 5 x 3 mL, 100 units/mL :** Insulin detemir = $109.86 Insulin glargine = $109.87*		
Average daily drug cost[8]	Insulin detemir = $1.41 Insulin glargine = $1.29		
Cost-effectiveness	Data regarding cost-effectiveness of insulin detemir versus insulin glargine are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; RCT=randomized controlled trial; WMD=weighted mean difference.
* Unit cost was recently reduced to $85.17 by the manufacturer.

1.2.2 Type 2 diabetes mellitus in adults

CERC recommends that either insulin glargine or insulin detemir be used in **adults with type 2 diabetes** taking oral antidiabetic agents if treatment with a long-acting insulin analogue is chosen.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	9/11
CERC Rating of Overall Quality of Clinical Evidence	High
Strength of Recommendation	**Strong**
Underlying values and preferences: • Primary consideration: the desirability of allowing patients and clinicians to choose between agents similar in cost and effectiveness.	
Context: • Overall quality of evidence was moderate. • The single study reporting this comparison primarily reported results regarding surrogate outcomes. No data were available for clinically important long-term outcomes. • There were no significant differences in A1C or hypoglycemia. • Insulin detemir was associated with significantly less weight gain than insulin glargine.[104] • Insulin detemir was dosed twice daily at the end of the study in 55% of patients. Insulin glargine was dosed once daily in all patients.[104] • The average daily dose of insulin detemir (0.78 units/kg) was higher than the average daily dose of insulin glargine (0.44 units/kg).[104]	

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee

Summary of findings table for insulin detemir versus insulin glargine in adults with type 2 diabetes (using oral antidiabetic agents)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD) change from baseline	1 RCT[104] (N = 543)	0.02 (-0.17,0.21)	Moderate
Severe hypoglycemia (relative risk)	1 RCT[104] (N = 582)	0.63 (0.21,1.89)	High
Severe hypoglycemia (rate ratio)	1 RCT[104] (N = 582)	1.13 (0.43,2.92)	High
Nocturnal hypoglycemia (relative risk)	1 RCT[104] (N = 582)	1.02 (0.81,1.29)	High
Nocturnal hypoglycemia (rate ratio)	1 RCT[104] (N = 582)	1.01 (0.87,1.17)	High
Overall hypoglycemia (relative risk)	1 RCT[104] (N = 582)	0.89 (0.76, 1.06)	High
Overall hypoglycemia (rate ratio)	1 RCT[104] (N = 582)	0.94 (0.85,1.04)	High
Weight gain (kg) (WMD)	1 RCT[104] (N = 482)	-0.9 (-2.01, 0.21)*	High
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin detemir = NA Insulin glargine = $55.07 **Cartridge, 5 x 3 mL, 100 units/mL :** Insulin detemir = $109.86 Insulin glargine = $109.87†		
Average daily drug cost[8]	Insulin detemir = $3.54 Insulin glargine = $3.24		
Cost-effectiveness	Data regarding cost-effectiveness of insulin detemir versus insulin glargine are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; NA=not applicable; RCT=randomized controlled trial; WMD=weighted mean difference.
* The difference in weight gain between insulin detemir and insulin glargine is reported as being statistically significant by the authors of the RCT, based on an analysis that was adjusted for region, type of OAD used, and baseline weight.[104] The estimate presented in the Summary of Findings table is the result of an unadjusted comparison.
† Unit cost was recently reduced to $85.17 by the manufacturer.

2 Rapid-acting insulin analogues

2.1 Regular human insulin versus rapid-acting insulin analogues

2.1.1 Type 1 diabetes mellitus in pre-adolescents

CERC suggests that **either** regular human insulin or a rapid-acting insulin analogue (i.e., insulin lispro or insulin aspart) be used in most **pre-adolescents with type 1 diabetes (CSII or MDI).**

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Lispro (MDI)	Aspart (MDI)	Lispro (CSII)
	9/11	10/11	10/11
CERC Rating of Overall Quality of Clinical Evidence	Low	Low	Low
Strength of Recommendation	**Weak**	**Weak**	**Weak**

Rationale for weak recommendations:

- CERC graded the recommendation as weak due to the low quality of the clinical evidence and lack of a cost-effectiveness analysis.

Underlying values and preferences:

- Primary consideration: Although cost effectiveness information was not available for this population, CERC assessed that the incremental cost of rapid-acting insulin analogues over regular human insulin was balanced by its benefit regarding convenience and dietary flexibility.

Clinical notes:

- The use of regular human insulin may be considered when:
  - affordability is an important consideration
  - more clinical experience is highly valued.
- The use of rapid-acting insulin analogues may be considered when flexibility of insulin administration regarding meals is of primary importance, and in patients with unpredictable dietary patterns.
- No RCTs comparing insulin aspart with regular human insulin in pre-adolescents using CSII were identified. However, one study[2] compared insulin aspart with insulin lispro, both administered as CSII, in a combined sample of pre-adolescents and adolescents (see Recommendation 2.2.1). Except for a somewhat lower rate of overall hypoglycemia in the insulin aspart arm, there were no statistically significant differences between insulin aspart and insulin lispro concerning A1C or hypoglycemia.[2]
  - Based on clinical opinion and limited evidence, CERC suggests that rapid-acting insulin analogues may be considered in patients who experience significant hypoglycemia while using regular human insulin, or for whom hypoglycemia is a major concern.
  - Some comparative studies demonstrated a reduced risk/incidence of hypoglycemia with insulin lispro versus regular human insulin. This benefit, however, was not observed consistently across all studies, comparisons, and types of hypoglycemia (i.e., severe, nocturnal, overall). Methodological limitations (e.g., lack of how hypoglycemia was defined, high degree of heterogeneity in the meta-analyses) associated with the outcome of hypoglycemia were also identified in most cases.
  - Subjects with a history of recurrent severe hypoglycemia were excluded in 1 of 6 trials comparing insulin lispro with regular human insulin that reported data on hypoglycemia outcomes, and in the only trial comparing insulin aspart with regular human insulin.

  Some members of CERC felt strongly that hypoglycemia, in particular nocturnal and severe hypoglycemia, is an important concern for some patients, and a potentially significant barrier to achieving optimal glycemic control.

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee; CSII=continuous subcutaneous insulin infusion; MDI=multiple daily injection

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Lispro (MDI)	Aspart (MDI)
	9/11	10/11
CERC Rating of Overall Quality of Clinical Evidence	Low	Low
Strength of Recommendation	**Weak**	

Context:

- Overall quality of evidence was low.
- Studies primarily reported results regarding surrogate outcomes. There were no data available for rapid-acting insulin analogues concerning clinically important long-term outcomes.
- There were no significant differences between treatments in A1C.
- Marginal benefits were observed in favour of insulin lispro regarding overall hypoglycemia in CSII users, but there were no significant differences in any hypoglycemia type in the MDI population.
- Statistically significant differences were reported in favour of insulin lispro regarding patient satisfaction in both CSII and MDI populations, and in favour of insulin aspart regarding parent satisfaction with continuing treatment. However, the magnitude of the observed differences was of uncertain clinical significance.
- Results from an abstract[3] comparing insulin aspart with regular human insulin and insulin lispro in 378 children aged 6 to 18 years with type 1 diabetes using MDI could not be pooled with the available peer-reviewed studies since data for the subgroup of pre-adolescent subjects were not reported. No significant differences between treatment groups in A1C or hypoglycemia rates were reported.
- The option of administering a rapid-acting insulin analogue after meals may be an important advantage for children < 5 years of age since administration of regular human insulin 20 to 30 minutes before meals is impractical for many families.
- For patients using CSII, the insulin pumps frequently need to be removed (i.e., due to line blockage or sporting activities); hence, the same insulin for MDI (in combination with a basal insulin) and CSII should be used.
- No studies were identified that compared insulin aspart with regular human insulin in pre-adolescents using CSII.

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee; CSII=continuous subcutaneous insulin infusion; MDI=multiple daily injection

Summary of findings table for insulin lispro versus regular human insulin in pre-adolescents with type 1 diabetes (using continuous subcutaneous insulin infusion)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 (N = 27)[122]	0.06 (-0.47 to 0.59)*	Very low
Severe hypoglycemia (relative risk)	1 (N = 27)[122]	1.00 (0.15 to 6.59)	Very low
Overall hypoglycemia (rate ratio)	1 (N = 27)[122]	0.82 (0.75 to 0.89)	Very low
HRQoL and patient satisfaction	There was a statistically significant increase in patient satisfaction with insulin lispro compared to regular human insulin (1 RCT;[122] N = 54).		
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin lispro = $25.79 Short-acting HI (Humulin R) = $17.20 Short-acting HI (Novolin ge Toronto) = $18.33 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin lispro = $51.59 Short-acting HI (Humulin R) = $35.68 Short-acting HI (Novolin ge Toronto) = $35.97		
Average daily cost of drugs	Data regarding average weight or insulin dose are not available for this population.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin lispro versus regular human insulin are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; HI=human insulin; HRQoL=Health-related quality of life; RCT=randomized controlled trial; WMD=weighted mean difference.

* Carry-over effect was reported for A1C and results are analyzed during the first period of treatment.

Summary of findings table for insulin lispro versus regular human insulin in pre-adolescents with type 1 diabetes (using multiple daily injection)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	4 (N = 286)[123-126]	0.14 (-0.18 to 0.46)*	Moderate
Severe hypoglycemia (relative risk)	3 (N = 222)[122,123,125]	0.69 (0.24 to 2.01)	Low
Nocturnal hypoglycemia (rate ratio)	3 (N = 234)[124-126]	0.96 (0.74 to 1.26)	Low
Overall hypoglycemia (rate ratio)	5 (N = 338)[122-126]	0.99 (0.88 to 1.12)$_h$	Low
HRQoL and patient satisfaction	Three studies[124-126] reported that parents of children with type 1 diabetes preferred insulin lispro over HI because of convenience, based on responses to questionnaires.		
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin lispro = $25.79 Short-acting HI (Humulin R) = $17.20 Short-acting HI (Novolin ge Toronto) = 18.33 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin lispro = $51.59 Short-acting HI (Humulin R) = $35.68 Short-acting HI (Novolin ge Toronto) = $35.97		
Average daily cost of drugs	Data regarding average weight or insulin dose are not available for this population.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin lispro versus regular human insulin are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; h=significant heterogeneity (I^2 > 50%); HI=human insulin; HRQoL=health-related quality of life; RCT=randomized controlled trial; WMD=weighted mean difference.

* One additional abstract[3] reporting a comparison of insulin lispro with regular human insulin in children aged 6 to 18 years with type 1 diabetes was identified. These results could not be pooled with the results presented in the Summary of Findings table since data for the subgroup of pre-adolescent subjects were not reported. This study reported no difference in A1C between insulin lispro and regular human insulin.

Summary of findings table for insulin aspart versus regular human insulin in pre-adolescents with type 1 diabetes (using multiple daily injection)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 RCT[127] (N = 24)	0.10 (-0.52,0.72)*	Low
Overall hypoglycemia (relative risk)	1 RCT[127] (N = 24)	1.06 (0.96,1.17)	Low
Parent satisfaction with diabetes treatment (DTSQ-M, question 1) (WMD)	1 RCT[127] (N = 24)	0.4 (-0.59,1.39)	Low
Parent satisfaction with continuing treatment (DTSQ-M, question 7) (WMD)	1 RCT[127] (N = 24)	1.1 (0.17,2.03)	Moderate
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin aspart = $25.34 Short-acting HI (Humulin R) = $17.20 Short-acting HI (Novolin ge Toronto) = 18.33 **Cartridge, 5 x 3 mL, 100 units/mL :** Insulin aspart = $50.71 Short-acting HI (Humulin R) = $35.68 Short-acting HI (Novolin ge Toronto) = $35.97		
Average daily cost of drugs	Data regarding average weight or insulin dose are not available for this population.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin aspart versus regular human insulin are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; DTSQ-M=Diabetes Treatment Satisfaction Questionnaire-Modified; HI=human insulin; RCT=randomized controlled trial; WMD=weighted mean difference.

*One additional abstract[3] reporting a comparison of insulin aspart with regular human insulin in children aged 6 to 18 years with type 1 diabetes was identified. These results could not be pooled with the results presented in the Summary of Findings table since data for the subgroup of pre-adolescent subjects were not reported. This study reported no difference in A1C between insulin aspart and regular human insulin.

2.1.2 Type 1 diabetes mellitus in adults using CSII

CERC recommends that **either** regular human insulin or a rapid-acting insulin analogue (i.e., insulin aspart or insulin lispro) be used in most **adults with type 1 diabetes** using CSII.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Lispro	Aspart
	10/11	10/11
CERC Rating of Overall Quality of Clinical Evidence	Low	Low
Strength of Recommendation	**Strong**	

Underlying values and preferences:

- Primary consideration: Although cost-effectiveness information was not available for this population, CERC assessed that the incremental cost of the rapid-acting insulin analogues over regular human insulin was balanced by their benefits (i.e., reduced likelihood of nocturnal hypoglycemia, and convenience and dietary flexibility.)

Clinical notes:

- The use of regular human insulin may be considered when:
  - affordability is an important consideration
  - more clinical experience is highly valued.
- The use of a rapid-acting insulin analogue may be considered when flexibility of insulin administration regarding meals is of primary importance, and for patients with unpredictable dietary patterns.
  - Based on CERC clinical opinion and limited evidence, a rapid-acting insulin analogue may be tried in patients who experience significant hypoglycemia while using regular human insulin, or for whom hypoglycemia is a major concern.
  - Some comparative studies demonstrated a reduced risk/incidence of hypoglycemia with rapid-acting insulin analogues versus regular human insulin. However, some effects were marginal and of uncertain clinical significance. Furthermore, statistically significant effects were not observed consistently across all studies, comparisons, and types of hypoglycemia (i.e., severe, nocturnal, overall). Methodological limitations (e.g., lack of how hypoglycemia was defined, high degree of heterogeneity in the meta-analyses) associated with the outcome of hypoglycemia were also identified in most cases.
  - Of studies that reported data on hypoglycemia outcomes, subjects with a history of severe hypoglycemia were excluded from both trials comparing insulin aspart with regular human insulin, and 2 of 6 trials comparing insulin lispro with regular human insulin.
  - Some members of CERC felt strongly that hypoglycemia, in particular nocturnal and severe hypoglycemia, is an important concern for some patients, and a potentially significant barrier to achieving optimal glycemic control.

Context:

- Overall quality of evidence was low.
- Studies primarily reported results regarding surrogate outcomes. There were no data available for rapid-acting insulin analogues concerning clinically important long-term outcomes.
- Results from an abstract were identified for the outcome of severe hypoglycemia in the comparison of regular human insulin and insulin lispro. Inclusion of this result did not significantly affect the overall result derived from published peer-reviewed research (as determined by sensitivity analyses).
- Differences in A1C were marginal.
- Statistically significant benefits of rapid-acting insulin analogues regarding patient satisfaction were observed inconsistently. Furthermore, the magnitude of the observed differences was of uncertain clinical significance. Similarly, quality-of-life data, where available, were inconclusive.
- For patients using CSII, the insulin pumps frequently need to be removed (i.e., due to line blockage or sporting activities); hence, the same insulin for MDI (in combination with a basal insulin) and CSII should be used.

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee; CSII=continuous subcutaneous insulin infusion; MDI=multiple daily injection

Summary of findings table for insulin lispro versus regular human insulin in adults with type 1 diabetes (using continuous subcutaneous insulin infusion)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	6 (N = 595)[128-133]	-0.18 (-0.32 to -0.05)	Moderate
2-hour post-prandial glucose (mmol/L) (WMD)	1 (N = 116)[131]	-2.89 (-4.48 to -1.3)	Very low
Severe hypoglycemia (relative risk)	2 (N = 140)[128,131]	1.50 (0.26 to 8.65)*	Low
Nocturnal hypoglycemia (rate ratio)	1 (N = 67)[128]	0.67 (0.51 to 0.88)	Low
Overall hypoglycemia (rate ratio)	4 (N = 451)[128,131,132,134]	1.07 (0.98 to 1.16)$_h$	Low
Other surrogates	No difference between lispro and HI in body weight gain (4 RCTs, (N = 278).[129,131,133,135] No data for other surrogates.		
HRQoL and patient satisfaction	Two studies[130,134] reported no significant difference regarding satisfaction between lispro and regular human insulin, while two[132,135] reported statistically significant improvement in satisfaction with insulin lispro.		
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin lispro = $25.79 Short-acting HI (Humulin R) = $17.20 Short-acting HI (Novolin ge Toronto) = 18.33 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin lispro = $51.59 Short-acting HI (Humulin R) = $35.68 Short-acting HI (Novolin ge Toronto) = $35.97		
Average daily cost of drugs	Data regarding average weight or insulin dose are not available for this population.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin lispro versus regular human insulin are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; h=significant heterogeneity (I^2 > 50%); HI=human insulin; HRQoL=health-related quality of life; RCT=randomized controlled trial; WMD=weighted mean difference .
* One additional abstract[136] was identified; its inclusion in the meta-analysis did not significantly affect the overall estimate of effect on hypoglycemia.

Summary of findings table for insulin aspart versus regular human insulin in adults with type 1 diabetes (using continuous subcutaneous insulin infusion)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	2 (N = 147)[128,137]	-0.31 (-0.54 to -0.081)	Low
Severe hypoglycemia (relative risk)	1 (N = 118)[128]	0.33 (0.01 to 8.02)	Low
Nocturnal hypoglycemia (rate ratio)	1 (N = 118)[128]	0.55 (0.43 to 0.70)	Low
Overall hypoglycemia (rate ratio)	2 (N = 175)[128,137]	0.58 (0.40, 0.85)	Low
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin aspart = $25.34 Short-acting HI (Humulin R) = $17.20 Short-acting HI (Novolin ge Toronto) = $18.33 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin aspart = $50.71 Short-acting HI (Humulin R) = $35.68 Short-acting HI (Novolin ge Toronto) = $35.97		
Average daily cost of drugs	Data regarding average weight or insulin dose are not available for this population.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin aspart versus regular human insulin are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; HI=human insulin; RCT=randomized controlled trial; WMD= weighted mean difference.

2.1.3 Type 1 diabetes mellitus in adults using MDI

CERC recommends that **either** regular human insulin or a rapid-acting insulin analogue (i.e., insulin aspart or insulin lispro) be used in most **adults with type 1 diabetes** using MDI.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Lispro	Aspart
	8/11	8/11
CERC Rating of Overall Quality of Clinical Evidence	Moderate	Moderate
Strength of Recommendation	**Strong**	

Underlying values and preferences:

- Primary consideration: Results from the cost-effectiveness analyses demonstrated that the rapid-acting insulin analogues and regular human insulin are equivalent.

Clinical notes:

- The use of regular human insulin may be considered when:
  - affordability is an important consideration
  - more clinical experience is highly valued.
- The use of a rapid-acting insulin analogue may be considered when flexibility of insulin administration regarding meals is of primary importance, and for patients with unpredictable dietary patterns.
  - Based on CERC clinical opinion and limited evidence, a rapid-acting insulin analogue may be tried in patients who experience significant hypoglycemia while using regular human insulin, or for whom hypoglycemia is a major concern.
  - Some comparative studies demonstrated a reduced risk or incidence of hypoglycemia with rapid-acting insulin analogues versus regular human insulin. However, some effects were marginal and of uncertain clinical significance. Furthermore, statistically significant effects were not observed consistently across all studies, comparisons, and types of hypoglycemia (i.e., severe, nocturnal, overall). Methodological limitations (e.g., lack of how hypoglycemia was defined, high degree of heterogeneity in the meta-analyses) associated with the outcome of hypoglycemia were also identified in most cases.
  - Of studies that reported data on hypoglycemia outcomes, subjects with a history of severe hypoglycemia were excluded from 3 of 6 trials comparing insulin aspart with regular human insulin, and 3 of 13 trials comparing insulin lispro with regular human insulin.
  - Some members of CERC felt strongly that hypoglycemia, in particular nocturnal and severe hypoglycemia, is an important concern for some patients, and a potentially significant barrier to achieving optimal glycemic control.

Context:

- Overall quality of evidence was moderate.
- Studies primarily reported results regarding surrogate outcomes. There were insufficient data available for rapid-acting insulin analogues regarding clinically important long-term outcomes.
- In addition to the published peer-reviewed research, results from an abstract were also identified for the outcome of quality of life for the comparison of regular human insulin with insulin lispro. It reported statistically significant improvement with insulin lispro regarding overall well-being, depression, anxiety, and energy, but not in positive well-being. One abstract reporting significantly greater patient satisfaction with insulin aspart compared with regular human insulin was also identified.
- Differences in A1C were marginal.
- Statistically significant benefits of rapid-acting insulin analogues regarding patient satisfaction were observed inconsistently. Furthermore, the magnitude of the observed differences was of uncertain clinical significance. Similarly, the quality-of-life data, where available, were inconclusive.
- Differences across studies regarding the choice of basal insulin and frequency of dosing may have increased heterogeneity in the measurement of hypoglycemia (especially nocturnal).

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee; MDI=multiple daily injection.

Summary of findings table for insulin lispro versus regular human insulin in adults with type 1 diabetes (using multiple daily injection)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	16 (N = 5,426)[138-153]	-0.06 (-0.14 to 0.02)	Moderate
2-hour post-prandial plasma glucose (mmol/L) (WMD)	2 (N = 2,036)[138,141]	-0.99 (-1.54, -0.45)	Low
Severe hypoglycemia (relative risk)	6 (N = 4,221)[138,143-145,152,153]	0.78 (0.65 to 0.94)	Moderate
Nocturnal hypoglycemia (rate ratio)	3 (N = 658)[145,147,151]	0.58 (0.35, 0.98)$_h$	Low
Overall hypoglycemia (rate ratio)	12 (N = 5,193)[138-140,143-147,150,152-154]	0.96 (0.86 to 1.06)$_h$	Low
Other surrogates	No significant difference between treatments in body weight gain (7 RCTs).[138,140,145-147,149,155] No data for other surrogates.		
HRQoL and patient satisfaction	Three RCTs[140,147,156] showed a statistically significant increase in satisfaction with lispro compared to HI. Two RCTs[145,156] reported no statistically significant difference between lispro and HI using Well-being Questionnaire (WBQ). One RCT[156] also reported no statistically significant difference between the two treatments in WBQ anxiety and energy domains.*		
Cost-effectiveness[8]	**Incremental cost-utility analysis — base case:** • C = $182; • QALYs = 0.006; ICUR = $28,996 per QALY gained **Sensitivity analyses:** 1. WMD for A1C = 0: ICUR increases to $673,041 per QALY gained. 2. Cost of managing severe hypoglycemic episode increased to C$440: insulin lispro becomes cost-saving. 3. Incorporation of fear of hypoglycemia (disutility = 0.0052): ICUR decreases to $1,117 per QALY gained. 4. Changes to other parameters in the model did not significantly alter base case results.		

A1C=hemoglobin A1C; CI=confidence interval; h=significant heterogeneity (I^2 > 50%); HRQoL=health-related quality of life; ICUR=incremental cost-utility ratio; QALY=quality-adjusted life-year; RCT=randomized controlled trial; WMD=weighted mean difference; • C=difference in costs between strategies; • QALY=difference in QALYs gained between strategies.
*One additional abstract[157] reported statistically significant overall improvement in WBQ with insulin lispro, and improvement in the depression, anxiety, and energy domains, but not in the positive well-being domain.

Summary of findings table for insulin aspart versus regular human insulin in adults with type 1 diabetes (using multiple daily injection)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	5 (N = 2,888)[158-162]	-0.12 (-0.19 to -0.06)	Moderate
Severe hypoglycemia (relative risk)	3 (N = 1,696)[159,162,163]	0.83 (0.66 to 1.03)	Moderate
Overall hypoglycemia (rate ratio)	6 (N = 3,096)[158-163]	0.97 (0.88 to 1.08) $_{h}$	Very low
Other surrogates	No significant difference between treatments in BMI (1 RCT).[161] No data for other surrogates.		
HRQoL and patient satisfaction	One RCT[71] found significant superiority of insulin aspart over HI on overall treatment satisfaction.* Another RCT[162] showed no differences overall, although aspart provided more flexibility than HI.		
Cost-effectiveness[8]	**Incremental cost-utility analysis — base case:** Insulin aspart is cost-saving compared to regular human insulin (• C = -$620; • QALYs = 0.055, ICUR = Cost Saving) **Sensitivity analyses:** 1. WMD for A1C = 0: ICUR increases to $104,598 per QALY gained. 2. Changes to other parameters in the model did not alter base case results.		

A1C=hemoglobin A1C; BMI= body mass index; CI=confidence interval; h=significant heterogeneity (I^2 > 50%); HRQoL=health-related quality of life; ICUR=incremental cost-utility ratio; QALY=quality-adjusted life-year; RCT=randomized controlled trial; RR=relative risk; WMD=weighted mean difference; • C=difference in costs between strategies; • QALY=difference in QALYs gained between strategies.
*One additional abstract[164] was identified which reported greater satisfaction with insulin aspart compared to human insulin.

2.1.4 Type 1 diabetes mellitus in pregnant women

CERC suggests that **either** regular human insulin or a rapid-acting insulin analogue (i.e., insulin aspart or insulin lispro) be used in most **pregnant women who have type 1 diabetes**.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Lispro	Aspart
	7/11	8/11
CERC Rating of Overall Quality of Clinical Evidence	Low	Low
Strength of Recommendation	**Weak**	

Rationale for weak recommendations:

- CERC graded the recommendation as weak due to the low quality of the clinical evidence and lack of a cost effectiveness analysis. Members were also divided between the improved convenience and lifestyle benefits of the rapid-acting insulin analogues versus the more robust experience with regular human insulin and fetal safety.

Underlying values and preferences:

- Primary consideration: Although cost-effectiveness information was not available for this population, CERC assessed that the incremental cost of the rapid-acting insulin analogues over regular human insulin was balanced by their benefits in convenience and dietary flexibility.

Clinical notes:

- Although there is more clinical experience regarding the safety of regular human insulin in pregnancy as compared to the rapid-acting insulin analogues, the available data on the rapid-acting insulin analogues from observational studies was considered reassuring. As well, a companion publication[165] to the single RCT[166] comparing insulin aspart with regular human insulin in this population reported no statistically significant differences between treatments in fetal or perinatal outcomes, including fetal loss, birth weight, mean gestational age at delivery, perinatal mortality, and mode of delivery (including C-section). Although not statistically significant, there was a tendency towards lower rates of pre-term delivery in the insulin aspart arm.[165]
- CERC does not advocate switching insulin products in a patient with type 1 diabetes who becomes pregnant.
- The use of regular human insulin may be considered when:
  - affordability is an important consideration
  - more clinical experience for use in pregnancy is highly valued.
- The use of a rapid-acting insulin analogue may be considered when flexibility of insulin administration regarding meals is of primary importance, and in patients with unpredictable dietary patterns.
  - Based on CERC clinical opinion and limited evidence from other populations, a rapid-acting insulin analogue may be tried in pregnant patients who experience significant hypoglycemia while using regular human insulin, or for whom hypoglycemia is a major concern.
  - None of the studies in pregnant women demonstrated a statistically significant benefit regarding hypoglycemia for the rapid-acting insulin analogues versus regular human insulin.
  - Some members of CERC felt strongly that hypoglycemia, in particular nocturnal and severe hypoglycemia, is an important concern for some patients, and a potentially significant barrier to achieving optimal glycemic control.

Context:

- Overall quality of evidence was low.
- Most data were on surrogate outcomes. No studies reported 2-hour post-prandial blood glucose levels (which are related to increased birth weight), rates of kernicterus, rates of C-sections , or increased length of hospital stay.
- No significant differences in A1C.
- Insulin aspart was favoured for patient satisfaction; this difference was largely due to increased flexibility in the timing of doses. However, the magnitude of the observed difference was of uncertain clinical significance.
- Observational studies on rapid-acting insulin analogues in pregnancy do not demonstrate fetal or maternal risk.

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee; RCT=randomized controlled trial

Summary of findings table for insulin lispro versus regular human insulin in adult pregnant women with type 1 diabetes

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 (N = 33)[167]	0.20 (-1.03 to 1.43)	Very low
Severe hypoglycemia (relative risk)	1 (N = 33)[167]	0.21(0.01 to 4.10)	Very low
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin lispro = $25.79 Short-acting HI (Humulin R) = $17.20 Short-acting HI (Novolin ge Toronto) = 18.33 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin lispro = $51.59 Short-acting HI (Humulin R) = $35.68 Short-acting HI (Novolin ge Toronto) = $35.97		
Average daily cost of drugs	Data regarding average weight or insulin dose are not available for this population.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin lispro versus regular human insulin are not available for this population.		

A1C= hemoglobin A1C; CI= confidence interval; HI=human insulin; RCT= randomized controlled trial; WMD=weighted mean difference.

Summary of findings table for insulin aspart versus regular human insulin in adult pregnant women with type 1 diabetes*

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 (N = 322)[166]	-0.08 (-0.28 to 0.12)	Low
Severe hypoglycemia (relative risk)	1 (N = 322)[166]	0.72 (0.36 to 1.46)	Low
Nocturnal hypoglycemia (relative risk)	1 (N = 322)[166]	0.76 (0.57 to 1.03)	Low
Overall hypoglycemia (relative risk)	1 (N = 322)[166]	0.97 (0.66 to 1.44)	Low
HRQoL and patient satisfaction	Treatment with insulin aspart was associated with significantly greater patient satisfaction than HI (P = 0.031). Willingness to continue was also higher for the aspart group, but the statistical significance was not reported.		
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin aspart = $25.34 Short-acting HI (Humulin R) = $17.20 Short-acting HI (Novolin ge Toronto) = 18.33 **Cartridge, 5 x 3 mL, 100 units/mL :** Insulin aspart = $50.71 Short-acting HI (Humulin R) = $35.68 Short-acting HI (Novolin ge Toronto) = $35.97		
Average daily cost of drugs	Data regarding average weight or insulin dose are not available for this population.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin aspart versus regular human insulin are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; HRQoL=health-related quality of life; RCT=randomized controlled trial; WMD=weighted mean difference.

*A companion publication[165] to this study reported no statistically significant differences between treatments in fetal or perinatal outcomes, including fetal loss, birth weight, mean gestational age at delivery, perinatal mortality, and mode of delivery (including C-section). Although not statistically significant, there was a tendency towards lower rates of pre-term delivery in the insulin aspart arm.[165]

2.1.5 Gestational diabetes mellitus

CERC suggests that **either** regular human insulin or a rapid-acting insulin analogue (i.e., insulin lispro or insulin aspart) be used in most **women** who develop gestational diabetes.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Lispro	Aspart
	7/11	8/11
CERC Rating of Overall Quality of Clinical Evidence	Low	Low
Strength of Recommendation	**Weak**	**Weak**

Rationale for weak recommendations:

- CERC graded the recommendation as weak due to the low quality of the clinical evidence and lack of a cost-effectiveness analysis. Members were also divided between the improved convenience and lifestyle benefits of rapid-acting insulin analogues versus the more robust experience with regular human insulin regarding fetal safety.

Underlying values and preferences:

- Primary consideration: Although cost effectiveness information was not available for this population, CERC assessed that the incremental cost of rapid-acting insulin analogues over regular human insulin was balanced by its benefits of convenience and dietary flexibility.

Clinical notes:

- Although there is more clinical experience regarding the safety of regular human insulin in pregnancy as compared to the rapid-acting insulin analogues, the available data on the rapid-acting insulin analogues from observational studies was considered reassuring.
- The use of regular human insulin may be considered when:
  - affordability is an important consideration
  - more clinical experience for use in pregnancy is highly valued.
- The use of a rapid-acting insulin analogue may be considered when flexibility of insulin administration regarding meals is of primary importance, and in patients with unpredictable dietary patterns.
  - Based on CERC clinical opinion and limited evidence from other populations, a rapid-acting insulin analogue may be tried in women with gestational diabetes who experience significant hypoglycemia while using regular human insulin, or for whom hypoglycemia is a major concern.
  - None of the studies in gestational diabetes demonstrated a statistically significant benefit regarding hypoglycemia for rapid-acting insulin analogues versus regular human insulin.
  - Some members of CERC felt strongly that hypoglycemia, in particular nocturnal and severe hypoglycemia, is an important concern for some patients, and a potentially significant barrier to achieving optimal glycemic control.

Context:

- Overall quality of evidence was low.
- Most data were on surrogate outcomes. Neither study reported 2-hour post-prandial blood glucose levels (which are related to increased birth weight), rates of kernicterus, rates of C-sections, or increased length of hospital stay.
- No significant differences in A1C.
- Observational studies on rapid-acting insulin analogues in pregnancy do not demonstrate fetal or maternal risk.
- Gestational diabetes is usually diagnosed at 26 to 28 weeks, well past the organogenesis phase during which congenital abnormalities are an issue.

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee

Summary of findings table for insulin lispro versus regular human insulin in women with gestational diabetes

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	2 (N = 91)[168,169]	0.06 (-0.11 to 0.23)	Very low
Overall hypoglycemia (difference in mean % of all blood glucose readings that were <3 mmol/L)	1 RCT (N = 42)[168]	-1.32 (-3.07 to 0.43)	Very low
Other surrogates	No difference between treatments in mean body weight gain (1 RCT).[169] No data for other surrogates.		
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin lispro = $25.79 Short-acting HI (Humulin R) = $17.20 Short-acting HI (Novolin GE Toronto) = 18.33 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin lispro = $51.59 Short-acting HI (Humulin R) = $35.68 Short-acting HI (Novolin ge Toronto) = $35.97		
Average daily cost of drugs	Data regarding average weight or insulin dose are not available for this population.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin lispro versus regular human insulin are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; RCT=randomized controlled trial; WMD=weighted mean difference.

Summary of findings table for insulin aspart versus regular human insulin in women with gestational diabetes

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 RCT[170] (N = 27)	0.00 (-0.30,0.30)	Low
Severe hypoglycemia	1 RCT[170] (N = 27)	Not estimable*	Low
Nocturnal hypoglycemia (relative risk)	1 RCT[170] (N = 27)	3.71 (0.47,29.06)	Low
Nocturnal hypoglycemia (rate ratio)	1 RCT[170] (N = 27)	2.79 (0.56,13.80)	Low
Overall hypoglycemia (relative risk)	1 RCT[170] (N = 27)	2.04 (0.97,4.28)	Low
Overall hypoglycemia (rate ratio)	1 RCT[170] (N = 27)	5.37 (2.64,10.89)	Low
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin aspart = $25.34 Short-acting HI (Humulin R) = $17.20 Short-acting HI (Novolin ge Toronto) = 18.33 **Cartridge, 5 x 3 mL, 100 units/mL :** Insulin aspart = $50.71 Short-acting HI (Humulin R) = $35.68 Short-acting HI (Novolin ge Toronto) = $35.97		
Average daily cost of drugs	Data regarding average weight or insulin dose are not available for this population.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin aspart versus regular human insulin are not available for this population.		

A1C=hemoglobin A1C; RCT=randomized controlled trial; CI=confidence interval; WMD=weighted mean difference.
*No patients reported severe hypoglycemia in either treatment group.

2.1.6 Type 1 diabetes mellitus in adolescents using MDI

CERC suggests that insulin lispro be used **in preference to** regular human insulin in most **adolescents with type 1 diabetes** using MDI.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	8/11
CERC Rating of Overall Quality of Clinical Evidence	Low
Strength of Recommendation	**Weak**

Rationale for weak recommendations:

- CERC graded the recommendation as weak due to the low quality of the clinical evidence, marginal benefits of insulin lispro, and lack of a cost-effectiveness analysis.

Underlying values and preferences:

- Primary consideration: Although cost-effectiveness information was not available for this population, CERC assessed that the benefits of insulin lispro over regular human insulin (i.e., reduced incidence of nocturnal and overall hypoglycemia and flexibility of dosing) outweighed the incremental cost associated with insulin lispro. Insulin lispro also provides a better fit for individuals with unpredictable patterns of dietary intake and physical activity.
- Some Committee members favoured regular human insulin because there is greater clinical experience with this agent.

Context:

- Overall quality of evidence was low.
- Studies primarily reported results regarding surrogate outcomes. There were no data available for insulin lispro concerning clinically important long-term outcomes, patient satisfaction, or quality of life.
- No significant differences in A1C were observed.
- Except for nocturnal hypoglycemia, differences in hypoglycemia were marginal. The average number of episodes per patient per 30 days was 1.0 in the insulin lispro arm and 1.7 with regular human insulin.
- Results from an abstract[3] comparing insulin aspart with regular human insulin in children aged 6 to 18 years with type 1 diabetes using MDI were also considered. No significant differences between treatment groups in A1C or hypoglycemia rates were reported. However, insulin aspart was not included in the recommendation since subgroup data on adolescents were not presented, and because the results were not presented in a peer-reviewed publication.

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee; MDI=multiple daily injection.

Summary of findings table for insulin lispro versus regular human insulin in adolescents with type 1 diabetes (using multiple daily injection)

Outcome	# RCTs (Total sample size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 (N = 926)[171]	-0.01 (-0.21 to 0.19)*	Low
Severe hypoglycemia (relative risk)	1 (N = 926)[171]	1.0 (0.29 to 3.43)	Low
Nocturnal hypoglycemia (rate ratio)	1 (N = 926)[171]	0.61 (0.57 to 0.64)	Low
Overall hypoglycemia (rate ratio)	1 (N = 926)[171]	0.90 (0.88 to 0.93)	Low
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin lispro = $25.79 Short-acting HI (Humulin R) = $17.20 Short-acting HI (Novolin ge Toronto) = 18.33 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin lispro = $51.59 Short-acting HI (Humulin R) = $35.68 Short-acting HI (Novolin ge Toronto) = $35.97		
Average daily cost of drugs	Data regarding average weight or insulin dose are not available for this population.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin lispro versus regular human insulin are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; RCT=randomized controlled trial; WMD=weighted mean difference.
*One additional abstract[3] reporting a comparison of insulin lispro with regular human insulin in children aged 6 to 18 years with type 1 diabetes was identified. These results could not be pooled with the results presented in the Summary of Findings table since data for the subgroup of adolescent subjects were not reported. This study reported no difference in A1C between insulin lispro and regular human insulin.

2.1.7 Type 2 diabetes mellitus in adults

CERC suggests that regular human insulin be used in **preference to** the rapid-acting insulin analogues (i.e., insulin lispro and insulin aspart) in most **adults with type 2 diabetes** who require bolus insulin therapy.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	Aspart	Lispro
	8/11	8/11
CERC Rating of Overall Quality of Clinical Evidence	Low	Low
Strength of Recommendation	**Weak**	**Weak**

Rationale for weak recommendations

- CERC graded the recommendation as weak due to the low quality of the clinical evidence, and uncertainty in underlying values and preferences.

Underlying values and preferences:

- Primary consideration: The incremental cost of the rapid-acting insulin analogues over regular human insulin was not felt to be worthwhile considering the cost-effectiveness information.
- Other values and preferences:
  - reduction in hypoglycemia (especially nocturnal) — favours insulin lispro.
  - flexibility of insulin administration regarding meals — favours rapid-acting insulin analogues.
  - there is greater clinical experience with regular human insulin — favours regular human insulin.

Context:

- Overall quality of evidence was low.
- Studies primarily reported results regarding surrogate outcomes. There were sparse data available for rapid-acting insulin analogues concerning clinically important long-term outcomes.
- Results from an abstract were identified for the outcome of A1C and overall hypoglycemia in the comparison of regular human insulin and insulin aspart. Inclusion of this result rendered the A1C estimate derived from published peer-reviewed research statistically non-significant (as determined by sensitivity analyses), but did not significantly affect the overall result for overall hypoglycemia.
- An updated search of the literature from the cut-off date of the COMPUS meta-analysis (April 2007) to September 2008 yielded one additional RCT[172] comparing biphasic insulin lispro with biphasic human insulin, and one RCT[173] comparing insulin aspart with regular human insulin (both in combination with metformin), in adults with type 2 diabetes. In sensitivity analyses, these results did not have a significant impact on the existing pooled estimates of effect.
- No clinically significant differences in A1C were observed.
- There were no significant differences in patient satisfaction or quality of life (insulin lispro).
- Insulin aspart studies were variable regarding the basal insulin used, and the frequency of dosing. Some studies used biphasic insulin aspart.
- Hypoglycemia benefits in favour of rapid-acting insulin analogues were inconsistently observed. Clear definitions for hypoglycemia were not provided in all trials. Of studies that reported data on hypoglycemia outcomes, 3 of 11 trials comparing insulin lispro with regular human insulin, and none of the trials comparing insulin aspart with regular human insulin, excluded subjects with a history of severe hypoglycemia.
- Studies comparing biphasic insulin preparations (i.e., premixed rapid-acting insulin analogue versus premixed human insulin) were pooled with studies of monophasic preparations. There were no apparent differences in magnitude or direction of effect between the two subgroups regarding A1C or hypoglycemia.
- The incidence of hypoglycemia in type 2 diabetes is expected to be lower than in type 1 diabetes. Subgroups of patients prone to hypoglycemia may benefit from insulin lispro.

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee; RCT=randomized controlled trial.

Summary of findings table for insulin lispro versus regular human insulin in adults with type 2 diabetes

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	11 (N = 3,093)[139,142,151,153,174-180]	-0.03 (-0.12 to 0.06)*	Low
2-hour post-prandial plasma glucose (mmol/L) (WMD)	1 (N = 74)[181]	-1.10 (-2.21 to 0.01)	Low
Severe hypoglycemia (relative risk)	2 (N=1,622)[175,178]	0.43 (0.08 to 2.37)	Low
Severe hypoglycemia (rate ratio)	1 (N=1,444)[175]	0.20 (0.02 to 1.71)	Low
Nocturnal hypoglycemia (relative risk)	1 (N = 178)[178]	1.63 (0.71 to 3.73)	Low
Nocturnal hypoglycemia (rate ratio)	3 (N = 1,718)[151,175,179]	0.58 (0.48 to 0.70)	Moderate
Overall hypoglycemia (relative risk)	3 (N = 384)[175,178,180]	1.18 (0.91 to 1.54)	Moderate
Overall hypoglycemia (rate ratio)	8 (N = 2,746)[139,153,175-177,179,181,182]	0.97 (0.91 to 1.03)$_h$	Low
Other surrogates	No difference in weight (3 RCTs,[175,177,179] N = 1,682), BMI (1 RCT,[174] N = 40), LDL-cholesterol (2 RCTs,[174,175] N = 1,484), or total cholesterol: HDL ratio (2 RCTs,[174,175] N = 1,484). No data for other surrogates.		
Long-term complications / mortality	No difference in all cause mortality (1 RCT, N = 80).[180] No data for complications.		
HRQoL and patient satisfaction	No difference in patient satisfaction or HRQoL (energy, anxiety and flexibility) (1 RCT, N = 885).[156]		
Cost-effectiveness[8]	**Incremental cost-utility analysis — base case:** • C=$784; • QALYs=0.006; ICUR = $130,865 per QALY gained **Sensitivity analyses:** 1. WMD for A1C = 0: ICUR decreases to $80,445 per QALY gained. 2. Cost of managing severe hypoglycemic episode increased to C$440: insulin lispro becomes cost saving. 3. Incorporation of fear of hypoglycemia (disutility=0.0052): ICUR decreases to $12,115 per QALY gained. 4. Other SAs yielded ICURs>$100,000 per QALY gained. 5. The incremental cost-effectiveness scatter-plot revealed a large degree of dispersion (i.e., uncertainty) in the ICUR estimate. This was further demonstrated in the cost-effectiveness acceptability curve, which showed that the probability ILis was cost effective versus regular human insulin was only 46.3% and 49.4% at willingness to pay thresholds of $50,000 and $100,000 per QALY gained, respectively.		

A1C=hemoglobin A1C; BMI=body mass index; CI=confidence interval; h=significant heterogeneity (I^2 > 50%); HDL=high-density lipoprotein; HRQoL=health-related quality of life; LDL-C=low-density lipoprotein cholesterol; QALY=quality-adjusted life-year; RCT=randomized controlled trial; ICUR= incremental cost-utility ratio; SA=sensitivity analysis; WMD=weighted mean difference; • C=difference in costs between strategies; • QALY=difference in QALYs gained between strategies.

*An updated search of the literature from the cut-off date of the COMPUS meta-analysis (April 2007) to September 2008 yielded one additional RCT[172] comparing biphasic insulin lispro with biphasic human insulin in adults with type 2 diabetes. In sensitivity analyses, these results did not have a significant impact on the existing pooled estimates of effect.

Summary of findings table for insulin aspart versus regular human insulin in adults with type 2 diabetes

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	4 (N = 421)[183-186]	-0.18 (-0.24 to -0.12) [* †]	Low
Fasting plasma glucose (mmol/L) (WMD)	1 (N = 93)[186]	-0.67 (-2.47 to 1.13)	Low
Severe hypoglycemia (relative risk)	1 (N = 121)[183]	0.39 (0.11 to 1.36)[†]	Low
Nocturnal hypoglycemia (relative risk)	1 (N = 93)[186]	0.65 (0.28 to 1.53)	Low
Overall hypoglycemia (relative risk)	3 (N = 369)[183,184,186]	1.04 (0.85 to 1.28)[‡]	Moderate
Overall hypoglycemia (rate ratio)	2 (N = 276) [183,184]	0.72 (0.64 to 0.80) [†]	Moderate
Other surrogates	No difference in weight gain (2 RCTs,[183,186] N = 214) or cholesterol: HDL ratio (1 RCT, N = 42). No data for other surrogates.		
Long-term complications/mortality	No difference in congestive heart failure (1 RCT, N = 125) and all cause mortality (1 RCT, N = 125).[183] No data for other complications.		
Cost-effectiveness[8]	**Incremental cost-utility analysis — base case:** • C=$333; • QALYs=0.015; ICUR = $22,488 per QALY gained **Sensitivity analyses:** 1. WMD for A1C = 0: ICUR increases to $543,584 per QALY gained. 2. Cost of managing severe hypoglycemic episode increased to C$440: insulin aspart becomes cost-saving. 3. Incorporation of fear of hypoglycemia (disutility = 0.0052): ICUR decreases to $4,429 per QALY gained. 4. Changes to other parameters in the model did not significantly alter base-case results; ICUR < $25,000 per QALY gained. 5. The incremental cost-effectiveness scatter-plot revealed a large degree of dispersion (i.e., uncertainty) in the ICUR estimate. This uncertainty was further demonstrated in the cost-effectiveness acceptability curve, which showed that the probability that insulin aspart was cost-effective versus regular human insulin was only 51.1% and 53.6% at willingness-to-pay thresholds of $50,000 and $100,000 per QALY gained, respectively.		

A1C=hemoglobin A1C; CI=confidence interval; HDL=high-density lipoprotein; ICUR=incremental cost-utility ratio; QALY=quality-adjusted life-year; RCT=randomized controlled trial; WMD=weighted mean difference; • C= difference in costs between strategies; • QALY= difference in QALYs gained between strategies

*Two additional abstracts[187,188] were identified; their inclusion in the meta-analysis resulted in a statistically non-significant difference in A1C.

† An updated search of the literature from the cut-off date of the COMPUS meta-analysis (April 2007) to September 2008 yielded one additional RCT[173] comparing insulin aspart with regular human insulin (both in combination with metformin), in adults with type 2 diabetes. In sensitivity analyses, these results did not have a significant impact on the existing pooled estimates of effect.

‡ One additional abstract[187] was identified; its inclusion in the meta-analysis did not significantly affect the overall estimate of effect on hypoglycemia.

2.2 Insulin lispro versus insulin aspart

2.2.1 Type 1 diabetes mellitus in children

CERC recommends that either insulin lispro or insulin aspart be used in **children with type 1 diabetes using CSII** if treatment with a rapid-acting insulin analogue is chosen.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	10/11
CERC Rating of Overall Quality of Clinical Evidence	Moderate
Strength of Recommendation	**Weak**
Underlying values and preferences: • Primary consideration: The desirability of allowing patients and clinicians to choose between agents similar in cost and effectiveness.	
Context: • Overall quality of evidence was low. • Studies primarily reported results regarding surrogate outcomes. There were no data on the effects of insulin aspart versus insulin lispro on clinically important long-term outcomes. • There was no significant difference in A1C. • The rate of overall hypoglycemia was slightly reduced in the insulin aspart arm versus insulin lispro. No other differences in hypoglycemia were observed. • For patients using CSII, the insulin pumps frequently need to be removed (i.e., due to line blockage or sporting activities); hence, the same insulin for MDI and CSII should be used.	

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee; CSII=continuous subcutaneous insulin infusion; MDI=multiple daily injection.

Summary of findings table for insulin lispro versus insulin aspart in children with type 1 diabetes (using continuous subcutaneous insulin infusion)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 RCT[2] (N = 296)	-0.10 (-0.27, 0.07)	Moderate
Severe hypoglycemia (relative risk)	1 RCT[2] (N = 298)	1.20 (0.54, 2.64)	Moderate
Severe hypoglycemia (rate ratio)	1 RCT[2] (N = 298)	1.40 (0.65, 3.01)	Moderate
Nocturnal hypoglycemia (relative risk)	1 RCT[2] (N = 298)	1.06 (0.86, 1.31)	Moderate
Nocturnal hypoglycemia (rate ratio)	1 RCT[2] (N = 298)	0.93 (0.78, 1.12)	Moderate
Overall hypoglycemia (relative risk)	1 RCT[2] (N = 298)	1.01 (0.95, 1.07)	Moderate
Overall hypoglycemia (rate ratio)	1 RCT[2] (N = 298)	1.20 (1.13, 1.26)	Moderate
Other surrogates	No significant difference in body weight (1 RCT[2], N=296).		
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin lispro = $25.79 Insulin aspart = $25.34 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin lispro = $51.59 Insulin aspart = $50.71		
Average daily cost of drugs	Data regarding average weight or insulin dose are not available for this population.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin lispro versus insulin aspart are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; RCT=randomized controlled trial; WMD=weighted mean difference.

2.2.2 Type 1 diabetes mellitus in adults

CERC recommends that either insulin lispro or insulin aspart be used in **adults with type 1 diabetes using CSII** if treatment with a rapid-acting insulin analogue is chosen.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	11/11
CERC Rating of Overall Quality of Clinical Evidence	Low
Strength of Recommendation	**Strong**
Underlying values and preferences: • Primary consideration: The desirability of allowing patients and clinicians to choose between agents similar in cost and effectiveness.	
Context: • Overall quality of evidence was low. • Studies primarily reported results regarding surrogate outcomes. There were no data on the effects of insulin aspart versus insulin lispro on clinically important long-term outcomes. • There was no significant difference in A1C. • Overall hypoglycemia was slightly reduced in the insulin aspart arm in type 1 diabetes. No other differences in hypoglycemia were observed. • For patients using CSII, the insulin pumps frequently need to be removed (i.e., due to line blockage or sporting activities); hence, the same insulin for MDI and CSII should be used.	

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee; CSII=continuous subcutaneous insulin infusion; MDI=multiple daily injection

Summary of findings table for insulin lispro versus insulin aspart in adults with type 1 diabetes (using continuous subcutaneous insulin infusion)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 (N = 87)[128]	0.25 (-0.20 to 0.71)	Low
Nocturnal hypoglycemia (rate ratio)	1 (N = 87)[128]	1.20 (0.89 to 1.68)	Low
Overall hypoglycemia (rate ratio)	1 (N = 87)[128]	1.49 (1.37 to 1.63)	Low
Unit cost of drugs[8]	**Vial, 1 x 10 mL, 100 units/mL:** Insulin lispro = $25.79 Insulin aspart = $25.34 **Cartridge, 5 x 3 mL, 100 units/mL:** Insulin lispro = $51.59 Insulin aspart = $50.71		
Average daily cost of drugs	Data regarding average weight or insulin dose are not available for this population.		
Cost-effectiveness	Data regarding cost-effectiveness of insulin lispro versus insulin aspart are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; RCT=randomized controlled trial; WMD=weighted mean difference.

2.2.3 Type 2 diabetes mellitus in adults

CERC recommends that either biphasic insulin lispro or biphasic insulin aspart be used in **adults with type 2 diabetes using multiple daily injection** if treatment with a biphasic rapid-acting insulin analogue preparation is chosen.

Vote Results (Number of CERC Members in Favour/Number Participating in Meeting)	11/11
CERC Rating of Overall Quality of Clinical Evidence	Low
Strength of Recommendation	**Strong**
Underlying values and preferences: • Primary consideration: The desirability of allowing patients and clinicians to choose between agents similar in cost and effectiveness.	
Context: • Overall quality of evidence was low. • Studies primarily reported results in terms of surrogate outcomes. There were no data on the effects of insulin aspart versus insulin lispro on clinically important long-term outcomes. • There was no significant difference between treatments in terms of hypoglycemia.	

A1C=hemoglobin A1C; CERC=COMPUS Expert Review Committee

Summary of findings table for biphasic insulin lispro versus biphasic insulin aspart in adults with type 2 diabetes (using multiple daily injection, not using oral antidiabetic agents)

Outcome	# RCTs (Total Sample Size)	Effect Estimate (95% CI)	Quality of Evidence
A1C (%) (WMD)	1 (N = 133)[189]	0.14 (-0.03 to 0.31)	Low
Overall hypoglycemia (rate ratio)	1 (N = 133)[189]	0.90 (0.77 to 1.07)	Low
Unit cost of drugs[8]	**Cartridge, 5 x 3 mL, 100 units/mL:** Biphasic insulin lispro = $51.59 Biphasic insulin aspart = $49.78		
Cost-effectiveness	Data regarding cost-effectiveness of biphasic insulin lispro versus biphasic insulin aspart are not available for this population.		

A1C=hemoglobin A1C; CI=confidence interval; RCT=randomized controlled trial; WMD=weighted mean difference.

3 Clinical findings of insulin analogues

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 insulin analogues. 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 insulin analogues. CERC's optimal therapy recommendations for insulin analogues are presented in summary form (Section 5.1) and detailed form (Appendix B).

Long-acting Insulin Analogues
Either insulin NPH **or** insulin glargine can be used in: • pre-adolescents, adolescents, or adults with type 1 diabetes • adults with type 2 diabetes who are using a pre-meal bolus insulin or using oral antidiabetic agents.
Either insulin NPH **or** insulin detemir can be used in: • pre-adolescents or adolescents with type 1 diabetes • adults with type 2 diabetes who are using a pre-meal bolus insulin.
Insulin detemir can be used over insulin NPH in: • adults with type 1 diabetes • adults with type 2 diabetes who are concurrently using oral antidiabetic agents.
Either insulin detemir or insulin glargine can be used in adults with type 1 diabetes who choose to use a long-acting insulin analogue.

Rapid-acting Insulin Analogues
Insulin lispro can be used over regular human insulin in adolescents with type 1 diabetes using MDI.
Either regular human insulin **or** a rapid-acting insulin analogue (lispro or aspart) can be used in: • pre-adolescents with type 1 diabetes using CSII or MDI (lispro) • women who develop gestational diabetes (lispro) and pregnant women (lispro, aspart) with type 1 diabetes • adults with type 1 diabetes using CSII (lispro, aspart) or MDI (lispro, aspart) • adults with type 2 diabetes who require bolus insulin therapy (lispro, aspart).
There were no significant differences found in the following direct comparisons: • insulin aspart and insulin lispro in adults with type 1 diabetes using CSII • biphasic insulin lispro and biphasic insulin aspart in adults with type 2 diabetes.

CSII=continuous subcutaneous insulin infusion; MDI=multiple daily injection

11 APPENDIX C: DETAILED CERC PROCESS

The steps that CERC followed for generating draft 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. Committee 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 Grading of Recommendations Assessment, Development and Evaluation (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 generated to reflect the body of generated information, contained:

- Key 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 single most important value or preference 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 commissioned by COMPUS. Where one treatment strategy appeared to be more effective than the alternative, CERC assessed whether 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. 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.

Draft recommendations and GRADE Summary of Findings tables containing both the clinical and cost/cost effectiveness data are provided in Appendix B.

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/cost-effectiveness evidence. Where the clinical-effectiveness and cost/cost-effectiveness evidence failed to demonstrate important differences between treatments, recommendations were formulated to reflect that either treatment is considered appropriate. 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.[12] 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.[12]

A "strong" recommendation:

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

A "weak" recommendation:

1. is likely to be followed by the majority of well-informed patients; however, a significant minority would choose not to follow the recommendation.
2. requires careful consideration of patient values and preferences. Decision aids may be helpful in determining the course of action.
3. 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 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 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 was collated and provided to CERC for consideration prior to drafting of the final optimal therapy recommendations for insulin analogues.

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