

OPTIMAL THERAPY REPORT

COMPUS

June 2008

(Draft) Optimal Therapy Recommendations for
the Prescribing and Use of Insulin Analogues

Disclaimer

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 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 policymakers 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 judgement in respect of the care of a particular patient or other professional judgement 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	hemoglobin A1c
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
LAIA	long-acting insulin analogue
MDI	multiple daily injection
NPH	neutral protamine Hagedorn
QALY	quality adjusted life years
RAIA	rapid-acting insulin analogue
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.

Carryover 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 confidence 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, all subjects switch to the alternative treatment.

Diabetes mellitus: A group of common metabolic disorders characterized by hyperglycemia 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 the intended outcomes when deployed under routine circumstances.

Efficacy: The extent 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 8 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 glycosylated form of hemoglobin. Hemoglobin A1c levels reflect average glycemia over the past 90-120 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: 1) autonomic or neuroglycopenic symptoms characteristic of low blood glucose (e.g., trembling, sweating, hunger, confusion, weakness) that respond to carbohydrate intake; 2) a plasma glucose level below a specific value (threshold is usually between 3.4-4.0 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 analogue, 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 24:00 h to 6:00 h.

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 analogue, 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.

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.

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.

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: TIAs are episodes of stroke symptoms that last only briefly; the current definition of duration is < 24 h, but the average duration of TIA is about 12 min.

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 aetiology 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 in clinical practice, then proposing evidence-based interventions to address these gaps, and
- supporting the implementation of these interventions.

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

- The [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 CERC

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 in respect of 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. The remaining six Core Members hold qualifications as physicians, pharmacists, health economists or other relevant qualifications with expertise in one or more areas, such as, but not limited to: family practice; institutional or community clinical pharmacy; pharmacoconomics; 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 is to provide recommendations and advice to the COMPUS Directorate at CADTH on assigned topics that relate to the identification, evaluation and promotion of best 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 management of diabetes mellitus as being 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
- the extent that evidence is available

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, insulin glargine) are greater than those for conventional insulin products (e.g., insulin neutral protamine Hagedorn [NPH], regular human insulin). In view of 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

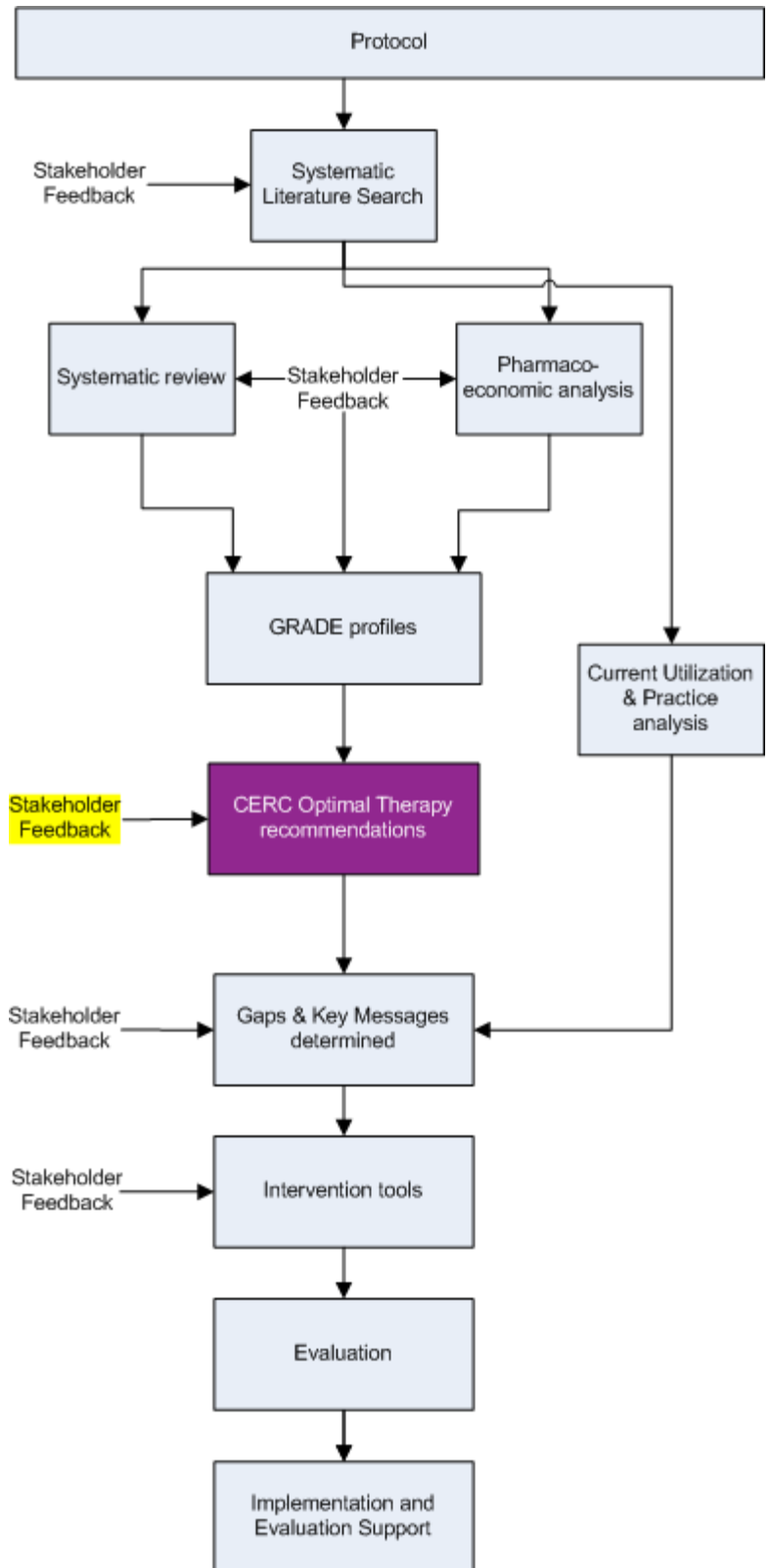
The objective of this report is to provide recommendations for the optimal prescribing and use of long- and rapid-acting insulin analogues for policy decision makers, health care professionals and patients.

4 Project Overview

Once a topic is selected, COMPUS undertakes activities related to key areas in the COMPUS procedure. The CAC provide 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 health technologies. A broad range of stakeholders are invited to provide feedback at various stages in the COMPUS process.

To identify and promote the implementation of evidence-based and cost-effective 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 draft report represents the stakeholder feedback step (yellow highlight) following the production of draft optimal therapy recommendations by CERC (purple box). Stakeholder feedback will be collated and considered by CERC in the production of final recommendations.



5 RESULTS

5.1 Draft Optimal Therapy Recommendations

Basal Insulin¹

When a basal insulin is required, insulin NPH is recommended² over the long-acting insulin analogues, such as glargine or detemir, in children with type 1 diabetes and adults with type 1 and type 2 diabetes. If a long-acting insulin analogue is used there is no preference between the available agents.

Bolus Insulin³

When a bolus insulin is required, either regular human insulin or the rapid-acting insulin analogues, such as aspart and lispro are recommended in all patients with type 1 diabetes, with the exception of adolescents. In adolescents with type 1 diabetes, insulin lispro is suggested over regular human insulin and insulin aspart cannot be recommended due to a lack of evidence. 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 there is no preference between the available agents (with the exception of adolescents with type 1 diabetes addressed above).

Detailed draft recommendations along with summaries of available evidence are presented in Appendix B.

5.2 Research Gaps

An important aspect of COMPUS' mandate includes the identification and dissemination of research gaps. The following sections outline gaps in research related to the use of insulin analogues. These gaps will be of benefit to researchers, graduate students and research funding organizations when planning future research in clinical practice. Further research can impact knowledge that will lead to improved practice and outcomes for patients with diabetes. Such knowledge can be assimilated by COMPUS.

5.2.1 Populations and comparisons with insufficient evidence

Populations and comparisons for which insufficient randomized controlled trial (RCT) evidence was identified are shown in Table 1. 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. No publicly available RCT evidence could be located that

¹ Longer-acting insulin that controls blood glucose levels between meals and overnight

² 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...”).

³ Faster-acting insulin that provides the boost of insulin needed to stop the rise in blood glucose levels that occurs after meals

compared insulin aspart to either regular human insulin or insulin lispro in any pediatric population. The efficacy of biphasic RAIAs has not been compared with biphasic human insulin in any population. The LAIAs have not been compared to insulin NPH nor to each other in pregnant women. Intra-class comparisons are also lacking in children. Evidence for the intra-class comparison of the LAIAs in adults with type 2 diabetes consists of two conference abstracts. CERC made recommendations only for comparisons in which there was at least one published peer-reviewed study; therefore this comparison is listed as a research gap.

Table 1: 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						
Preadolescent type 1 diabetes			X	B [†]	X	X
Adolescent type 1 diabetes				X*	X	X
Preadolescent 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			X	B	B	M
Pregnant women type 1 diabetes	X	X	X	B	B	X
Pregnant women type 2 diabetes	X	X	X	X	X	X
Pregnant women Gestational diabetes	X	X	X	B	X	X

X = no comparative trials were identified; B = no comparative trials comparing biphasic preparations were identified; M = no trials comparing monophasic preparations were identified.

* No studies of monophasic preparations in patients using CSII; no studies of biphasic preparations in patients using MDI.

† In patients using MDI.

One of the objectives of the systematic reviews upon which CERC’s optimal therapy recommendations are based was to identify ethnic groups that may benefit from the insulin analogues. First Nations populations were of special interest given the high prevalence of diabetes. No studies comparing insulin analogues to conventional insulins in this population were identified.

5.2.2 Outcomes with insufficient evidence

Evidence was sparse or lacking 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 in terms of 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 studies.

6 The Evidence

The clinical evidence for the insulin analogues was derived from [two systematic reviews](#) conducted by COMPUS.^{2,3} These reviews were updates of existing systematic reviews on the [rapid-acting insulin analogues](#) and [long-acting insulin analogues](#) from CADTH.^{4,5} 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. However, 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 (CDM). The results of those analyses are presented in an [Economic Report](#).⁶ Stakeholder feedback was requested and where appropriate (as directed by CERC) incorporated into both systematic reviews and the economic analyses.

7 Consideration of the Evidence

CERC members consider both clinical effectiveness (i.e., benefits, harms, and burdens) and cost/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/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. The Committee also develops context statements related, but not limited to, safety, quality and

quantity of evidence, cost-effectiveness, and directness of evidence, to assist in knowledge transfer to the intended audiences.

COMPUS applied the [Grades of Recommendation Assessment, Development and Evaluation \(GRADE\)](#) approach to summarize the available evidence and facilitate the generation of optimal therapy recommendations by CERC. The GRADE Working Group, an international collaboration of methodologists developed the GRADE methodology to provide committees charged with formulating recommendations a framework for evaluating evidence. GRADE provides a systematic and transparent approach to judge quality of evidence, weigh the balance of benefits versus harms, identify underlying values and preferences, and rate the overall strength of generated recommendations.⁷ The GRADE methodology is used by a number of organizations around the world including the World Health Organization⁸ and the American Thoracic Society¹. 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.⁹

The process by which CERC used the GRADE evidence profiles and economic data to generate optimal therapy recommendations for insulin analogues consisted of six main steps. Each of these steps is described in further detail in Appendix C.

1. Reviewed and provided Feedback on GRADE evidence profiles
2. Discussion of clinical effectiveness evidence and feedback
3. Generating clinical findings based on clinical evidence of effectiveness and safety
4. Generating draft optimal therapy recommendations based on clinical conclusions and cost/cost effectiveness information
5. Identification of underlying values and preferences for each recommendation
6. Grading of the strength of recommendations

8 Next Steps

The draft optimal therapy recommendations on insulin analogues are posted for stakeholder feedback for 20 business days. Feedback received will be considered by CERC for the production of final optimal therapy recommendations. Once finalized, 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](#)¹⁰ and [utilization](#)¹¹ of these agents in Canada.

Key messages to promote the optimal prescribing and utilization of insulin analogues will be developed to address identified gaps in practice/knowledge. Intervention tools will be populated with the key messages and related evidence for implementation in Canada.

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APPENDIX A: Expert Committee and Contributors

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Conflicts of Interest

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Dr. Heather Dean has received financial support from Eli Lilly to attend an investigators' meeting on Growth Hormone in 2005. (November 28, 2006).

Dr. Ehud Ur has received honoraria for educational lectures, honoraria for organizing conferences or other honoraria for \$5000 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 (February 9, 2007).

None of the other CERC members declared any conflicts of interest. [Conflict of interest guidelines](#) are posted on the CADTH web site.

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APPENDIX B: Detailed Draft Recommendations with supporting evidence

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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	
<p>Underlying values and preferences</p> <ul style="list-style-type: none"> • Primary consideration: The incremental cost of LAIAs over insulin NPH outweighs their modest clinical benefits. • Other values and preferences: <ul style="list-style-type: none"> ➢ Patient convenience and lifestyle benefits associated with reduced frequency of injections - favours insulin NPH; ➢ Larger body of evidence on long-term safety and outcomes available for insulin NPH – favours insulin NPH; ➢ Reduced incidence of hypoglycemia (especially nocturnal) - favours LAIAs. 		
<p>Clinical Note</p> <ul style="list-style-type: none"> • Based on clinical opinion and limited evidence, CERC suggests that LAIAs can be tried in patients who experience significant hypoglycemia, particularly nocturnal and severe hypoglycemia, while using insulin NPH. <ul style="list-style-type: none"> ➢ Some comparative studies demonstrated a reduced risk/incidence of hypoglycemia with LAIAs 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. 		
<p>Context</p> <ul style="list-style-type: none"> • Overall quality of evidence was low to moderate. • Studies primarily reported results in terms of surrogate outcomes and sparse data were available for LAIAs in terms of clinically important long-term outcomes. • Results from abstracts were identified for the outcomes of A1c, weight gain, nocturnal 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). • Only insulin glargine demonstrated a small but statistically significant difference in A1c compared with insulin NPH (0.12%) which was not considered clinically significant. • Patient satisfaction favoured LAIAs but was of unknown clinical significance. • Incremental cost utility ratios for long-acting insulin analogues relative to insulin NPH in adults ranged from approximately \$90K (glargine) to \$390K (detemir) per QALY gained. • Results from studies that compared a LAIA in combination with a RAIA 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. 		

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=2406)	-0.12 (-0.25 to -0.01) _h ¹	Very low
Severe hypoglycemia (relative risk)	6 (N=2113)	0.81 (0.49 to 1.36) ²	Very low
Severe hypoglycemia (rate ratio)	3 (N=1278)	0.88 (0.54 to 1.43) ³	Moderate
Nocturnal hypoglycemia (relative risk)	5 (N=1943)	0.97 (0.87 to 1.09) _h	Very low
Nocturnal hypoglycemia (rate ratio)	4 (N=916)	0.67(0.37 to 1.23) _h	Low
Overall hypoglycemia (relative risk)	5 (N=1893)	1.02 (0.97 to 1.07) _h ²	Low
Overall hypoglycemia (rate ratio)	2 (N=670)	0.82(0.52 to 1.28) _h	Low
Other surrogates	Mean difference in body weight favoured insulin glargine over NPH [3 RCTs, (N=1138) 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. No data for other complications. All cause mortality not estimable.		
HRQoL and Patient Satisfaction	No difference between treatments for HRQoL. Significantly higher patient satisfaction with insulin glargine as measured by the DTSQ [1 RCT, N=517, WMD = 1.83 (0.82, 2.84), moderate quality].		
Cost-effectiveness	<p><u>Incremental Cost-Utility Analysis - Base case</u> $\Delta C = \\$3,423$; $\Delta QALYs = 0.039$; ICUR = \$87,932 per QALY gained</p> <p><u>Sensitivity Analyses (change in input variable: resultant ICUR)</u></p> <ol style="list-style-type: none"> 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 		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; NPH = neutral protamine Hagedorn; HRQoL = Health-related quality-of-life; DTSQ = Diabetes Treatment Satisfaction Questionnaire; ΔC = difference in costs between strategies; $\Delta QALY$ = difference in QALYs gained between strategies; QALY= quality adjusted life-year; ICUR= incremental cost-utility ratio; SA = sensitivity analysis; h = significant heterogeneity ($I^2 > 50\%$).

1 Three additional abstracts were identified; their inclusion in the meta-analysis did not significantly affect the overall estimate of effect on A1c.

2 One additional abstract was identified; its inclusion in the meta-analysis did not significantly affect the overall estimate of effect on weight gain or hypoglycemia.

3 Two additional abstracts were identified; their 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=2558)	WMD = -0.06 (-0.13 to 0.02)	Moderate
Severe hypoglycemia (relative risk)	7 (N=2442)	RR = 0.74 (0.58 to 0.96)	Moderate
Severe hypoglycemia (rate ratio)	7 (N=2442)	0.95 (0.65 to 1.38) _h	Low
Nocturnal hypoglycemia (relative risk)	6 (N=2311)	0.92 (0.85 to 0.98)	Low
Nocturnal hypoglycemia (rate ratio)	8 (N=2695)	0.66 (0.60 to 0.73) _h	Low
Overall hypoglycemia (relative risk)	6 (N=2110)	1.00 (0.96 to 1.04)	Moderate
Overall hypoglycemia (rate ratio)	6 (N=2109)	0.84 (0.74 to 0.97) _h	Low
Other surrogates	Mean body weight difference favoured detemir group over NPH group [6 RCTs, N=2302, WMD -0.73 (-1.42 to -0.03) _h , low quality]; No data for other surrogates.		
Long-term complications / mortality	No difference between treatments in terms of ischemic heart disease, retinopathy, stroke/transient ischemic attack (TIA). No difference between treatments in terms of all cause mortality.		
Cost-effectiveness	<u>Incremental Cost-Utility Analysis - Base case</u> ΔC=\$4,344; Δ QALYs=0.011; ICUR = \$387,729 per QALY gained <u>Sensitivity Analyses</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; NPH = neutral protamine Hagedorn; ΔC= difference in costs between strategies; ΔQALY= difference in QALYs gained between strategies; QALY= quality adjusted life-year; ICUR= incremental cost-utility ratio; SA = sensitivity analysis; h = significant heterogeneity ($I^2 > 50\%$), NA=not available in Canada as a vial (i.e., 1x10mL, 100units/mL); TIA, Transient Ischemic Attack.

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
CERC Rating of Overall Quality of Clinical Evidence	Low	Low
Strength of recommendation	Weak	
Rationale for weak recommendation <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> ➢ Patient convenience and lifestyle benefits associated with reduced frequency of injections - favours insulin NPH; ➢ Larger body of evidence on long-term safety and outcomes available for insulin NPH – favours insulin NPH; ➢ Reduced incidence of hypoglycemia (especially nocturnal) - favours long-acting insulin analogues. 		
Clinical Note <ul style="list-style-type: none"> Based on clinical opinion and limited evidence, CERC suggests that long-acting insulin analogues can be tried in patients who experience significant hypoglycemia, particularly nocturnal and severe hypoglycemia, while using insulin NPH. <ul style="list-style-type: none"> ➢ 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. 		
Context <ul style="list-style-type: none"> Overall quality of evidence was low. Studies primarily reported results in terms of surrogate outcomes and sparse data were available for long-acting insulin analogues in terms of 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). 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. About 30% of patients have very good control with insulin NPH. Unlike insulin NPH, children treated with long-acting insulin analogues require an injection of bolus insulin at lunchtime. This may be impractical during school hours for young children (<14 years of age), since teachers usually cannot administer, or supervise the administration of insulin. 		

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)	-0.22 (-0.53 to 0.09) ¹	Low
Severe hypoglycemia (relative risk)	1 (N=349)	0.80 (0.56 to 1.15) ¹	Low
Nocturnal hypoglycemia (relative risk)	1 (N=349)	0.71 (0.43 to 1.18)	Low
Overall hypoglycemia (relative risk)	1 (N=349)	1.01 (0.90 to 1.12) ¹	Moderate
Other surrogates	No difference between treatments in terms of BMI. No data for other surrogates.		
Unit Cost of Drugs	<u>Vial, 1x10mL, 100 units/mL</u> Insulin glargine= \$55.07 Insulin NPH(Humulin N)=\$17.20 Insulin NPH(Novolin ge NPH)=18.33 <u>Cartridge, 5x3mL, 100 units/mL</u> 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 NPH are not available for this population.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; NPH = neutral protamine Hagedorn; BMI= body mass index.

1 Three additional abstracts were identified; their inclusion in the meta-analysis did not significantly affect the overall estimate of effect on A1c or hypoglycemia.

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)	0.10 (-0.1 to 0.3)	High
Severe hypoglycemia (relative risk)	1 (N=347)	0.80 (0.5 to 1.28)	High
Severe hypoglycemia (rate ratio)	1 (N=347)	0.94 (0.68 to 1.3)	High
Nocturnal hypoglycemia (relative risk)	1 (N=347)	0.85 (0.77 to 0.94)	High
Nocturnal hypoglycemia (rate ratio)	1 (N=347)	0.77 (0.7 to 0.84)	High
Overall hypoglycemia (relative risk)	1 (N=347)	0.98 (0.94 to 1.01)	High
Overall hypoglycemia (rate ratio)	1 (N=347)	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)). No data for other surrogates.		
Unit Cost of Drugs	<u>Vial, 1x10mL, 100 units/mL</u> Insulin detemir= NA Insulin NPH(Humulin N)=\$17.20 Insulin NPH(Novolin GE NPH)=18.33 <u>Cartridge, 5x3mL, 100 units/mL</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; NPH = neutral protamine Hagedorn; NA=not available in Canada as a vial (i.e., 1x10mL, 100units/mL).

1.1.3. Type 2 diabetes mellitus in adults taking oral anti-diabetic 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	
<p>Underlying values and preferences</p> <ul style="list-style-type: none"> • Primary consideration: The incremental cost of LAIAs over insulin NPH outweighs their modest clinical benefits. • Other values and preferences: <ul style="list-style-type: none"> ➢ Patient convenience and lifestyle benefits associated with reduced frequency of injections - favours insulin NPH; ➢ Larger body of evidence on long-term safety and outcomes available for insulin NPH – favours insulin NPH; ➢ Reduced incidence of hypoglycemia (especially nocturnal) - favours LAIAs. 		
<p>Clinical Note</p> <ul style="list-style-type: none"> • Based on clinical opinion and limited evidence, CERC suggests that LAIAs can be tried in patients who experience significant hypoglycemia, particularly nocturnal and severe hypoglycemia, while using insulin NPH. <ul style="list-style-type: none"> ➢ Some studies demonstrated a reduced risk/incidence of hypoglycemia with LAIAs 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. 		
<p>Context</p> <ul style="list-style-type: none"> • Overall quality of evidence was low to moderate. • Studies primarily reported results in terms of surrogate outcomes and sparse data were available for LAIAs in terms of 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 \$640K per QALY gained, while insulin glargine was dominated by insulin NPH (i.e., it was less effective and more costly). • 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. 		

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=3397)	-0.05 (-0.13 to 0.04)	Moderate
Fasting plasma glucose (mmol/L) (WMD)	6 (N=2406)	-0.10 (-0.28 to 0.07)	Moderate
Severe hypoglycemia (relative risk)	7 (N=2866)	0.66 (0.29 to 1.48) _h	Very low
Severe hypoglycemia (rate ratio)	3 (N=1680)	0.51 (0.51 to 1.79) _h	Very low
Nocturnal hypoglycemia (relative risk)	7 (N=2532)	0.56 (0.47 to 0.68)	Low
Nocturnal hypoglycemia (rate ratio)	4 (N=1705)	0.41 (0.29 to 0.59) _h	Low
Overall hypoglycemia (relative risk)	8 (N=2642)	0.87 (0.81 to 0.93)	Low
Overall hypoglycemia (rate ratio)	4 (N=1705)	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 ($\leq 7\%$).		
Long-term complications / mortality	No difference between treatments in terms of ischemic heart disease. 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, N=481, WMD (95%CI) = 0.60 (0.07 to 1.13), moderate quality.		
Cost-effectiveness	<u>Incremental Cost-Utility Analysis - Base case</u> $\Delta C = \$4,945$; $\Delta QALYs = 0.008$; ICUR = \$642,994 per QALY gained <u>Sensitivity Analyses</u> 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		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; NPH = neutral protamine Hagedorn; OAD = oral antidiabetic agent; HRQoL = Health-related quality-of-life; BMI= body mass index; LDL-C = low-density lipoprotein cholesterol; ΔC = difference in costs between strategies; $\Delta QALY$ = difference in QALYs gained between strategies; QALY= quality adjusted life-year; ICUR= incremental cost-utility ratio; SA = sensitivity analysis; h = significant heterogeneity ($I^2 > 50\%$).

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)	0.14 (-0.03 to 0.28) ¹	Moderate
Fasting plasma glucose (mmol/L) (WMD)	2 (N=784)	-0.14 (-1.02 to 0.74) _h ²	Low
Severe hypoglycemia (relative risk)	2 (N=808)	0.75 (0.03 to 20.01) _h	Very low
Severe hypoglycemia (rate ratio)	1 (N=463)	0.13 (0.02 to 0.91)	Low
Nocturnal hypoglycemia (relative risk)	2 (N=808)	0.53 (0.31 to 0.91) _h	Moderate
Nocturnal hypoglycemia (rate ratio)	2 (N=798)	0.45 (0.38 to 0.54) ²	Moderate
Overall hypoglycemia (relative risk)	2 (N=808)	0.65 (0.39 to 1.07) _h	Low
Overall hypoglycemia (rate ratio)	3 (N=798)	0.54 (0.50 to 0.58) ²	Moderate
Other surrogates	Mean difference in body weight favoured insulin detemir over insulin NPH: 2 RCTs (N=782); WMD (95%CI) = -1.27 (-1.95 to -0.58) _h ² , low quality. No difference between treatments in percentage of patients who reached target A1C (≤7%) (1 RCT, N=463). No data for other surrogate outcomes.		
Long-term complications / mortality	No data for long-term complications; No difference between treatments in terms of all cause mortality (1 RCT, N=333, low quality)		
Cost-effectiveness	<u>Incremental Cost-Utility Analysis - Base case</u> ΔC=\$6,521; Δ QALYs= -0.034; ICUR = Dominated <u>Sensitivity Analyses</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; NPH = neutral protamine Hagedorn; OAD = oral antidiabetic agent; ΔC= difference in costs between strategies; ΔQALY= difference in QALYs gained between strategies; QALY= quality adjusted life-year; ICUR= incremental cost-utility ratio; h = significant heterogeneity ($I^2 > 50\%$).

1 One additional abstract was identified; its inclusion in the meta-analysis resulted in an overall effect on A1c that was statistically significant in favour of insulin NPH.

2 One additional abstract was identified; its inclusion in the meta-analysis did not significantly affect the overall estimate of effect on FPG, 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	
<p>Underlying values and preferences</p> <ul style="list-style-type: none"> • 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 LAIAs over insulin NPH outweighs their modest clinical benefits. • Other values and preferences: <ul style="list-style-type: none"> ➢ Patient convenience and lifestyle benefits associated with reduced frequency of injections - favours insulin NPH; ➢ Larger body of evidence on long-term safety and outcomes available for insulin NPH – favours insulin NPH; ➢ Reduced incidence of hypoglycemia (especially nocturnal) - favours LAIAs. 		
<p>Clinical Note</p> <ul style="list-style-type: none"> • Based on clinical opinion and limited evidence, CERC suggests that LAIAs can be tried in patients who experience significant hypoglycemia, particularly nocturnal and severe hypoglycemia, while using insulin NPH. <ul style="list-style-type: none"> ➢ Some studies demonstrated a reduced risk/incidence of hypoglycemia with LAIAs 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. 		
<p>Context</p> <ul style="list-style-type: none"> • Overall quality of evidence was low to moderate. • Studies primarily reported results in terms of surrogate outcomes. No data were available for LAIAs in terms of clinically important long-term outcomes. • There were no significant benefits of LAIAs in terms of A1c. • Insulin detemir was associated with significantly less weight gain than insulin NPH. • Results from studies in which the combination of a LAIA and RAIA was compared with the combination of insulin NPH and regular HI in adult type 2 diabetes were generally similar to those in which the same bolus insulin was used in both treatment arms. • Approximately 20 percent of adult patients with type 2 diabetes are users of basal-bolus therapy, typically older patients. • 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. 		

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)	0.28 (0.07 to 0.49)	Moderate
Nocturnal hypoglycemia (relative risk)	1 (N=518)	0.78 (0.62 to 0.98)	Moderate
Overall hypoglycemia (relative risk)	1 (N=518)	0.92 (0.81 to 1.05)	Moderate
Other surrogates	No difference in terms of body weight (1 RCT, N=518) and percentage that reached target A1C ($\leq 7\%$) (1 RCT, N=100). No data for other surrogates.		
Unit Cost of Drugs	<u>Vial, 1x10mL, 100 units/mL</u> Insulin glargine= \$55.07 Insulin NPH (Humulin N)=\$17.20 Insulin NPH (Novolin GE NPH)=18.33 <u>Cartridge, 5x3mL, 100 units/mL</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; NPH = neutral protamine Hagedorn.

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)	0.10 (-0.18 to 0.38)	Moderate
Fasting plasma glucose (mmol/L) (WMD)	1 (N=461)	0.10 (-0.61 to 0.81)	Moderate
Nocturnal hypoglycemia (relative risk)	1 (N=505)	0.66 (0.45 to 0.96)	Moderate
Overall hypoglycemia (relative risk)	1 (N=505)	0.91 (0.75 to 1.11)	Moderate
Other surrogates	Mean difference in body weight favoured insulin detemir over insulin NPH: 1 RCT, N=505, WMD -0.80 (-1.46 to -0.14), moderate quality. No data for other surrogates.		
Unit Cost of Drugs	<u>Vial, 1x10mL, 100 units/mL</u> Insulin detemir= NA Insulin NPH(Humulin N)=\$17.20 Insulin NPH(Novolin GE NPH)=18.33 <u>Cartridge, 5x3mL, 100 units/mL</u> 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 detemir versus NPH are not available for this population.		

Abbreviations: 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 and 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 <ul style="list-style-type: none">• 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 <ul style="list-style-type: none">• Overall quality of evidence was moderate.• The single study reporting this comparison primarily reported results in terms of surrogate outcomes. No data were available for clinically important long-term outcomes.• There were no significant differences in A1c.• A reduction in hypoglycemia (severe and nocturnal) was observed in favour of insulin detemir according to some measures but not others. 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.• 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.	

Summary of findings table for insulin detemir versus insulin glargine in adults 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=320)	-0.03 (-0.26 to 0.2)	High
Severe hypoglycemia (relative risk)	1 (N=320)	0.25 (0.07 to 0.86)	Moderate
Severe hypoglycemia (rate ratio)	1 (N=320)	0.41 (0.2 to 0.86)	High
Nocturnal hypoglycemia (relative risk)	1 (N=320)	0.94 (0.75 to 1.17)	High
Nocturnal hypoglycemia (rate ratio)	1 (N=320)	0.66 (0.58 to 0.76)	High
Overall hypoglycemia (relative risk)	1 (N=320)	1.05 (0.93 to 1.19)	High
Overall hypoglycemia (rate ratio)	1 (N=320)	0.96 (0.92 to 1.02)	High
Other surrogates	No difference between treatments in terms of body weight. No data for other surrogates.		
Unit Cost of Drugs	<u>Vial, 1x10mL, 100 units/mL</u> Insulin detemir= NA Insulin glargine= \$55.07 <u>Cartridge, 5x3mL, 100 units/mL</u> Insulin detemir= \$109.86 Insulin glargine= \$109.87		
Average Daily drug cost	Insulin detemir = \$1.41 Insulin glargine= \$1.29		
Cost-effectiveness	Data regarding cost-effectiveness of detemir versus glargine are not available for this population.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; NPH = neutral protamine Hagedorn.

2. Rapid-acting insulin analogues

2.1. Regular human insulin versus rapid-acting insulin analogues

2.1.1. Type 1 diabetes mellitus in preadolescents

CERC suggests that **either** regular human insulin or insulin lispro be used in most **preadolescents with type 1 diabetes** (CSII or MDI).

Vote results (Number of CERC members in favour/number participating in meeting)	CSII 10/11	MDI 9/11
CERC Rating of Overall Quality of Clinical Evidence	Low	Low
Strength of recommendation	Weak	Weak
<p>Rationale for weak recommendations</p> <ul style="list-style-type: none"> CERC graded the recommendation as weak due to the low quality of the clinical evidence and lack of a cost effectiveness analysis. 		
<p>Underlying values and preferences</p> <ul style="list-style-type: none"> Primary consideration: Although cost effectiveness information was not available for this population, CERC assessed that the incremental cost of insulin lispro over regular human insulin was balanced by its benefit in terms of convenience and dietary flexibility. 		
<p>Clinical Notes</p> <ul style="list-style-type: none"> Regular human insulin may be preferred to insulin lispro when <ul style="list-style-type: none"> Affordability is an important consideration; More experience with long-term safety is highly valued. Insulin lispro may be used in preference to regular human insulin when flexibility of insulin administration with respect to meals is of primary importance. Based on clinical opinion and limited evidence, CERC suggests that insulin lispro may be preferred in patients who experience significant hypoglycemia while using regular human insulin, or for whom hypoglycemia is a major concern. <ul style="list-style-type: none"> 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. 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. 		
<p>Context</p> <ul style="list-style-type: none"> Overall quality of evidence was low. Studies primarily reported results in terms of surrogate outcomes. There were no data available for insulin lispro in terms of clinically important long-term outcomes. There were no significant differences between treatments in A1c. Marginal benefits were observed in favour of insulin lispro in terms of overall hypoglycemia in CSII users, but there were no significant differences in any hypoglycemia type in the MDI population. Marginal differences of uncertain clinical significance were reported in favour of insulin lispro in terms of patient satisfaction in both CSII and MDI populations. The option of giving insulin lispro after meals may be an important advantage for children < 5 years of age since administration of regular human insulin 20-30 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 and CSII should be used. No studies were identified that compared insulin aspart with regular human insulin in preadolescents. 		

Summary of findings table for insulin lispro versus regular human insulin in preadolescents 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)	0.06 (-0.47 to 0.59) ¹	Very low
Severe hypoglycemia (relative risk)	1 (N= 54)	1.00 (0.15 to 6.59)	Very low
Overall hypoglycemia (rate ratio)	1 (N= 54)	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; N=54).		
Unit Cost of Drugs	<u>Vial, 1x10mL, 100units/mL</u> Insulin lispro= \$25.79 Short-acting HI (Humulin R)=\$17.20 Short-acting HI (Novolin GE Toronto)=18.33 <u>Cartridge, 5x3mL, 100 units/mL</u> Insulin lispro= \$51.59 Short-acting HI (Humulin R)= \$35.68 Short-acting HI (Novolin GE Toronto)=\$35.97 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; HRQoL = Health-related quality-of-life.

1 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 preadolescents 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)	0.14 (-0.18 to 0.46)	Moderate
Severe hypoglycemia (relative risk)	3 (N=222)	0.69 (0.24 to 2.01)	Low
Nocturnal hypoglycemia (rate ratio)	3 (N= 234)	0.96 (0.74 to 1.26)	Low
Overall hypoglycemia (rate ratio)	5 (N= 338)	0.99 (0.88 to 1.12) _h	Low
HRQoL and Patient Satisfaction	Three studies 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	<u>Vial, 1x10mL, 100 units/mL</u> Insulin lispro= \$25.79 Short-acting HI (Humulin R)=\$17.20 Short-acting HI (Novolin GE Toronto)=18.33 <u>Cartridge, 5x3mL, 100 units/mL</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; HRQoL = Health-related quality-of-life; h = significant heterogeneity ($I^2 > 50\%$).

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
CERC Rating of Overall Quality of Clinical Evidence	Low	Low
Strength of Recommendation	Strong	
<p>Underlying values and preferences</p> <ul style="list-style-type: none"> Primary consideration: Although cost effectiveness information was not available for this population, CERC assessed that the incremental cost of the RAIAs over regular human insulin was balanced by their benefits (i.e., reduced likelihood of nocturnal hypoglycemia and convenience and dietary flexibility.) 		
<p>Clinical Notes</p> <ul style="list-style-type: none"> Regular human insulin may be preferred to a rapid-acting insulin analogue when <ul style="list-style-type: none"> Affordability is an important consideration; More experience with long-term safety is highly valued. A RAIA may be used in preference to regular human insulin when flexibility of insulin administration with respect to meals is of primary importance. Based on clinical opinion and limited evidence, CERC suggests that a RAIA may be preferred in patients who experience significant hypoglycemia while using regular human insulin, or for whom hypoglycemia is a major concern. <ul style="list-style-type: none"> Some comparative studies demonstrated a reduced risk/incidence of hypoglycemia with RAIAs 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 glycemetic control. 		
<p>Context</p> <ul style="list-style-type: none"> Overall quality of evidence was low. Studies primarily reported results in terms of surrogate outcomes. There were no data available for RAIAs in terms of clinically important long-term outcomes. Results from an abstract were identified for the outcome of severe hypoglycemia for 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 at best. Benefits of RAIAs in terms of patient satisfaction were observed inconsistently and were 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 and CSII should be used. 		

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)	-0.18 (-0.32 to -0.05)	Moderate
2 hour post-prandial glucose (mmol/L) (WMD)	1 (N=116)	-2.89 (-4.48 to -1.3)	Very low
Severe hypoglycemia (relative risk)	2 (N=140)	1.50 (0.26 to 8.65) ¹	Low
Nocturnal hypoglycemia (rate ratio)	1 (N=67)	0.67 (0.51 to 0.88)	Low
Overall hypoglycemia (rate ratio)	4 (N= 281)	1.86 (0.54 to 6.46) _h	Low
Other surrogates	No difference between lispro and HI in body weight gain. No data for other surrogates.		
HRQoL and Patient Satisfaction	Two studies reported no significant difference in terms of satisfaction between lispro and regular human insulin, while two reported statistically significant improvement in satisfaction with insulin lispro.		
Unit Cost of Drugs	<u>Vial, 1x10mL, 100 units/mL</u> Insulin lispro= \$25.79 Short-acting HI (Humulin R)=\$17.20 Short-acting HI (Novolin GE Toronto)=18.33 <u>Cartridge, 5x3mL, 100 units/mL</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; HRQoL = Health-related quality-of-life; h = significant heterogeneity ($I^2 > 50\%$).

¹ One additional abstract 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)	-0.31 (-0.54 to -0.081)	Low
Severe hypoglycemia (relative risk)	1 (N = 118)	0.33 (0.01 to 8.02)	Low
Nocturnal hypoglycemia (rate ratio)	1 (N=118)	0.55 (0.43 to 0.70)	Low
Overall hypoglycemia (rate ratio)	2 (N=175)	0.58 (0.40, 0.85)	Low
Unit Cost of Drugs	<u>Vial, 1x10mL, 100 units/mL</u> Insulin aspart= \$25.34 Short-acting HI (Humulin R)=\$17.20 Short-acting HI (Novolin GE Toronto)=18.33 <u>Cartridge, 5x3mL, 100 units/mL</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; 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	
<p>Underlying values and preferences</p> <ul style="list-style-type: none"> Primary consideration: Results from the cost-effectiveness analyses demonstrated that the rapid-acting insulin analogues and regular human insulin are equivalent. 		
<p>Clinical Notes</p> <ul style="list-style-type: none"> Regular human insulin may be preferred to a rapid-acting insulin analogue when <ul style="list-style-type: none"> Affordability is an important consideration; More experience with long-term safety is highly valued. A RAIA may be used in preference to regular human insulin when flexibility of insulin administration with respect to meals is of primary importance. Based on clinical opinion and limited evidence, CERC suggests that a RAIA may be preferred in patients who experience significant hypoglycemia while using regular human insulin, or for whom hypoglycemia is a major concern. <ul style="list-style-type: none"> Some comparative studies demonstrated a reduced risk/incidence of hypoglycemia with RAIAs 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 glycaemic control. 		
<p>Context</p> <ul style="list-style-type: none"> Overall quality of evidence was moderate. Studies primarily reported results in terms of surrogate outcomes. There were insufficient data available for RAIAs in terms of 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 and insulin lispro. It reported statistically significant improvement with insulin lispro in terms of 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 at best. Benefits of RAIAs in terms of patient satisfaction were observed inconsistently and were of uncertain clinical significance. Similarly, the quality-of-life data, where available, were inconclusive. Differences across studies in terms of the choice of basal insulin and frequency of dosing may have increased heterogeneity in the measurement of hypoglycemia (especially nocturnal). 		

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=5426)	-0.06 (-0.14 to 0.02)	Moderate
2-hour post-prandial plasma glucose (mmol/L) (WMD)	2 (N=2036)	-0.99 (-1.54, -0.45)	Low
Severe hypoglycemia (relative risk)	6 (N=4221)	0.78 (0.65 to 0.94)	Moderate
Nocturnal hypoglycemia (rate ratio)	3 (N=658)	0.58 (0.35, 0.98) _h	Low
Overall hypoglycemia (rate ratio)	12 (N=5193)	0.96 (0.86 to 1.06) _h	Low
Other surrogates	No significant difference between treatments in body weight gain (7 RCTs). No data for other surrogates.		
HRQoL and Patient Satisfaction	Three studies showed a statistically significant increase in satisfaction with lispro compared to HI. Two RCTs reported no statistically significant difference between lispro and HI using Well being Questionnaire (WBQ). One study also reported no statistically significant difference between the two treatments in WBQ anxiety and energy domains. ¹		
Cost effectiveness	<p><u>Incremental Cost-Utility Analysis - Base case</u> $\Delta C = \\$182$; $\Delta QALYs = 0.006$; ICUR = \$28,996 per QALY gained</p> <p><u>Sensitivity Analyses</u></p> <ol style="list-style-type: none"> 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. 		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; HRQoL = Health-related quality-of-life; ΔC = difference in costs between strategies; $\Delta QALY$ = difference in QALYs gained between strategies; QALY= quality adjusted life-year; ICUR= incremental cost-utility ratio; h = significant heterogeneity ($I^2 > 50\%$).

¹ One additional abstract reported statistically significant overall improvement in WBQ with ILis, 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=2888)	-0.12 (-0.19 to -0.06)	Moderate
Severe hypoglycemia (relative risk)	3 (N= 1696)	0.83 (0.66 to 1.03)	Moderate
Overall hypoglycemia (rate ratio)	6 (N=3096)	0.97 (0.88 to 1.08) _h	Very low
Other surrogates	No significant difference between treatments in BMI (1 RCT). No data for other surrogates.		
HRQoL and Patient Satisfaction	One RCT found significant superiority of aspart over HI on overall treatment satisfaction. ¹ Another RCT showed no differences overall, although aspart provided more flexibility than HI.		
Cost effectiveness	<u>Incremental Cost-Utility Analysis - Base case</u> Insulin aspart is cost saving relative to regular human insulin ($\Delta C = -\$620$; $\Delta QALYs = 0.055$, ICUR = Cost Saving) <u>Sensitivity Analyses</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; RR = relative risk; HRQoL = Health-related quality-of-life; BMI= body mass index; ΔC = difference in costs between strategies; $\Delta QALY$ = difference in QALYs gained between strategies; QALY= quality adjusted life-year; ICUR= incremental cost-utility ratio; h = significant heterogeneity ($I^2 > 50\%$).

¹ One additional abstract was identified which reported greater satisfaction with IAsp compared to HI.

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	
<p>Rationale for weak recommendations</p> <ul style="list-style-type: none"> 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 RAIAs versus the more robust experience with regular human insulin in terms of fetal safety. 		
<p>Underlying values and preferences</p> <ul style="list-style-type: none"> Primary consideration: Although cost effectiveness information was not available for this population, CERC assessed that the incremental cost of the RAIAs over regular human insulin was balanced by their benefits in terms of convenience and dietary flexibility. 		
<p>Clinical Notes</p> <ul style="list-style-type: none"> Although there is more clinical experience regarding the safety of regular human insulin in pregnancy as compared to the RAIAs, the available data on the RAIAs from observational studies was considered reassuring. CERC does not advocate switching insulin products in a patient with type 1 diabetes who becomes pregnant. Regular human insulin may be preferred to a rapid-acting insulin analogue when <ul style="list-style-type: none"> Affordability is an important consideration; More experience with safety during pregnancy is highly valued. A RAIA may be used in preference to regular human insulin when flexibility of insulin administration with respect to meals is of primary importance. Based on clinical opinion and limited evidence from other populations, CERC suggests that a RAIA may be preferred in pregnant patients who experience significant hypoglycemia while using regular human insulin, or for whom hypoglycemia is a major concern. <ul style="list-style-type: none"> None of the studies in pregnant women demonstrated a statistically significant benefit in terms of hypoglycemia for the RAIAs 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 glycemetic control. 		
<p>Context</p> <ul style="list-style-type: none"> 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, C-sections rates, or increased length of hospital stay. No significant differences in A1c. Insulin aspart was favoured in terms of patient satisfaction; this difference was largely due to increased flexibility in timing of doses. The clinical significance of the observed effect is uncertain. Observational studies on RAIAs in pregnancy do not demonstrate fetal or maternal risk. 		

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)	0.20 (-1.03 to 1.43)	Very low
Severe hypoglycemia (relative risk)	1 (N=33)	0.21(0.01 to 4.10)	Very low
Unit Cost of Drugs	<u>Vial, 1x10mL, 100 units/mL</u> Insulin lispro= \$25.79 Short-acting HI (Humulin R)=\$17.20 Short-acting HI (Novolin GE Toronto)=18.33 <u>Cartridge, 5x3mL, 100 units/mL</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; 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)	-0.08 (-0.28 to 0.12)	Low
Severe hypoglycemia (relative risk)	1 (N=322)	0.72 (0.36 to 1.46)	Low
Nocturnal hypoglycemia (relative risk)	1 (N=322)	0.76 (0.57 to 1.03)	Low
Overall hypoglycemia (relative risk)	1 (N=322)	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	<u>Vial, 1x10mL, 100 units/mL</u> Insulin aspart= \$25.34 Short-acting HI (Humulin R)=\$17.20 Short-acting HI (Novolin GE Toronto)=18.33 <u>Cartridge, 5x3mL, 100 units/mL</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; HRQoL = Health-related quality-of-life.

2.1.5. Gestational diabetes mellitus

CERC suggests that **either** regular human insulin or insulin lispro be used in most **women** who develop gestational diabetes.

Vote results (Number of CERC members in favour/number participating in meeting)	7/11
CERC Rating of Overall Quality of Clinical Evidence	Low
Strength of Recommendation	Weak
<p>Rationale for weak recommendations</p> <ul style="list-style-type: none"> 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 insulin lispro versus the more robust experience with regular human insulin in terms of fetal safety. 	
<p>Underlying values and preferences</p> <ul style="list-style-type: none"> Primary consideration: Although cost effectiveness information was not available for this population, CERC assessed that the incremental cost of insulin lispro over regular human insulin was balanced by its benefits in terms of convenience and dietary flexibility. 	
<p>Clinical Notes</p> <ul style="list-style-type: none"> Although there is more clinical experience regarding the safety of regular human insulin in pregnancy as compared to the RAIAs, the available data on the RAIAs from observational studies was considered reassuring. Regular human insulin may be preferred to insulin lispro when: <ul style="list-style-type: none"> Affordability is an important consideration; More experience with safety during pregnancy is highly valued. Insulin lispro may be used in preference to regular human insulin when flexibility of insulin administration with respect to meals is of primary importance. Based on clinical opinion and limited evidence from other populations, CERC suggests that insulin lispro may be preferred in women with gestational diabetes who experience significant hypoglycemia while using regular human insulin, or for whom hypoglycemia is a major concern. <ul style="list-style-type: none"> Neither of the studies in gestational diabetes demonstrated a statistically significant benefit in terms of hypoglycemia for insulin lispro 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. 	
<p>Context</p> <ul style="list-style-type: none"> 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, C-sections rates, or increased length of hospital stay. No significant differences in A1c. Observational studies on RAIAs 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. No studies were identified that compared insulin aspart with regular human insulin in gestational diabetes. 	

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)	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)	-1.32 (-3.07 to 0.43)	Very low
Other surrogates	No difference between treatments in mean body weight gain (1 RCT). No data for other surrogates.		
Unit Cost of Drugs	<u>Vial, 1x10mL, 100 units/mL</u> Insulin lispro= \$25.79 Short-acting HI (Humulin R)=\$17.20 Short-acting HI (Novolin GE Toronto)=18.33 <u>Cartridge, 5x3mL, 100 units/mL</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference.

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
<p>Rationale for weak recommendations</p> <ul style="list-style-type: none"> 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. 	
<p>Underlying values and preferences</p> <ul style="list-style-type: none"> 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 was felt to provide a better fit to the unpredictable patterns of dietary intake and physical activity that are characteristic of this population. Some Committee members favoured regular human insulin due to the availability of more robust evidence regarding long-term safety and efficacy. 	
<p>Context</p> <ul style="list-style-type: none"> Overall quality of evidence was low. Studies primarily reported results in terms of surrogate outcomes. There were no data available for insulin lispro in terms of 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. No studies were identified that compared insulin aspart with regular human insulin in adolescents using MDI. 	

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)	-0.01 (-0.21 to 0.19)	Low
Severe hypoglycemia (relative risk)	1 (N=926)	1.0 (0.29 to 3.43)	Low
Nocturnal hypoglycemia (rate ratio)	1 (N=926)	0.61 (0.57 to 0.64)	Low
Overall hypoglycemia (rate ratio)	1 (N=926)	0.9 (0.88 to 0.93)	Low
Unit Cost of Drugs	<u>Vial, 1x10mL, 100 units/mL</u> Insulin lispro= \$25.79 Short-acting HI (Humulin R)=\$17.20 Short-acting HI (Novolin GE Toronto)=18.33 <u>Cartridge, 5x3mL, 100 units/mL</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference.

2.1.7. Type 2 diabetes mellitus in adults

<p>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.</p>		
<p>Vote results (Number of CERC members in favour/number participating in meeting)</p>	Aspart	Lispro
	8/11	8/11
CERC Rating of Overall Quality of Clinical Evidence	Low	Low
Strength of Recommendation	Weak	Weak
<p>Rationale for weak recommendations</p> <ul style="list-style-type: none"> CERC graded the recommendation as weak due to the low quality of the clinical evidence, and uncertainty in underlying values and preferences. 		
<p>Underlying values and preferences</p> <ul style="list-style-type: none"> Primary consideration: The incremental cost of the rapid-acting insulin analogues over regular human insulin was not felt to be worthwhile in light of the cost effectiveness information. Other values and preferences: <ul style="list-style-type: none"> ➤ Reduction in hypoglycemia (especially nocturnal) - favours insulin lispro. ➤ Flexibility of insulin administration with respect to meals – favours RAIAs. ➤ Long-term experience with respect to safety – favours regular human insulin. 		
<p>Context</p> <ul style="list-style-type: none"> Overall quality of evidence was low. Studies primarily reported results in terms of surrogate outcomes. There were sparse data available for RAIAs in terms of clinically important long-term outcomes. Results from an abstract were identified for the outcome of A1c and overall hypoglycemia for 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. No 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 in terms of the basal insulin used, and the frequency of dosing. Some studies used biphasic insulin aspart. Hypoglycemia benefits in favour of RAIAs 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. 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. 		

Summary of findings table for insulin lispro versus regular human insulin in adults with type 2 diabetes (not using oral antidiabetic agents)

Outcome	# RCTs and (Total sample size)	Effect Estimate (95% CI)	Quality of Evidence
A1c (%) (WMD)	11 (N = 3093)	-0.03 (-0.12 to 0.06)	Low
2-hour post-prandial plasma glucose (mmol/L) (WMD)	1 (N = 74)	-1.10 (-2.21 to 0.01)	Low
Severe hypoglycemia (relative risk)	2 (N=1622)	0.43 (0.08 to 2.37)	Low
Severe hypoglycemia (rate ratio)	1 (N=1444)	0.20 (0.02 to 1.71)	Low
Nocturnal hypoglycemia (relative risk)	1 (N = 178)	1.63 (0.71 to 3.73)	Low
Nocturnal hypoglycemia (rate ratio)	3 (N = 1718)	0.58 (0.48 to 0.70)	Moderate
Overall hypoglycemia (relative risk)	3 (N = 384)	1.18 (0.91 to 1.54)	Moderate
Overall hypoglycemia (rate ratio)	8 (N = 2746)	0.97 (0.91 to 1.03) _h	Low
Other surrogates	No difference in weight (3 RCTs, N = 1682), BMI (1 RCT, N = 40), LDL-cholesterol (2 RCTs, N = 1484), or total cholesterol: HDL ratio (2 RCTs, N = 1484). No data for other surrogates.		
Long-term complications / mortality	No difference in all cause mortality (1 RCT, N = 80). No data for complications.		
HRQoL and Patient Satisfaction	No difference in patient satisfaction or HRQoL (energy, anxiety and flexibility) (1 RCT, N = 885).		
Cost effectiveness	<p><u>Incremental Cost-Utility Analysis - Base case</u> $\Delta C = \\$784$; $\Delta QALYs = 0.006$; ICUR = \$130,865 per QALY gained</p> <p><u>Sensitivity Analyses</u></p> <ol style="list-style-type: none"> 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. 		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; HRQoL = Health-related quality-of-life; BMI= body mass index; LDL-C = low-density lipoprotein cholesterol; HDL = high-density-lipoprotein; ΔC = difference in costs between strategies; $\Delta QALY$ = difference in QALYs gained between strategies; QALY= quality adjusted life-year; ICUR= incremental cost-utility ratio; SA = sensitivity analysis; h = significant heterogeneity ($I^2 > 50\%$).

Summary of findings table for insulin aspart versus regular human insulin in adults with type 2 diabetes (not using oral antidiabetic agents)

Outcome	# RCTs (Total sample size)	Effect Estimate (95% CI)	Quality of Evidence
A1c (%) (WMD)	4 (N = 421)	-0.18 (-0.24 to -0.12) ¹	Low
Fasting plasma glucose (mmol/L) (WMD)	1 (N = 93)	-0.67 (-2.47 to 1.13)	Low
Severe hypoglycemia (relative risk)	1 (N = 121)	0.39 (0.11 to 1.36)	Low
Nocturnal hypoglycemia (relative risk)	1 (N = 93)	0.65 (0.28 to 1.53)	Low
Overall hypoglycemia (relative risk)	3 (N = 369)	1.04 (0.85 to 1.28) ²	Moderate
Overall hypoglycemia (rate ratio)	2 (N = 276)	0.72 (0.64 to 0.80)	Moderate
Other surrogates	No difference in weight gain (2 RCTs, 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). No data for other complications.		
Cost effectiveness	<p><u>Incremental Cost-Utility Analysis - Base case</u> $\Delta C = \\$333$; $\Delta QALYs = 0.015$; $ICUR = \\$22,488$ per QALY gained</p> <p><u>Sensitivity Analyses</u></p> <ol style="list-style-type: none"> 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 IAsp 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. 		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference; HDL = high-density lipoprotein; ΔC = difference in costs between strategies; $\Delta QALY$ = difference in QALYs gained between strategies; QALY= quality adjusted life-year; ICUR= incremental cost-utility ratio.

1 Two additional abstracts were identified; their inclusion in the meta-analysis resulted in a statistically non-significant difference in A1c.

2 One additional abstract 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 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 <ul style="list-style-type: none">• Primary consideration: The desirability of allowing patients and clinicians to choose between agents similar in cost and effectiveness.	
Context <ul style="list-style-type: none">• 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 in A1c.• Overall hypoglycemia was slightly reduced in the insulin aspart arm in type 1 diabetics. 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.	

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)	0.25 (-0.20 to 0.71)	Low
Nocturnal hypoglycemia (rate ratio)	1 (N=87)	1.20 (0.89 to 1.68)	Low
Overall hypoglycemia (rate ratio)	1 (N=87)	1.49 (1.37 to 1.63)	Low
Unit Cost of Drugs	<u>Vial, 1x10mL, 100units/mL</u> Insulin lispro= \$25.79 Insulin aspart= \$25.34 <u>Cartridge, 5x3mL, 100 units/mL</u> 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.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference.

2.2.2. 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.

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
<p>Underlying values and preferences</p> <ul style="list-style-type: none"> • Primary consideration: The desirability of allowing patients and clinicians to choose between agents similar in cost and effectiveness. • Some members expressed a preference for biphasic insulin lispro over biphasic aspart due to the statistically significant difference between agents in terms of A1c, although other members felt that the difference was unlikely to be of clinical significance. 	
<p>Context</p> <ul style="list-style-type: none"> • 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. • A significant difference in A1c was observed in favour of biphasic insulin lispro in type 2 diabetics, however, this may have been due to a carryover effect in the crossover RCT. • There was no significant difference between treatments in terms of hypoglycemia. 	

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)	0.14 (0.008 to 0.275) ¹	Low
Overall hypoglycemia (rate ratio)	1 (N = 133)	0.90 (0.77 to 1.07)	Low
Unit Cost of Drugs	<u>Vial, 1x10mL, 100units/mL</u> Insulin lispro= \$25.79 Insulin aspart= \$25.34 <u>Cartridge, 5x3mL, 100 units/mL</u> Insulin lispro= \$51.59 Insulin aspart= \$50.71		
Average daily Cost of Drugs ³	Biphasic insulin lispro = \$3.77; Biphasic insulin aspart = \$3.56		
Cost effectiveness	Data regarding cost effectiveness of insulin lispro versus insulin aspart are not available for this population.		

Abbreviations: A1c= hemoglobin A1c; RCT= randomized controlled trial; CI= confidence interval; WMD = weighted mean difference.

1. 90% Confidence Interval (as opposed to 95%).

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** for the optimal prescribing and use of insulin analogues. The CERC's draft optimal therapy recommendations for insulin analogues are presented in **Section 5.1** (summary form) and Appendix B, Sections 1 and 2 (detailed form).

Long-acting Insulin Analogues

Either insulin NPH **or** insulin glargine can be used in:

- a. preadolescents, adolescents or adults with type 1 diabetes;
- b. adults with type 2 diabetes who are using a premeal bolus insulin or using oral antidiabetic agents.

Either insulin NPH **or** insulin detemir can be used in

- a. preadolescents or adolescents with type 1 diabetes;
- b. adults with type 2 diabetes who are using a premeal bolus insulin.

Insulin detemir can be used over insulin NPH in

- a. adults with type 1 diabetes;
- b. adults with type 2 diabetes who are concurrently using oral antidiabetic agents.

There were no significant differences found in the direct comparison of insulin detemir and insulin glargine in adults with type 1 diabetes.

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:

- a. preadolescents with type 1 diabetes using CSII or MDI (lispro);
- b. women who develop gestational diabetes (lispro) and pregnant women (lispro, aspart) with type 1 diabetes;
- c. adults with type 1 diabetes using CSII (lispro, aspart) or MDI (lispro, aspart);
- d. adults with type 2 diabetes who require bolus insulin therapy (lispro, aspart).

There were no significant differences found in the following direct comparisons:

- a. insulin aspart and insulin lispro in adults with type 1 diabetes using CSII;
- b. biphasic insulin lispro and biphasic insulin aspart in adults with type 2 diabetes.

APPENDIX C: Detailed CERC Process

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

Feedback on GRADE evidence profiles

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.

CERC discussion of clinical effectiveness evidence and feedback

CERC members discussed the evidence presented in the GRADE evidence profiles and the associated feedback. Context and clinical issues raised during the discussion were recorded for each evidence profile. GRADE Summary of Findings tables, which were 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.

Consideration of 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.⁴ Points of discussion relating to the clinical finding statement were documented as context. A summary of the clinical findings is provided in Appendix B.

Generating draft recommendations based on clinical findings and cost/cost-effectiveness information

CERC reviewed and discussed the results from the pharmacoeconomic analyses commissioned by COMPUS. Where one treatment strategy appears 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. The draft recommendation could be modified by CERC during their deliberations. GRADE Summary of Findings tables for all comparisons containing both the clinical and cost/cost effectiveness data are provided in Appendix B.

4

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.

Underlying values and preferences

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.

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.¹ 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.¹

A ‘strong’ recommendation:

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

A ‘weak’ recommendation:

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

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

1. Is the available evidence of lower quality?
2. Is there uncertainty regarding the balance of benefits versus harms and burdens?
3. Is there uncertainty or are there differences in values and preferences?
4. Is there uncertainty about whether 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.

Identifying 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.