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OPTIMAL THERAPY REPORT

COMPUS

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Second-Line Therapy for Patients with Diabetes Inadequately Controlled on Metformin — PROJECT PROTOCOL

Supporting Informed Decisions

À l'appui des décisions éclairées

This report has been prepared by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS), a service of the Canadian Agency for Drugs and Technologies in Health (CADTH). It contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation. The conclusions [statements] were provided by experts. The authors have also considered input from other stakeholders.

The information in this report is intended to help health care decision makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

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ABBREVIATIONS

A1C	glycosylated hemoglobin
AMSTAR	a meaSurement tool to assess reviews
CAC	COMPUS Advisory Committee
CDA	Canadian Diabetes Association
CERC	COMPUS Expert Review Committee
DPP-4	dipeptidyl peptidase-4
EQ-5D	EuroQol 5-dimension index
FPG	fasting plasma glucose
GRADE	Grades of Recommendations Assessment, Development and Evaluation
NPH	neutral protamine Hagedorn
ODB	Ontario Drug Benefit
PDP	private drug plan
RCT	randomized controlled trial
SD	standard deviation
SE	standard error
SIGN	Scottish Intercollegiate Guidelines Network
TZD	thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study

GLOSSARY

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

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

AMSTAR: An instrument developed specifically to quantify the methodological quality of systematic reviews. AMSTAR scores range from 0 to 11 points. A score of 6 or more indicates good quality.

Bayesian statistics: A statistical analysis conducted according to Bayesian principles. It involves incorporation of existing information regarding the likelihood of an event (i.e., "priors") to estimate the likelihood based on additional information (i.e., "posteriors").

Carry-over effect: The residual effect that occurs when the treatment given in the first period of a crossover clinical trial confounds the interpretation of results in the second period.

Case series: A descriptive observational study that reports the characteristics of a group or cluster of individuals with the same disease or symptoms. The aim is to quantify various aspects of the group and present a relatively complete profile of the disease or symptoms.

Case-control study: A retrospective observational study in which participants are selected according to outcome status before exposure status is determined.

Closed network: A type of network in which all elements are connected to one another.

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

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

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

Credible interval: In Bayesian statistics, an interval in which the actual value of a parameter of interest lies with a defined probability.

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

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

Diabetic ketoacidosis: An acute complication of diabetes caused by increased fatty acid metabolism and the accumulation of keto acids. It was formerly considered a hallmark of type 1 diabetes mellitus, but it also occurs in individuals who lack the immunologic features of type 1 diabetes mellitus and who can subsequently be treated with oral antidiabetes drugs (in type 2 diabetes mellitus).

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

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

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

Frequentist statistics: A statistical approach that involves estimation of one or more parameters of a sample distribution based on assumptions concerning the shape of that distribution.

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

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 regarding either specific health conditions or life as a whole from the perspective of the individual.

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.

Hyperosmolar, hyperglycemic, non-ketotic coma: A syndrome consisting of extreme hyperglycemia, serum hyperosmolarity, and dehydration in the absence of ketoacidosis.

Hypoglycemia: A qualitative term used to describe blood glucose that is below the normal range and defined by 1) the development of autonomic or neuroglycopenic symptoms, 2) a low plasma glucose level (< 4.0 mmol/L for patients treated with insulin or an insulin secretagogue), and 3) symptoms responding to the administration of carbohydrate (Canadian Diabetes Association 2008).

Ischemic heart disease: Heart disease, due to inadequate blood perfusion of the myocardium, which causes 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 of human insulin. They do not mimic basal endogenous insulin secretion; rather, they promote a prolonged, non-fluctuating basal level of insulin activity.

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

Mixed treatment comparisons: An extension of standard pairwise meta-analysis for A versus B trials, to data structures that include, for example, A versus B, B versus C, and A versus C trials. There are two roles for mixed treatment comparisons: one is to strengthen inference concerning the relative efficacy of two treatments by including both "direct" and "indirect" comparisons. The other is to facilitate simultaneous inference regarding all treatments in order to select the best treatment.

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

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

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

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

Publication bias: Unrepresentative publication of research reports that is not due to the scientific quality of the research but to other characteristics; for example, tendencies of investigators to submit, and publishers to accept, positive research reports (i.e., ones with results showing a beneficial treatment effect of a new intervention) over negative research reports.

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

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

Rapid-acting insulin analogues: An class of insulin analogue, produced by introducing alterations in the amino acid sequence of human insulin, which more closely mimics the short duration of action of meal-induced endogenous insulin in non-diabetic patients than does regular human insulin.

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

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

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

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

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

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

Transient ischemic attack: Episodes of stroke symptoms that last only briefly. The current definition of duration is fewer than 24 hours, but the average duration is about 12 minutes.

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

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

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

WinBUGS: A statistical software used for Bayesian modelling.

1 INTRODUCTION

In March 2004, the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) — now the Canadian Agency for Drugs and Technologies in Health (CADTH) — launched the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) 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 CADTH's COMPUS program 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
- supporting the implementation of these interventions.

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

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

1.1 COMPUS Expert Review Committee

CERC consists of eight Core Members appointed to serve for all topics under consideration during their term of office and three or more Specialist Experts appointed to provide their expertise in recommending optimal therapy for one or more specific topics. For the project on second-line therapy for patients with type 2 diabetes mellitus not adequately controlled on metformin monotherapy, the four individuals appointed as Specialist Experts are endocrinologists or diabetes specialists. Two of the Core Members are Public Members who bring a lay perspective. The remaining six Core Members hold qualifications as physicians, pharmacists, or health economists or have other relevant qualifications with expertise in one or more areas such as, but not limited to, family practice, institutional or community clinical pharmacy, pharmacoeconomics, clinical epidemiology, drug utilization expertise, methodology, effecting 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 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

CAC has identified management of diabetes mellitus as being a priority area for optimal practice initiatives based on the following criteria:

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

Within diabetes mellitus management, second-line therapy for patients with type 2 diabetes mellitus not adequately controlled on metformin monotherapy was identified by CAC as a priority topic.

Treatment of patients with type 2 diabetes mellitus usually begins with lifestyle modification and treatment with oral antidiabetes drugs. Metformin is recommended as the first-line oral antidiabetes drug in most patients with type 2 diabetes mellitus when glycemic control cannot be achieved by lifestyle interventions alone.[1-5] Recent utilization data indicate that approximately 90% of patients with type 2 diabetes mellitus initiating pharmacotherapy in Canada are started on metformin.[6] As type 2 diabetes mellitus is a progressive disease, glycemic levels are likely to worsen over time. Most patients eventually require two or more oral antidiabetes drugs, or the addition of an insulin regimen, to achieve or maintain target blood glucose levels.[7,8] Existing guidelines[1-3,9-11] recommend several options for second-line therapy when metformin alone is no longer effective. However, guidelines generally lack specific recommendations regarding which agent(s) are optimal as second-line therapy for patients with type 2 diabetes mellitus not adequately controlled on metformin monotherapy. Rather, a general recommendation that a stepwise approach be used to add agents from various classes is often provided. Guideline recommendations in this area are based primarily on evidence regarding clinical efficacy and safety; cost-effectiveness is often not considered.

Canadians spent approximately $17.10 per capita on oral antidiabetes drugs in 2007, for a total of $563 million.[12] The average cost per oral antidiabetes drug prescription in publicly funded drugs plans in Canada nearly doubled over the course of a decade, from $11.31 in 1998 to $20.77 in 2007.[6] The increase in costs may have at least partly been due to the introduction of more costly antidiabetes drugs to the market. For example, the thiazolidinediones (TZDs) (i.e., rosiglitazone and pioglitazone) represented only 9.4% of all prescriptions for antidiabetes drugs in 2008, yet they accounted for 33% of total expenditures.[13] Given the large, growing population of patients with type 2 diabetes mellitus in Canada, suboptimal use of second-line antidiabetes drugs is likely to have a detrimental effect on both health outcomes and cost-effective use of drugs. Therefore, there is a need for clear recommendations based on clinical- and cost-effectiveness evidence to guide second-line therapy for patients with type 2 diabetes not adequately controlled on metformin monotherapy.

2.1 Diabetes Mellitus

Diabetes mellitus is a chronic disease characterized by the body's inability to produce sufficient insulin and/or properly use insulin.[14] Type 1 diabetes mellitus occurs in approximately 10% of patients with diabetes, and it results when little or no insulin is produced by the body.[15] Type 2 diabetes mellitus is a metabolic disorder caused by varying degrees of insulin resistance; the body usually produces insulin but is unable to use it properly.[15] When inadequately managed, diabetes is likely to result in poor glycemic

control.[14] Impaired glycemic control, if prolonged, may result in diabetes-related complications (e.g., ischemic heart disease, stroke, blindness, end-stage renal disease, lower limb amputation).[16,17]

The global prevalence of diabetes is estimated to be 177 million and is projected to increase to 300 million by 2025. In 2004/2005, approximately 1.8 million (5.5%) Canadians aged 20 years and older had diagnosed diabetes.[18] However, it is estimated that 2.7% of the general adult population has undiagnosed type 2 diabetes mellitus,[1] and the true prevalence of diabetes may approach 1.9 million.[19]

2.1.1 Management of blood glucose levels in type 2 diabetes mellitus

One goal of diabetes management is to maintain control of blood glucose levels to reduce the patient's risk of developing long-term diabetes-related complications. Lifestyle modifications (i.e., weight control, proper nutrition, and adequate exercise) and use of antidiabetes drugs such as oral agents or insulin are recommended approaches for improving glycemic control.[1]

2.1.2 Technology description — Second-line antidiabetes drugs

Seven classes of antidiabetes drugs that may be used as second-line therapy for patients with type 2 diabetes inadequately controlled on metformin monotherapy are available in Canada: sulfonylureas, meglitinides, α-glucosidase inhibitors, TZDs, incretin agents, weight-loss agents, and insulins (human and insulin analogues). Agents belonging to an eighth class, amylin analogues, are currently not available in Canada. These second-line antidiabetes drugs are presented in Table 1.

3 OBJECTIVE

The objectives of this project are to:

- Identify and appraise the clinical evidence pertaining to use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy .
- Identify and appraise information related to cost-effectiveness of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy, and if necessary due to lack of evidence, conduct a cost-effectiveness analysis.
- Identify recommendations for optimal prescribing and use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy, taking into consideration the clinical- and cost-effectiveness evidence.
- Identify current utilization of second-line antidiabetes drugs for patients with type 2 diabetes in Canada inadequately controlled on metformin monotherapy.
- Identify current practices of physicians, diabetes educators, and patients with respect to the use of second-line antidiabetes drugs for patients with type 2 diabetes in Canada inadequately controlled on metformin monotherapy.
- Identify differences (i.e., the gaps) between optimal prescribing and use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy (as supported by the evidence) and actual current utilization and practice.
- Identify potential barriers to optimal use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy.
- Identify key messages to encourage optimal prescribing and use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy.

- Identify effective activities and strategies (interventions), which could be directed towards a variety of audiences such as health and allied health professionals, patients, or government decision-makers, to encourage optimal prescribing and use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy.
- Develop intervention tools (evidence-based recommendations, menu of tools to support interventions, and support for implementing, monitoring and evaluating the tools and resulting interventions) to support optimal prescribing and use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy.
- Develop appropriate evaluation mechanisms to measure the impact of intervention tools.
- Support implementation of tools and evaluation.

Table 1: Classes of Second-Line Antidiabetes Drugs		
Drug Class	**Products**	**Mechanism of Action and Clinical Use**
Sulfonylureas	Gliclazide (Diamicron, Diamicron MR, Gen-Gliclazide, PMS-Gliclazide); glimepiride (Amaryl); glyburide/glibenclamide (Diabeta, Euglucon, Gen-Glybe, Novo-Glyburide, Nu-Glyburide, PMS-Glyburide, ratio-Glyburide, Sandoz Glyburide); chlorpropamide (Apo-chlorpropamide); tolbutamide (Apo-tolbutamide); Glipizide (Glucotrol, Glucotrol XL, GlipiZIDE XL)[20,21] (not marketed in Canada)	• Sulfonylureas stimulate insulin secretion from the beta cells of the pancreas. • Indicated for use alone or in combination with other oral agents or insulin in the management of type 2 diabetes mellitus.
Meglitinides	Repaglinide (GlucoNorm); nateglinide (Starlix)	• Similar mechanism of action as sulfonylureas, i.e., stimulation of pancreatic insulin release. • Administered at each meal to decrease postprandial plasma glucose. • Indicated as monotherapy or in combination with metformin or rosiglitazone for patients with type 2 diabetes mellitus when hyperglycemia cannot be controlled satisfactorily by diet and exercise alone.
Alpha-glucosidase inhibitors	Acarbose (Glucobay) and miglitol (Glyset)[20,22,23] (not marketed in Canada)	• Decrease postprandial plasma glucose levels by inhibiting alpha-glucosidase activity. • Indicated as monotherapy for the management of blood glucose levels in patients with type 2 diabetes mellitus that is inadequately controlled by diet alone. Both agents may also be used in combination with sulfonylurea, metformin, or insulin to improve glycemic control in patients with type 2 diabetes mellitus.
Thiazolidinediones	Rosiglitazone (Avandia); pioglitazone (Actos)	• Agonists of peroxisome proliferator-activated receptor-gamma (PPAR). • Decrease insulin resistance in the periphery and liver, thereby increasing insulin-dependent glucose uptake and decreasing hepatic glucose output. • Indicated as monotherapy or in combination with a sulfonylurea or metformin in patients with type 2 diabetes mellitus not controlled by diet and exercise alone. • Use of rosiglitazone in combination with metformin and a sulfonylurea (i.e., triple therapy), or insulin, is not indicated for safety reasons.

Table 1: Classes of Second-Line Antidiabetes Drugs		
Drug Class	**Products**	**Mechanism of Action and Clinical Use**
Incretin agents	DPP-4 inhibitors: sitagliptin (Januvia); vildagliptin (Galvus) (not marketed in Canada) Glucagon-like peptide-1 analogues: exenatide (Byetta) (not marketed in Canada)[24]	• Sitagliptin is a potent and highly selective inhibitor of DPP-4, an enzyme that metabolizes incretin hormones including glucagon-like peptide-1 and glucose-dependent insulinotropic peptide. DPP-4 inhibitors increase insulin release and decrease glucagon levels by enhancing the effect of incretins. • Sitagliptin is indicated in combination with metformin in adult patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy. • Vildagliptin has a similar mechanism of action to sitagliptin. • Exenatide is a glucagon-like peptide-1 analogue that is administered by subcutaneous injection.[24-27]
Weight-loss agents	Orlistat (Xenical); sibutramine (Meridia)	• Both orlistat and sibutramine are indicated for patients with type 2 diabetes mellitus with a body mass index ≥ 27 kg/m^2. • Orlistat is a reversible inhibitor of gastric and pancreatic lipases that inhibits fat absorption from the gastrointestinal tract. • Sibutramine is a serotonin-norepinephrine reuptake inhibitor that has been shown to reduce body weight through two actions: reduction of food intake through enhancement of satiety and increased energy expenditure by induction of thermogenesis. • Weight loss induced by orlistat and sibutramine improves glucose intolerance and glycemic control in patients with diabetes. • Orlistat can be used in combination with antidiabetes drugs to improve blood glucose control in overweight or obese patients with type 2 diabetes mellitus that is inadequately controlled by diet, exercise, and one or more of a sulfonylurea, metformin, or insulin.
Human insulins	Short-acting (Humulin R, Novolin ge Toronto) Intermediate-acting: neutral protamine Hagedorn insulin (NPH) (Humulin N, Humulin 30/70, Novolin ge NPH, Novolin ge 30/70, Novolin ge 40/60, Novolin ge 50/50); lente insulin (no longer available in Canada)	• Human insulins have the same amino acid sequence as endogenously secreted insulin and are prepared using recombinant DNA technology.

Table 1: Classes of Second-Line Antidiabetes Drugs		
Drug Class	**Products**	**Mechanism of Action and Clinical Use**
	Long-acting: ultralente insulin (no longer available in Canada)	
Insulin analogues	Rapid-acting insulin analogues: insulin lispro (Humalog, Humalog Mix); insulin aspart (NovoRapid, NovoMix 30); insulin glulisine (Apidra) Long-acting insulin analogues: insulin glargine (Lantus); insulin detemir (Levemir)	• Alterations in the amino acid sequence of human insulin were introduced to develop agents that more closely mimic the time-action profile of endogenously secreted basal and postprandial insulin. • Rapid-acting insulin analogues mimic the short duration of action of endogenous post-prandial insulin in non-diabetic patients. • Long-acting insulin analogues provide a prolonged, non-fluctuating basal level of insulin activity.
Amylin analogues	Pramlintide (Symlin) (not marketed in Canada)	• Pramlintide is an injectable analogue of amylin, a small peptide hormone released postprandially into the bloodstream by the -cells of the pancreas along with insulin.[2,28] Like insulin, amylin is deficient in individuals with diabetes. • By augmenting endogenous amylin, pramlintide aids in the absorption of glucose by slowing gastric emptying, promoting satiety, and inhibiting inappropriate secretion of glucagon.

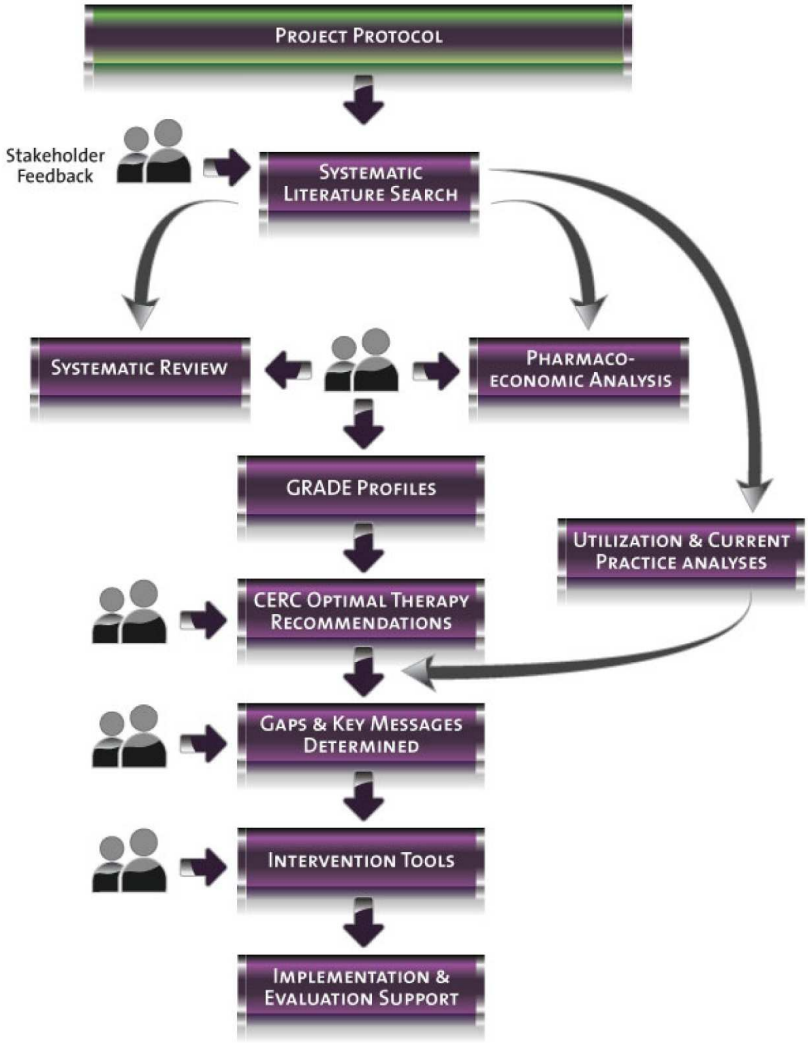
DPP = dipeptidyl peptidase-4.

4 PROJECT OVERVIEW

Once a topic is selected, CADTH undertakes activities related to key areas in the COMPUS procedure. CAC provides advice and guidance throughout the process. 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 second-line therapy for patients with diabetes in Canada inadequately controlled on metformin monotherapy, CADTH follows the COMPUS process outlined in the flow chart to the right.

This report represents the initial step (green box) toward the development of optimal therapy recommendations for the prescribing and use of second-line therapy for patients with diabetes in Canada inadequately controlled on metformin . The protocol document is reviewed and approved by CERC, with input from CAC.



5 RESEARCH QUESTIONS

The following types of research questions were developed for the project objectives requiring a research component: clinical, economic, current utilization, and current practice. The remaining objectives are based on, or derived from, a research component and also require a multi-faceted approach involving consultation with experts and key stakeholders. The research questions developed for the remaining objectives include gap analysis; identification of key messages, including barriers to optimal use; and selection of intervention tools. Processes for completing these objectives are presented in Section 6.

5.1 Clinical

What is the comparative efficacy and safety of second-line antidiabetes drug(s) in patients with type 2 diabetes mellitus initially treated with metformin monotherapy who:

- require additional glucose-lowering therapy because of inadequate glycemic control (i.e., glycosylated hemoglobin [A1C] > 6.5% or fasting plasma glucose [FPG] > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L)?
- require a switch from metformin to another glucose-lowering agent(s) because of inadequate glycemic control (i.e., A1C > 6.5% or FPG > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L)?
- require a switch from metformin to another glucose-lowering agent(s) because of intolerable adverse effects or the development of contraindications to metformin?

Throughout this document, "inadequately controlled on metformin" refers to any one of the above three scenarios.

5.1.1 Populations of interest

For each research question in this section, the following patient groups will be examined:
- Adults with type 2 diabetes mellitus treated with metformin monotherapy (≥ 18 years of age)
- Children with type 2 diabetes mellitus treated with metformin monotherapy (< 18 years of age).

If data are available, the research questions will be addressed for the following subgroups:
- Seniors ≥ 65 years old (further subgroup ≥ 75 years old)
- First Nations people
- Race/ethnic minorities
- Patients requiring second agent(s) because of loss of glycemic control (e.g., A1C > 6.5%) versus those requiring therapy switch because of metformin intolerance or contraindication
- Patients on maximal metformin dose (≥ 2.55 g/day) when a second agent is added versus sub-maximal doses
- Body mass index (≤ 30 versus > 30 kg/m^2)
- Duration of metformin monotherapy at stable doses before therapy is added (< 3 months versus ≥ 3 months)
- A1C ≥ 9% on metformin monotherapy versus A1C < 9.0%
- Criteria used in trials to define "inadequately controlled" (i.e., A1C > 6.5% versus FPG > 7 mmol/L versus two-hour postprandial glucose > 10 mmol/L).

5.1.2 Interventions of interest

All classes of second-line antidiabetes drugs will be assessed, including sulfonylureas, meglitinides, TZDs, incretin agents, insulins and insulin analogues, alpha-glucosidase inhibitors, and weight-loss agents. A complete list of agents that will be assessed is provided in Appendix 1.

5.1.3 Comparators

For patients switching from metformin to another agent:

- One or more of the agents listed under "Interventions of interest" above.

For patients adding another agent to metformin:

- Metformin (at any dose) + placebo or no antidiabetes therapy
- Metformin (at any dose) + one or more of the agents listed under "Interventions of interest."

5.1.4 Outcomes of interest

CERC members identified possible outcomes of interest in considering evidence related to second-line therapies in type 2 diabetes mellitus and developing recommendations for their optimal use. Members then individually ranked the importance of each outcome identified using a nine-point scale. A score between 7 and 9 was assigned for outcomes considered to be "critical" for making recommendations, between 4 and 6 for outcomes considered to be "important," and between 1 and 3 for outcomes considered "not important." Outcomes were scored separately for adults and children with type 2 diabetes mellitus, although the rankings were similar for both populations. Mean scores for each outcome were calculated across CERC members to determine "critical" and "important" outcomes; decimals were rounded up to the next whole number. Data on these outcomes will be extracted and analyzed in the systematic review (Table 2).

Table 2: Summary of Outcomes Considered by Members of CERC as Being "Critical" or "Important" in Developing Optimal Therapy Recommendations for Use of Second-Line Therapies in Adults and Children with Diabetes Indequately Controlled on Metformin

Outcome	Importance
Glycemic control	
Hemoglobin A1C	Critical
Long-term clinical complications of diabetes	
Congestive heart failure	Critical
Ischemic heart disease	Critical
Stroke/TIA	Critical
Peripheral vascular disease	Critical
Retinopathy	Critical
Nephropathy	Critical
Neuropathy	Critical
Mortality	Critical
Short-term complications of diabetes or antidiabetes treatment	
Hypoglycemia — Overall	Critical
Hypoglycemia — Severe	Critical
Hypoglycemia — Nocturnal	Critical
Hyperosmolar hyperglycemic non-ketotic coma	Important

Table 2: Summary of Outcomes Considered by Members of CERC as Being "Critical" or "Important" in Developing Optimal Therapy Recommendations for Use of Second-Line Therapies in Adults and Children with Diabetes Indequately Controlled on Metformin	
Outcome	**Importance**
Quality-of-life	
Health-related quality-of-life — Generic	Critical
Health-related quality-of-life — Diabetes-specific[a]	Critical
Patient satisfaction	
Patient satisfaction with diabetes care	Important
Patient satisfaction with diabetes treatment	Important
Other	
Weight / weight gain / BMI	Critical
Serious adverse events	Critical
Pancreatitis — For incretin agents only	Critical
Upper extremity fractures — For TZDs only	Critical
Macular edema — For TZDs only	Critical

A1C = glycosylated hemoglobin; BMI = body mass index; CERC = COMPUS Expert Review Committee; COMPUS = Canadian Optimal Medication Prescribing and Utilization Service; TIA = transient ischemic attack.
[a]Upon discussion, CERC deemed this outcome to be "critical" even though the mean score across individual members was less than 6.

5.1.5 Study design of interest

Randomized controlled trials (RCTs).

5.2 Economic

What is the cost-effectiveness of second-line antidiabetes agent(s) in the management of adult patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy?

Inadequate control and intolerance will be defined in the same manner as described in Section 5.1. The populations, interventions, and comparators of interest in the assessment of cost-effectiveness will also be the same as those listed in Section 5.1.

5.3 Current Utilization

The following research questions will be addressed:

- In patients with type 2 diabetes mellitus initiated on metformin monotherapy in Canada, what are the most commonly prescribed second-line antidiabetes drug(s)?
- What are the mean and median times to switch or add on second-line antidiabetes agent(s) in Canada among patients with type 2 diabetes mellitus initiated on metformin monotherapy?

5.4 Current Practice

There are two overarching questions to be answered:

- What are the experiences and preferences of health care professionals in Canada who provide care for patients with type 2 diabetes mellitus regarding the use of second-line antidiabetes drugs for patients inadequately controlled on metformin monotherapy?
- What are the experiences and preferences of patients with type 2 diabetes mellitus in Canada relating to the use of second-line antidiabetes drugs who are inadequately controlled on metformin monotherapy?

5.4.1 Populations of interest

- Adult patients with type 2 diabetes mellitus
- Health care professionals including endocrinologists, family physicians, diabetes educators, pharmacists, and nurse practitioners.

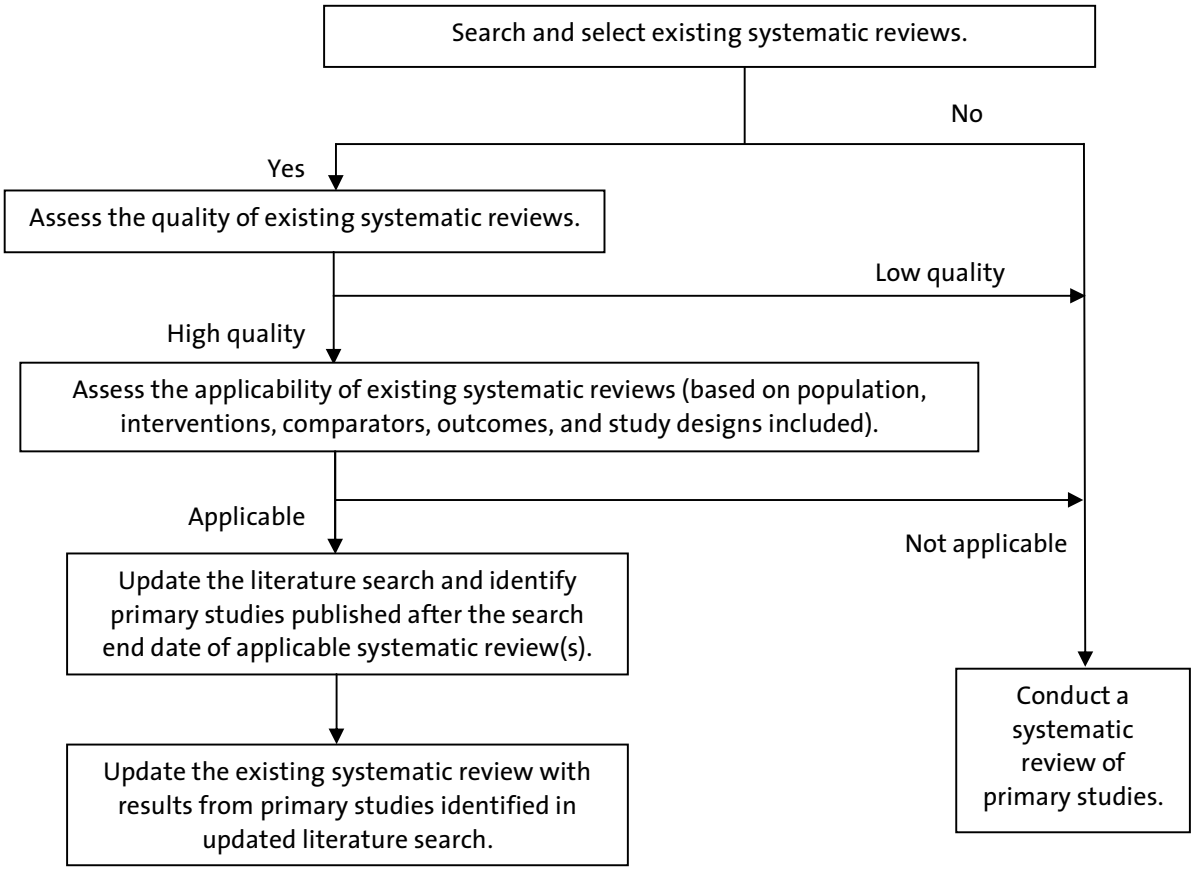
6 METHODS

6.1 Clinical

Where possible, COMPUS builds on existing applicable Canadian and international initiatives and research. Therefore, the first stage in the research process will be to conduct a literature review to identify existing systematic reviews that have examined the efficacy and safety of second-line antidiabetes drugs in the treatment of patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. Should relevant, recently published, high-quality systematic review(s) be identified, they will be used, as described in Section 6.3, as a basis for development of optimal therapy recommendations by CERC. If necessary, the literature search used in existing systematic review(s) will be updated, and results from eligible studies published after the review search end date will be incorporated with results from the systematic review(s). If no suitable systematic reviews are identified, CADTH will conduct its own systematic review of primary studies. Where appropriate, studies will be pooled and meta-analyses will be performed. Otherwise, results will be summarized and presented in narrative form.

The overall methodology for the clinical review is presented in the figure below:

Figure 1: Clinical Review Methodology



6.1.1 Identification of existing systematic reviews

a) Selection criteria

A systematic review will be considered as the basis for development of optimal therapy recommendations if it meets all of the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

- Study design — Systematic review or health technology assessment
- Populations, interventions, comparators, and outcomes included as described in Section 5.1.

Exclusion criteria

- Reviews in which research methods were inadequately described*
- Non-English publications.

*Factors such as search strategy, selection criteria, quality assessment of included studies, and data analysis were not clearly or comprehensively defined.

b) Literature search

Several major databases (MEDLINE, EMBASE, Cochrane) will be searched for existing systematic reviews, meta-analyses, and health technology assessments examining second-line therapy for patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. The search will be broad, using general key words (e.g., second-line therapy, metformin failure) to capture studies published in English between 1990 and March 2009 (Appendix 2). The Internet will be searched to identify unpublished (grey) literature from websites and databases of health care associations and related agencies.

c) Systematic review selection

Two reviewers will independently select systematic reviews for consideration based on the predefined inclusion and exclusion criteria listed above. Each reviewer will independently perform an initial screening of 10% of the citations (or 20 citations, whichever is less) identified through the literature search by examining titles and abstracts for relevance to the review topic, reach agreement with the other reviewer, then independently screen the remaining citations. Abstracts of articles will be assessed and categorized as "included" or "excluded." If the relevance of an article is uncertain, it will be retained in the included list. Citations with discrepant selection results will be re-selected by a third reviewer. The judgment of the third reviewer will be considered final.

Full-text articles of the citations included by both reviewers or by the third reviewer will be ordered then independently selected by two reviewers. Exclusion reasons will be recorded and compared. Discrepancies between reviewers will be discussed until consensus is reached; the judgment of a third reviewer will be considered final if consensus cannot be reached by the first two reviewers. In the event that a systematic review is reported in more than one publication, the most recent or informative systematic review will be selected for inclusion.

If existing systematic review(s) or/and meta-analyses are selected, reviewers will complete the following steps. Otherwise, reviewers will proceed to Section 6.1.2.

d) Assessment of systematic review quality

AMSTAR,[29] an instrument developed specifically to quantify the methodological quality of systematic reviews, will be used by two reviewers to independently assess the quality of systematic reviews selected for consideration (see Appendix 3). Systematic reviews that score 6 or more (out of a maximum of 11) will be considered to be of high quality and will be retained for use as the potential basis for generating optimal therapy recommendations. Systematic reviews that score lower than 6 will be considered to be of low quality and will be excluded. However, the following criteria must be fulfilled for inclusion irrespective of the overall AMSTAR score: 1) An "a priori" design must be provided where the research question and inclusion criteria are established before the review was conducted; 2) The literature search performed in the systematic review must be conducted on at least two databases; and 3) The review process must include two reviewers. Reviewers will compare their individual ratings, discuss discrepancies, and reach agreement before assigning a final quality rating to each systematic review. Unresolved discrepancies will be resolved by a third reviewer.

If the selected systematic review(s) are of high quality, reviewers will complete the following steps. Otherwise, reviewers will proceed to Section 6.1.2.

e) Data extraction of included systematic review(*s)*

General information regarding included systematic reviews of high quality, such as the year of publication, source, organization, funding sources, and type and number of included primary studies, will be extracted

from all included systematic reviews in a predefined table (Appendix 4-1) along with consensus AMSTAR quality assessment scores. The literature search strategy, research questions, population, interventions, comparators, outcomes assessed, and key findings will be extracted in a second predefined table (see Appendix 4-2). For systematic reviews found to be applicable based on the assessment described under (f) below, all primary studies included in each review will be listed in a third table (see Appendix 4-3). One reviewer will extract data and a second reviewer will verify their accuracy. Discrepancies will be resolved by consensus; the decision of a third reviewer will be considered final for unresolved discrepancies.

f) Applicability assessment of systematic review(s)

The overall process of applicability assessment of included systematic review(s) is outlined in Appendix 4-4. Existing high-quality systematic reviews will be selected as a basis for generating optimal therapy recommendations based on four main considerations: relevance in terms of the population, interventions, comparators, outcomes, and study designs considered; degree to which the selection criteria used by the authors correspond with the selection criteria listed in Section 6.1.2 (a); currency of the search dates; and degree of effort required to update the systematic review. Systematic reviews of diabetes pharmacotherapy that are broader in scope than the research questions listed in Section 5.1 will be considered as a basis for generating optimal therapy recommendations if they report appropriate subgroup analyses or provide enough study-level data to conduct a subgroup analysis.

Members of CERC will be consulted regarding the decision on whether existing systematic review(s) will be used as the basis of optimal therapy recommendations for second-line antidiabetes drugs. The results of this assessment and the proposed approach to use existing systematic review(s) will be summarized and presented in a table (see Appendix 4-5). If one or more reviews are chosen, reviewers will complete steps (g) and (h) below to update the selected review(s) with new evidence published after the literature search end date of the corresponding systematic review(s). If none of the systematic reviews considered is deemed appropriate as a basis for CERC to develop optimal therapy recommendations, a systematic review of primary studies will be conducted as described in Section 6.1.2

g) Updating of systematic review literature search

A literature search will be conducted to identify relevant primary studies published after the search end date of selected systematic review(s) identified through applicability assessment. The search strategy will be based on the strategy used by the authors of the systematic review, although it may be modified to reflect the research questions of interest or to ensure it conforms to COMPUS standards. Similarly, the inclusion and exclusion criteria applied by the authors of the included systematic reviews may be modified if necessary. Identified studies will be evaluated for quality and data extracted as described in Section 6.1.2.

h) Incorporation of updating data

If no new primary studies are identified, the selected systematic reviews will be used as the basis of optimal therapy recommendations. If new primary studies are identified, these results will be summarized in narrative form to augment the results of the selected systematic reviews. If deemed necessary by members of CERC, and where appropriate based on clinical and methodological considerations, data from studies selected from the update search may be pooled with studies included in the systematic review(s). Pooling will be conducted according to the methods described in Section 6.1.2.

6.1.2 Systematic review and meta-analysis of primary studies

As noted in Section 6.1, if no suitable systematic reviews are identified, COMPUS will conduct its own systematic review of primary studies (i.e., RCTs).

a) Selection criteria

A study will be included if it meets all of the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

- Population — Patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy
- Intervention — One or more of the agents listed in Appendix 1
- Comparator — One or more of the agents listed in Appendix 1, or placebo / no therapy
- Outcomes — As shown in Table 2, Section 5.1
- Study design — RCTs (including parallel, crossover, placebo-controlled, active comparator).

Exclusion criteria

- Studies of patients inadequately controlled on initial monotherapy regardless of the antidiabetes drug(s) used, in which:
  - more than 15% of the sample used a drug(s) other than metformin as initial therapy, and
  - no subgroup analysis was reported for patients inadequately controlled on metformin monotherapy.
- Studies in which initial therapy consisted of a combination of metformin with another antidiabetes drug(s).
- Studies comparing addition of second-line antidiabetes drug(s) to metformin monotherapy versus switching to second-line therapy on discontinuation of metformin monotherapy.
- Studies evaluating the switch from metformin to another antidiabetes drug(s) in which the comparator was placebo or no antidiabetes therapy (i.e., no active comparator).
- Studies with a duration of less than four weeks.
- Non-English publications.

b) Literature search

A detailed search strategy will be developed and applied to several major electronic databases (MEDLINE, EMBASE, BIOSIS, Cochrane). The search will use MeSH (medical subject headings) and keywords for each oral antidiabetes drug plus more general terms (e.g., hypoglycemic drugs, oral antidiabetes drug) to capture RCTs published in English from 1980 to May 2009 if a full systematic review is required, or determined according to the search cut-off date(s) of existing systematic review(s) if an update is performed. The search strategy will be attached in the CADTH review report as an appendix. These searches will be supplemented by reviewing bibliographies of selected articles (i.e., included primary studies and existing systematic reviews), conference proceedings, and clinical trial registries. The Internet will be searched to identify unpublished (grey) literature from websites and databases of health professional associations, health technology assessment agencies, and related entities. Regular alerts will be established in the electronic databases to capture studies published after May 2009 until data analysis is completed. Searches to update the grey literature will be performed.

c) Study selection

Two reviewers will independently select articles for inclusion in the review based on the above selection criteria. The process of study selection will be as described in Section 6.1.1. A flow chart (based on the

QUOROM statement) will be generated to illustrate the study selection process. The list of included studies will be posted on the CADTH website to elicit stakeholder feedback. Studies provided by stakeholders will be considered for inclusion based on previously stated selection criteria.

d) Assessment of study quality

The methodological quality of included RCTs will be assessed using a modified version of the Scottish Intercollegiate Guidelines Network (SIGN) 50 checklist[30] (see Appendix 5). Two reviewers will independently assess methodological quality for each study and assign a rating of "very good," "good," or "poor." Reviewers will compare ratings and come to a consensus for each attribute of the SIGN 50 checklist and for the overall rating. The judgment of a third reviewer will be considered final if consensus cannot be achieved. Before proceeding with quality assessment of all included studies, a pilot test will be conducted on one or more studies to improve consistency between reviewers in how the checklist is applied. To determine the impact of study quality, a sensitivity analysis will be performed by excluding low-quality studies (see "Sensitivity and subgroup analyses" later in this section).

e) Data extraction

Data extraction forms designed a priori in Microsoft Excel will be used to document and tabulate all relevant information in studies selected for inclusion in the systematic review (see Appendix 6). Two reviewers will independently extract data on outcomes of interest from included studies using these forms. For data related to study and patient characteristics, one reviewer will independently extract data, and the second reviewer will verify accuracy and completeness. Discrepancies between reviewers will be identified and resolved by consensus; the judgment of a third reviewer will be considered final if consensus cannot be reached. Authors of included studies will be contacted for any missing or incomplete data, where necessary. Before proceeding with data extraction of all included studies, a pilot test will be conducted using a small number of studies to assess the usability of the data extraction form and improve the consistency of data extraction between reviewers.

Caution will be exercised to ensure that duplicate or companion publications of the same study are identified. Where duplicate or companion publications exist, data from the most recent or informative article will be used. As well, subgroup or single-centre results will be excluded if the corresponding main analyses are included in the review, unless they provide data on additional outcomes.

f) Handling of conference abstracts

In an effort to include the most recent research findings (that is, those not yet published in peer-reviewed journals) authors of conference abstracts will be contacted to determine the publication status of their work. Data from abstracts will be included in primary analyses if the following conditions are met:

- A full-text article of the abstract has been accepted for publication in a peer-reviewed journal.
- Authors provide a manuscript to COMPUS for review and give permission for the data to be included in the CADTH report.

It is estimated that only half of all abstracts presented at conferences are later published as full-text articles and that publication is positively associated with the reporting of positive trial results.[31] If this is the case, excluding abstracts from analyses may lead to biased results that overestimate the effects of interventions. To determine the impact, if any, of excluding unpublished evidence, data from all conference abstracts will be included in sensitivity analyses (see "Sensitivity and subgroup analyses" later in this section).

g) Handling of crossover randomized controlled trials

Data from crossover RCTs will be included in the same meta-analyses as parallel trials using the results of paired analyses. If paired analyses are not reported, study authors will be contacted for the necessary data. If the necessary information is not provided, a correlation coefficient between comparator arms will be calculated from similar studies reporting complete summary data (i.e., means and standard deviations for each treatment arm as well as the mean and standard deviation of the paired difference between arms), as described by Elbourne et al.[32] For crossover trials reporting a significant carryover effect, only the data from the pre-crossover phase will be included in meta-analyses. In the absence of reported carryover effects, data from the pre-crossover phase will be preferred; otherwise, mixed data from pre- and after-crossover phases will be combined with those from parallel trials in a single meta-analysis (sample sizes will be doubled accordingly).

h) Outcome ascertainment

Continuous outcomes

For continuous outcomes such as A1C or body weight, the difference between treatment groups in mean change from baseline will be meta-analyzed. If estimates of variability (such as standard error) for mean change from baseline are not reported, they will be imputed based on standard errors from similar studies. In instances when imputation is not possible, or when a study reports only mean values at endpoint, study authors will be contacted for the required data. Mean values at endpoint will be meta-analyzed only when efforts to obtain adequate change from baseline data have failed.

Quality-of-life and patient satisfaction will be recorded based on the measures reported in primary studies. It is expected that most studies will report mean change from baseline, allowing for meta-analysis as a continuous outcome. If studies employ various instruments to measure quality-of-life or patient satisfaction, results will be summarized qualitatively.

Dichotomous outcomes

Dichotomous outcomes, such as diabetes-related complications or mortality, will be analyzed using relative risk as an effect measure. Dichotomous categories will be defined as "no event" or "one or more events." Similarly, hypoglycemia (severe, nocturnal, and overall) will be analyzed to determine the relative risk of experiencing at least one event. In pairwise comparisons, this outcome will also be analyzed using the rate ratio; that is, the ratio of the number of events per patient per unit of time observed in each treatment arm.[33-35]

i) Data synthesis and analysis

Data from studies in adults will be analyzed and synthesized separately from studies in children. The analysis will be conducted at the level of individual agents, where possible, as well as drug classes. Where quantitative pooling of results from included studies is appropriate, meta-analysis will be used to estimate treatment efficacy. Ideally, comparison of the relative effects of all treatments of interest would be based on direct evidence from multi-arm, head-to-head RCTs. However, in the absence of such evidence, efforts will be made to determine estimates of efficacy using indirect methods. Mixed treatment comparison meta-analysis[36-39] will be employed in this review to derive estimates of relative effectiveness in a single framework. Mixed treatment comparison meta-analysis is a Bayesian approach that combines direct and indirect evidence in a single analysis, thus enabling simultaneous comparison of multiple treatment interventions.[36-39] This unified approach enables one to determine the probability that each intervention is best for a particular outcome in a population of interest.[36-39] Informal comparisons between the estimated effects from the direct head-to-head evidence and the mixed treatment comparison meta-analyses will be made to verify the validity of results obtained by mixed treatment comparison meta-analyses.

Data from head-to-head, direct treatment comparisons will be combined using random-effects meta-analyses. Results of individual studies will be pooled only if populations, interventions, comparators, and outcome measures across studies are sufficiently similar to produce a clinically meaningful result. Otherwise, results will be summarized qualitatively. Heterogeneity will be ascertained using the I^2 statistic.[40] The I^2 statistic describes the proportion of unexplained variability in effect estimates across studies in a meta-analysis. An I^2 of 50% represents moderate heterogeneity.[40] For analyses above this threshold, we will explore possible causes of heterogeneity through comparison of population and methodological and treatment characteristics across included studies. Pooled results will not be reported for meta-analyses demonstrating I^2 values of more than 75%. Instead, individual study results will be summarized qualitatively. The potential for publication bias will be assessed in meta-analyses that include more than 10 studies, using funnel plots.[33,41]

For mixed treatment comparison meta-analyses, all evidence that forms a closed network will be synthesized.[36-39] Routines developed at the universities of Bristol and Leicester to conduct Bayesian mixed treatment comparison meta-analyses (www.bris.ac.uk/cobm/research/mpes/mixed-treatment-comparisons.html) using Winbugs software (www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml) will be employed for all mixed treatment comparison evidence syntheses. Posterior densities for all unknown parameters will be estimated using Markov chain Monte Carlo methods.[42] Non-informative prior distributions for overall effects of interest and study-specific effect estimates will be assigned.[42] Point estimates and 95% confidence intervals[42] will be used to summarize findings. The probability that a treatment is most efficacious will be estimated for each outcome based on the proportion of Markov chain Monte Carlo simulations in which it had the largest effect. Incoherence in the evidence network and model convergence will also be assessed.[43,44]

Data will be analyzed by a single reviewer. A second reviewer will verify the process used in data analysis and verify the results.

j) Sensitivity and subgroup analyses

To determine robustness of the results, sensitivity analyses will be performed for both head-to-head direct treatment comparison meta-analyses and mixed treatment comparison meta-analyses. In a sensitivity analysis, the effect of including studies with a particular characteristic in a meta-analysis is assessed by determining the impact of removing such studies from the analysis. The following sensitivity analyses will be performed to explore methodological or reporting differences across individual studies:

- Inclusion of studies reported as abstracts or other forms that are not subjected to peer review
- Removal of crossover studies
- Removal of studies assessed as being of low quality (i.e., a SIGN 50[30,45,46] rating of "-")
- For analyses of A1C, removal of studies of less than three months' duration, because A1C is a long-term measure of glycemia that is unlikely to be significantly affected in trials of shorter duration[47]
- Removal of studies in which some patients were inadequately controlled on initial monotherapy with agents other than metformin
- Removal of studies in which inadequate control on metformin was defined by an A1C threshold of less than 7%
- Removal of studies that did not report intention-to-treat analyses
- Removal of studies that used fixed, sub-maximal doses of second-line therapies.

Subgroup analyses will be conducted based on patient and treatment characteristics that are based on the evaluation structure presented in Appendix 7.

k) Stakeholder feedback

The results of the analysis will be presented in the form of a draft systematic review report that will be posted on the CADTH website to elicit stakeholder feedback. Relevant stakeholder feedback will be incorporated into the final version of the systematic review based on input from CERC.

6.2 Economic

A literature search will be conducted to identify existing studies regarding the cost-effectiveness or cost-utility of various second-line antidiabetes drugs in Canada. If no relevant studies are identified, a cost-utility analysis will be conducted using the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model.[48]

6.2.1 Model structure and validation

The UKPDS Outcomes Model[48] is a computer simulation model that can be used to forecast long-term health outcomes and cost consequences of diabetes-related complications. The UKPDS Outcomes Model[48] was developed by the University of Oxford Diabetes Trial Unit. Progression of diabetes complications are modelled by mathematical algorithms that take into account patient characteristics, risk factors, and complication history using data derived from the UKPDS. Validation analyses have been performed to compare UKPDS Outcomes Model[48] predictions with results observed in published clinical and epidemiological studies.[49]

6.2.2 Target population

The target population for these analyses will include adults with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. Demographic characteristics for the simulated cohort will be obtained from published RCTs and cross-referenced with epidemiological studies to ensure that they are reflective of the clinical context.

6.2.3 Treatment comparators

Comparators of interest are outlined in section 5.1.2 and 5.1.3. Patient-relevant and clinical outcomes for comparators will be derived from meta-analyses of RCTs.

6.2.4 Audience and perspective

The target audiences for this economic evaluation are decision-makers in public drug benefit programs, health professionals, and patients with type 2 diabetes mellitus. The economic evaluation takes the perspective of a third-party provincial payer.[50]

6.2.5 Time horizon

The model will forecast the occurrence of diabetes-related complications over a patient's lifetime.[50,51]

6.2.6 Valuing outcomes

Health-related quality-of-life scores will be obtained from a US catalogue of EuroQol 5-dimension index (EQ-5D) scores for chronic conditions.[52,53] The EQ-5D[54] is a widely used preference-based instrument for the measurement of health status.[55] The US catalogue,[52,53] which was generated using nationally representative data from the Medical Expenditure Panel Survey,[56] is recommended for use in pharmacoeconomic analyses by the Washington Panel on Cost-Effectiveness in Health and Medicine.[52,53] Preference scores in the US catalogue were generated from an American sample and should be generalizable to Canadians, as instrument scores travel well and are applicable in other countries.[50,57] Where disutility estimates are not available from the US catalogue, they will be obtained from other sources that utilize the EQ-5D instrument.[58-61]

Disutilities for chronic health states experienced within the first year will be based on EQ-5D scores for relevant International Classification of Diseases, 9th revision[62] codes or clinical classification category.[53,62] For subsequent years, disutilities will be based on quality priority conditions estimates,[52,53] where individuals were asked if they had *ever been diagnosed with the condition in the past* (e.g., Did you ever have a stroke before?). In instances where quality priority conditions estimates[52,53] are unavailable, it will be assumed that the disutility for the chronic condition will remain constant over time.

6.2.7 Resource use and costs

a) Prescription drug costs

Only direct costs to the publicly funded health care system will be considered. Unit costs for prescription drugs will be obtained from the PPS Pharma Buyers Guide, Ontario Edition, July 2009. When unit costs are not available from the PPS Pharma Buyers Guide, Ontario Edition,[63] costs will be obtained from the Ontario Drug Benefits Formulary / Comparative Drug Index.[64]

b) Costs of managing diabetes complications

Resource utilization and costs associated with diabetes-related complications will be obtained from the Ontario Diabetes Economic Model.[65] Inpatient and outpatient costs, cost of emergency department visits, subsequent prescription drugs claims, and long-term care and home care costs for managing diabetes-related complications will be included.[65] If resource use and costs for a health state are not available from the Ontario Diabetes Economic Model,[65] data will be obtained from published costing studies or other literature. Costs will be inflated to 2009 Canadian dollars using the Consumer Price Index.

6.2.8 Discount rate

Both costs and quality-adjusted life-years will be discounted at a rate of 5%.[50]

6.2.9 Analysis of uncertainty

Univariate and multivariate sensitivity analyses[66] will be performed to explore uncertainty of results. Sensitivity analyses to be performed include, but are not limited to, changes in the differences between treatments in A1C, costs of antidiabetes drugs, dosing, baseline A1C, demographic characteristics, duration of diabetes, discount rate, time horizon of analysis, risk of hypoglycemia (for insulin and insulin secretagogues), disutilities associated with various health states in the model, and management costs for diabetes-related complications. Incremental cost-effectiveness scatter plots[66] and cost-effectiveness acceptability curves[67,68] will be generated to illustrate uncertainty of results.

6.2.10 Stakeholder feedback

Results from the economic analysis will be presented in a draft report that will be posted on the CADTH website to elicit stakeholder feedback. Relevant stakeholder feedback will be incorporated into the final version of the economic report based on input from CERC.

6.3 Development of Optimal Therapy Recommendations

CADTH will apply 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 and others with an interest in grading quality of evidence and strength of recommendations, developed the GRADE methodology to provide committees charged with formulating recommendations with 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.[69] The GRADE methodology is used by a number of organizations around the world, such as the World Health Organization[70] and the American Thoracic Society, to generate recommendations.[71] Evidence for consideration by the panel will be presented as GRADE profiles, which consist of summaries of findings and evidence quality assessments. A sample GRADE profile form is presented in Appendix 8.

6.3.1 Formulating recommendations

When formulating recommendations, CERC considers both clinical-effectiveness regarding benefits, harms, and burdens as well as cost-effectiveness. Members of the committee bring their individual expertise and experience to bear (as experts, general practitioners, interventionists, and members of the public) and draw upon their own values and preferences to discuss the evidence and reach conclusions. The process by which recommendations are formulated by CERC consists of two main stages. First, the committee considers the clinical evidence regarding safety and effectiveness and draws conclusions regarding clinically important differences (if any) among the interventions in question. The committee then reviews the pharmacoeconomic evidence and considers the cost-effectiveness of the clinical conclusions. This sequential consideration of the evidence allows for clear delineation of the impact that cost-effectiveness considerations may have on the final recommendations. Thus, optimal therapy recommendations are formulated based on efficacy, safety, and pharmacoeconomic data.

When formulating the recommendations, CERC will take the perspective of health care policy-makers pursuing maximal health outcomes for the Canadian population given finite health care system resources. Where possible, the recommendations developed by CERC will provide guidance regarding specific patient subgroups that may benefit from alternate treatment approaches.

CERC will provide clinical notes to provide guidance based on clinical judgment where there is insufficient evidence. Context statements related to, but not limited to, quality and quantity of evidence, cost-effectiveness, directness of evidence, and clinical issues will be developed by CERC for inclusion in the recommendations to augment knowledge transfer to the intended audiences.

To generate optimal therapy recommendations, CERC will use the GRADE evidence profiles on second-line antidiabetes drugs for patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. The process will consist of six main steps:

- Feedback on GRADE profiles
- Discussion of clinical-effectiveness evidence and feedback
- Generating clinical findings based on clinical evidence of effectiveness and safety
- Generating draft recommendations based on clinical findings as well as cost and cost-effectiveness information
- Identification of underlying values and preferences for each recommendation
- Grading of the strength of recommendations.

Each of these steps is described in further detail in the following sections.

a) Feedback on GRADE profiles

CERC members will be provided with the GRADE evidence profiles and a feedback form for each profile. Committee members will complete a feedback form for each GRADE evidence profile. Feedback will be collated into a summary document for each profile and provided to members in advance of the subsequent committee meeting.

b) CERC discussion of clinical-effectiveness evidence and feedback

CERC members will discuss the evidence presented in the GRADE evidence profiles and the associated feedback form. Context and clinical issues raised during the discussion will be recorded for each evidence profile. GRADE Summary of Findings tables will be generated to reflect the body of generated information. Each Summary of Findings table will contain:

- 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.

c) Generating clinical findings

Each member of CERC participating in the meeting will vote for one of the clinical findings and the overall quality of the available evidence.[†] Points of discussion related to the clinical findings statements will also be documented and collated.

d) Generating draft recommendations

Where one intervention appears to be more effective and more costly than another, CERC will determine whether the intervention represents reasonable "value for money" over the alternative. There is no empirical basis for assigning a particular value (or values) to the cut-off between cost-effectiveness and cost-ineffectiveness.

Once the clinical findings have been voted on, CERC will review and discuss the results from the pharmacoeconomic analyses. Conclusions from the pharmacoeconomic analyses will be added to the GRADE Summary of Findings tables. Costing data will be supplied where cost-effectiveness results are not available. Draft recommendations, reflecting both clinical as well as cost and cost-effectiveness results, will be proposed for CERC's deliberation and voting.

[†]It is not necessary for all 12 CERC members to be present at all meetings. The quorum for all CERC matters that relate to a recommendation is five of the Core Members plus 66% of the Specialist Experts appointed in relation to the topic under consideration. Every voting member participating in a meeting is required to vote (i.e., a member cannot abstain from voting).

e) Underlying values and preferences

An important component of each draft optimal therapy recommendation will be a clear statement regarding the underlying values and preferences that support the choice of one alternative over another. These will reflect the values expressed by CERC over the course of the assessment of both the clinical-effectiveness as well as the cost and cost-effectiveness evidence. In situations where the evidence regarding clinical-effectiveness, cost, and cost-effectiveness fail to demonstrate important differences between treatments, the recommendations will be formulated to reflect that either treatment is appropriate. Associated values and preferences for each treatment option will be clearly outlined to help guide patients, clinicians, and decision-makers in selecting the most appropriate treatment alternative.

6.3.2 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.[71]

A proposed rating of strength (i.e., either "strong" or "weak") will be assigned to each recommendation, and feedback will be elicited from CERC members regarding the level of agreement with the ratings. To facilitate this process, a summary of all prior CERC deliberations for each recommendation will be distributed to members. This summary will contain the recommendation (with vote results), a rating of overall quality of evidence (with vote results), a listing of values and preferences (with vote results), a statement regarding key considerations resulting in the recommendation, Clinical Notes and contextual information, and a proposed strength of recommendation. The proposed strength of recommendation will be based on four questions put forward by the GRADE Working Group as points of consideration when evaluating recommendation strength:

- Is the available evidence of lower quality?
- Is there uncertainty regarding the balance of benefits versus harms and burdens?
- Is there uncertainty or are there differences in values and preferences?
- Is there uncertainty about whether the net benefits are worth the costs?

An affirmative answer to one or more of these questions may result in downgrading of a recommendation to "weak." As stipulated by the GRADE process, strength of recommendations is reflected by the use of the word "suggests" or "recommends" for weak and strong recommendations, respectively (i.e., "CERC suggests that..." versus "CERC recommends that..."). Where recommendations are graded as weak, the rationale supporting CERC's decision will be provided.

6.3.3 Identification of research gaps

CERC will identify instances where there is insufficient information with which to produce optimal therapy recommendations as gaps in research or knowledge. These will consist primarily of comparisons and populations for which no peer-reviewed reports of RCTs are identified. Research gaps will be also be identified when there is a paucity of comparative data on outcomes of interest for particular comparisons or populations.

6.3.4 Stakeholder feedback

A report containing the draft optimal therapy recommendations for second-line therapy for patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy, supporting evidence in the

form of summary of findings tables, and contextual material identified by CERC will be posted on the CADTH website to elicit stakeholder feedback. Stakeholder feedback will be collated by CADTH staff and considered by CERC as the final optimal therapy recommendations are developed.

6.4 Current Utilization

Utilization patterns among patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy will be assessed using administrative claims data from publicly and privately funded drug plans.

6.4.1 Data sources

Data will be obtained from Brogan Inc. The Brogan Inc., database is the largest source of drug payment information (i.e., claims data) in Canada.[72] Brogan Inc. databases comply with federal and provincial privacy legislation.[72] Claims-level data provided by Brogan Inc. are protected by means of anonymous identifiers to ensure patient confidentiality.

Claims-level data are available for the Ontario Drug Benefits Program and 65% of Canada's privately funded drug plans.[72] It is estimated that the Brogan Inc. dataset includes claims-level data for 34% of all prescriptions in Canada (i.e., the Ontario Drug Benefits Program and private drug plan claims represent 25% and 9% of all prescription claims, respectively) (*Nevzeta Bosnic, Brogan Inc., Ottawa, ON: personal communication, May 8, 2008*).

The proposal from Brogan Inc. for assessing utilization of second-line antidiabetes drugs is presented in Appendix 9.

6.4.2 Target drugs

New users of metformin therapy will be identified in the index period (see section 6.4.3). Course of therapy taken by patients inadequately controlled on metformin monotherapy will be stratified into groups, and combination therapy will be stratified based on therapeutic subclass (see below). Thiazolidinediones and insulins will be further broken down into subgroups:

- Thiazolidinediones
  - Pioglitazone
  - Rosiglitazone
- Insulins — all generic and brand name insulins
  - Rapid-acting insulin analogue
  - Long-acting human insulin analogue
  - Short-acting human insulin
  - Intermediate acting human insulin
  - Biphasic human insulin
  - Biphasic rapid-acting insulin analogue
- Incretin agents
- Sulfonylureas
- Alpha-glucosidase inhibitors
- Lipase inhibitors
- Meglitinides

- Combination oral antidiabetes drugs, broken down by chemical
- Other oral antidiabetes drugs.

6.4.3 Time period

The analysis will cover a nine-year period beginning January 1, 2000 and ending December 31, 2008. The study cohort will be tracked as follows:

- Index period for patient identification: January 1, 2005 to December 31, 2005.
- One-year time window (for each patient) to verify that patients are new to metformin therapy: for example, January 1, 2004 to December 31, 2004 (i.e., the patient must have no claims for any drug on the Target Drug List for 12 months prior to the follow-up period).
- Three-year follow-up period (for each individual patient) for core analysis: for example, January 1, 2006 to December 31, 2008.

6.4.4 Data analysis

New-to-therapy metformin patients will be identified during the first year and tracked for up to three years. Their claims will be analyzed from initiation of metformin monotherapy up to the earlier of the point of inadequate control of therapy or the end of the study period.

For the purposes of this study, inadequately controlled on metformin monotherapy will be defined as the first instance of an add-on or switch to diabetes management therapy from the target drug list (see Section 6.4.2). Switches and add-ons will be determined based on Brogan Inc.'s proven RxDynamics methodology.[72] Patients who are classified as an "add-on" will have a claim for metformin in the subsequent 90 days, whereas those classified as a "switch" will not (Ryan Long, Brogan Inc., Ottawa, ON; personal communication, April 10, 2009). Patients who terminate metformin monotherapy before the end of three years but neither add-on nor switch to additional therapies will be excluded from the study.

Results will be stratified by age, sex, geographical region (private drug plan data only), and course of therapy taken after inadequate control on metformin monotherapy. Summary statistics will be reported for each stratum, including average and median duration of metformin monotherapy (with standard deviations and interquartile ranges, respectively), number of patients, and percentage of patients relative to the total.

6.5 Current Practice

To understand how antidiabetes drugs are currently prescribed and used in the treatment of patients with type 2 diabetes mellitus in Canada inadequately controlled on metformin monotherapy, a qualitative approach will be employed. Specifically, data derived from focus groups of health care providers and patients will be used to identify and highlight current practice and perceptions surrounding the use of second-line antidiabetes drugs.

This portion of the project will be conducted under contract by Vision Research Inc. Copies of the moderator guides for health professionals and patients are provided in Appendix 10 and Appendix 11 respectively. Development of interview questions will be guided by the results of a comprehensive literature review and consultation with members of CADTH, CERC, and CAC and staff at Vision Research Inc.

Vision Research Inc. will use a thematic analysis approach to analyze the findings. Data from the focus groups will be sorted manually based on the overall direction of each response. A team of experienced analysts at

Vision Research Inc. will review the notes and audio tapes of all groups and summarize the results, noting any areas of consensus or directionality. Themes will be identified based on prevalence among the responses of all participants and organized around the structure of the moderator's guide. In analyzing the data, the focus will be not only on prevalence but also on range, indicating where participants diverged and noting the variety of responses. Questions around which a large majority of respondents agree, questions that prompt a split response (noting the two or three themes most prevalent), and questions that generate no consensus whatsoever (though these are rare, given the professional homogeneity of the group) will be identified and described. Underlying themes that emerge across the various groups studied and across questions will also be identified. Representative responses from the focus group participants will be used to support the findings of the analysis.

6.6 Identification of Gaps and Key Messages

The processes related to identification of gaps, development of key messages to close those gaps through development of intervention tools, and the implementation of the tools are part of the knowledge exchange planning process. A generic Knowledge Exchange Plan is available that guides the process for each individual COMPUS project — in this case, second-line therapy for patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. The generic plan identifies the types of interventions, related audiences, and potential tools that would be considered and adapted for each topic. The relative effectiveness of the interventions is well documented in the *Rx for Change* interventions database. *Rx for Change* is a publicly accessible database (www.rxforchange.ca) for health care policy-makers and health care professionals. It provides easy access to current research evidence about the effectiveness of strategies and programs to improve drug prescribing and use.

6.6.1 Gaps in practice

This phase of the project will address the following questions:

- What are the differences between recommendations for optimal prescribing and use of second-line antidiabetes drugs in the treatment of patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy (based on the available clinical and economic evidence), and current utilization and practice?
- Which of the identified gaps are practice gaps and which are knowledge gaps?

  Knowledge and practice gaps related to the use of second-line antidiabetes drugs in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy will initially be identified by CADTH and validated by CERC and CAC members through comparison of the Current Practice and Current Utilization analyses with the Optimal Therapy Recommendations developed by CERC. This analysis will focus on identifying the following:
- Discrepancies between the recommendations and actual practice, as indicated by the utilization data and responses in the Current Practice analysis. Quantitative patterns from the utilization analysis will be compared with the recommendations to identify evidence of suboptimal use.
- Discrepancies between the recommendations and perceptions regarding the optimal use of second-line antidiabetes drugs, as indicated by the Current Practice analysis. Prevalent views regarding the advantages or benefits of the optimal use of second-line antidiabetes drugs, and the clinical situations or patient groups for whom they might be useful, will be compared with the recommendations to identify perceptions that are not supported by the available evidence.
- Knowledge deficits with respect to the optimal use of second-line antidiabetes drugs identified in the Current Practice analysis.

6.6.2 Key messages

The identified gaps in practice and knowledge related to the use of second-line antidiabetes drugs will be scrutinized to determine relevancy to optimal prescribing and use of these agents. Issues to be considered include the following:

- What are the barriers to the implementation of recommendations for the optimal prescribing and use of second-line therapy for patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy?
- What action is needed to address those barriers?
- Are interventions and tools designed to address the gap likely to have significant impact, or is the gap unlikely to be amenable to change?
- Does the gap lend itself to the development and implementation of interventions, or is it difficult to address in a meaningful way?
- Would addressing the gap make a discernable difference in the prescribing and use of second-line antidiabetes drugs?

If multiple gaps are identified, they will be prioritized according to the urgency of the attention they require; that is, those most relevant to the optimal prescribing and use of second-line antidiabetes drugs. This will enable a focused approach to addressing gaps in practice and knowledge related to the optimal use of second-line antidiabetes drugs.

For gaps identified as being of highest priority, key messages related to the gaps will be developed based on the optimal therapy recommendations. When developing key messages, consideration will be given to the intended audiences, barriers to change, and how those barriers could potentially be overcome as well as factors favouring change (i.e., enablers). In addition, key messages are formulated as intended behaviour change statements where possible, rather than solely knowledge acquisition / reinforcement statements, and they are crafted in such a way that, where possible, behaviour change targets are measurable.

a) Feedback

A draft report outlining the identified gaps and key messages will be posted on the CADTH website to elicit stakeholder feedback. Feedback will also be sought from target audiences (ideally through focus groups); for example, physicians, pharmacists, diabetes educators, and patients with diabetes. CADTH will also solicit input from the Canadian Academic Detailing Collaboration, CADTH Liaison Officers, advisory committees (CERC and CAC), and focus groups as part of this process. All feedback will be collated by CADTH staff and considered by CERC and CAC as the final key messages are developed.

6.6.3 Intervention tools

In conjunction with CERC and CAC, CADTH will identify and explore barriers to the realization of the key messages and develop a collection of evidence-informed intervention tools and materials to address those barriers. The approach to development of intervention tools has been to start with the suite of tools developed for previous projects and augment these offerings with additional interventions specific to the new topic and target audiences. CADTH will solicit input from the Canadian Academic Detailing Collaboration, CADTH Liaison Officers, advisory committees (CERC and CAC), and focus groups as part of this process.

These interventions may include presentations, newsletters, prescribing aids, and academic detailing support materials. CADTH does not implement these interventions, because delivery of health care is a

jurisdictional responsibility. For this reason, a suite of intervention tools is developed to meet a variety of needs, from simple to complex interventions, and to meet health care professional and policy-maker needs.

The following steps describe the process for development of the intervention tools:

- Target audiences are identified and confirmed.
- Types and variety of tools required for the different audiences are identified and confirmed.
- Current suite of tools is validated as the starting point.
- Input is sought from CAC, CERC, the Canadian Academic Detailing Collaboration, CADTH Liaison Officers, and focus groups regarding additional intervention tools.
- A combination of external contractors and internal knowledge transfer resources are utilized to develop intervention tools.
- Content of the tools is adapted and presented at levels appropriate for each of the targeted audiences and to meet the needs of multiple users and interventionists.
- The accuracy of the information contained in all tools is validated by the COMPUS Project Team.

Draft versions of all tools will be provided to CERC and CAC for their input prior to circulation for stakeholder input. Stakeholder feedback on each tool may be elicited through a posting on the CADTH website, depending upon the tool's content. Stakeholder feedback will be collated by CADTH staff and considered by CERC and CAC as appropriate.

6.6.4 Evaluation of tools

A Generic Evaluation Framework is available on the CADTH website (www.cadth.ca) to guide CADTH and users of CADTH products in evaluation activities, from simple survey tools to more complex impact evaluations. The framework considers a variety of parameters that can be evaluated, recognizing that each of the parameters may not be applicable for each of the groups — such as the interventionists, jurisdictions, or CADTH — and thus, not each needs to be evaluated by each group. Some of the parameters that are considered include:

- Scope, usage, and reach: extent of dissemination and uptake of tools
- Awareness
- Perceived value and quality of the tools and interventions
- Enablers and barriers to implementation
- Sustainability: the cost-effectiveness of implementing the interventions
- Changes in attitudes, skills, and knowledge
- Changes in behaviour: prescriber and patient
- Changes in health outcomes (may not be feasible in all jurisdictions; may not be measurable in the short term)
- Changes in economic outcomes
- Changes in jurisdictional drug plan policies.

6.6.5 Implementation of tools

Implementation of these tools by jurisdictions, health care providers, and educators will serve to promote the optimal use of second-line antidiabetes drugs in patients with type 2 diabetes mellitus in Canada inadequately controlled on metformin monotherapy.

6.6.6 Tool adaptation

CADTH offers a tool adaptation service. In this way, the core suite of intervention tools may be modified to meet specific jurisdictional and other needs. Presentations for physicians and pharmacists are the most common tools adapted; however, newsletters and prescribing aids are other examples where adaptation has been requested.

All adapted tools are subject to a scientific validation by CADTH to ensure the content is an accurate representation of the evidence.

7 PROTOCOL MODIFICATIONS

Major modifications required after posting of this project protocol will be made using the Change Request Form presented in Appendix 12.

8 EXECUTION OF THE PROJECT

To promote timely execution of this project, roles and responsibilities for individual project members have been formulated, and the structure of the project has been drafted.

Major modifications to this protocol will be documented using the Change Request Form (Appendix 12).

9 DELIVERABLES

On completion of this project, reports and intervention tools will be made available on the CADTH website at http://www.cadth.ca/index.php/en/compus.

The reports will include:

- Systematic review of the clinical evidence surrounding optimal use of second-line antidiabetes drugs in patients with diabetes inadequately controlled on metformin
- Pharmacoeconomic analysis of second-line antidiabetes drugs in patients with diabetes inadequately controlled on metformin
- Current utilization analysis of second-line antidiabetes drugs in Canada
- Current practice analysis of second-line antidiabetes drugs in Canada
- Optimal therapy recommendations for the use of second-line therapy for patients with diabetes inadequately controlled on metformin
- Gap analysis and key messages report
- Project summary reports (Overview and Project in Brief, with an Executive Summary if warranted).

The final selection of intervention tools to be developed may include:

- Physician education sessions — didactic and interactive
- Physician education materials — newsletters, alternative prescription pad, quick reference prescribing aid
- Pharmacist education sessions — didactic and interactive
- Patient education materials — patient information brochure
- Academic detailing tools
- Others as directed.

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APPENDIX 1: Antidiabetes Drugs Used in the Management of Type 2 Diabetes Mellitus (except metformin, which was used as the first-line therapy)*

Sulfonylureas
Gliclazide (Diamicron, Diamicron MR, Gen-Gliclazide, PMS-Gliclazide)
Glimepiride (Amaryl)
Glyburide/Glibenclamide (Diabeta, Euglucon, Gen-Glybe, Novo-Glyburide, Nu-Glyburide, PMS-Glyburide, ratio-Glyburide, Sandoz Glyburide)
Chlorpropamide (APO-Chlorpropamide)
Glipizide (Glucotrol, Glucotrol XL, Glipizide XL)
Tolbutamide (APO-Tolbutamide)

Thiazolidinediones (TZDs)
Pioglitazones (Actos, CO Pioglitazone, Gen-Pioglitazone, PMS-Pioglitazone, ratio-Pioglitazone, Sandoz Pioglitazone)
Rosiglitazone (Avandia) and combined formulations: Rosiglitazone with metformin (Avandamet)
Combined formulations: Rosiglitazone with Glimepiride (Avandaryl)

Meglitinides
Nateglinide (Starlix)
Repaglinide (GlucoNorm)

Alpha-glucosidase inhibitors
Acarbose (Glucobay)
Miglitol (Glyset)

Incretin agents
Sitagliptin (Januvia)
Vildagliptin (Galvus)
Exenatide (Byetta)

Amylin analogue
Pramlintide (Symlin)

Weight-loss agents
Orlistat (Xenical)
Sibutramine (Meridia)

Insulins

*Miglitol, vildagliptin, exenatide, and pramlintide were identified from available guidelines and systematic reviews, but are not available in Canada.

Rapid-acting insulin analogues
Aspart (NovoRapid)
Lispro (Humalog)
Glulisine (Apidra)

Rapid-acting human insulin
Regular human insulin (Humulin-R, Novolin ge Toronto)

Intermediate-acting insulin
NPH (Humulin-N, Novolin ge NPH)

Long-acting insulin analogues
Detemir (Levemir)
Glargine (Lantus)

Premixed insulins
Premixed regular NPH (Humulin 30/70, Novolin ge 30/70, 40/60, 50/50)
Biphasic insulin aspart ([NovoMix 30] Insulin)
Biphasic insulin lispro (Humalog Mix25, Mix50)

APPENDIX 2: Search Strategy for Systematic Reviews and Meta-analyses

OVERVIEW	
Interface:	Ovid
Databases:	EMBASE <1996 to 2009 Week 12>; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 13, 2006>; Ovid MEDLINE(R) <1966 to March Week 3 2009> * Note: Subject headings have been customized for each database.
Date of Search:	March 19, 2009
Alerts:	None
Study Types:	Systematic reviews; meta-analyses; technology assessments
Limits:	Publication years 1990-present
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
$	Truncation symbol, or wildcard: retrieves plural or variations of a word
*	Indicates that the marked subject heading is a primary topic
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

#	Searches	Results
1	Diabetes Mellitus/	72,746
2	exp Diabetes Mellitus, Type 2/	52,962
3	Lipoatrophic Diabetes Mellitus/	165
4	((adult onset or ketosis-resistant or maturity-onset or late-life or non-insulin dependent or noninsulin dependent or slow-onset or stable or type 2 or type II or lipoatrophic) adj2 diabet$).ti,ab.	52,684
5	(Mody or niddm).ti,ab,hw.	7,266
6	or/1-5	136,703
7	((first or second or third) adj2 (line or therapy or therapies or treatment or treatments or agent or agents or drug or drugs or pharmaceutical or pharmaceuticals)).ti,ab.	49,017
8	(lines of therapy or treatment failure or algorithms or algorithm).ti,ab.	82,945
9	or/7-8	130,883
10	6 and 9	1,259
11	Metformin/	3,777
12	Metformin?.ti,ab,rn,hw.	5,328
13	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab,rn.	74
14	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novo-metformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab,rn.	98
15	(Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab,rn.	84
16	(Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmgg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or Dimethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab,rn.	176
17	(657-24-9 or 1115-70-4).rn.	3,777
18	or/11-17	5,545
19	Treatment Failure/	17,988
20	18 and 19	43
21	((fail or failed or failing or failure or inadequately or poorly controlled or resistance or resistant or intolerance or intolerant or contraindications or contraindication or suboptimally controlled or refractory) adj4 metformin).ti,ab.	342
22	20 or 21	374
23	10 or 22	1,609
24	meta-analysis.pt.	20,575
25	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/	36,097
26	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or	22,589

#	Searches	Results
	overview*))).ti,ab.	
27	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.	3,335
28	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.	5,289
29	(data synthes* or data extraction* or data abstraction*).ti,ab.	7,700
30	(handsearch* or hand search*).ti,ab.	2,959
31	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.	8,029
32	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.	1,375
33	(meta regression* or metaregression* or mega regression*).ti,ab.	797
34	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	50,371
35	(medline or Cochrane or pubmed or medlars).ti,ab,hw.	40,858
36	(cochrane or health technology assessment or evidence report).jw.	6,564
37	(meta-analysis or systematic review).md.	0
38	or/24-37	101,197
39	23 and 38	89
40	limit 39 to (english language and yr="1990 - 2009")	81

EMBASE 1988 to 2009 Week 12

#	Searches	Results
1	*Maturity Onset Diabetes Mellitus/	450
2	*Non Insulin Dependent Diabetes Mellitus/	34,883
3	*Lipoatrophic Diabetes Mellitus/	51
4	((adult onset or ketosis-resistant or maturity-onset or late-life or non-insulin dependent or noninsulin dependent or slow-onset or stable or type 2 or type II or lipoatrophic) adj2 diabet$).ti,ab.	45,614
5	(Mody or niddm).ti,ab.	6,195
6	or/1-5	53,040
7	((first or second or third) adj2 (line or therapy or therapies or treatment or treatments or agent or agents or drug or drugs or pharmaceutical or pharmaceuticals)).ti,ab.	42,885
8	(lines of therapy or treatment failure or algorithms or algorithm).ti,ab.	58,665
9	or/7-8	100,527
10	6 and 9	868
11	*Metformin/	3,290
12	Metformin?.ti,ab.	4,319
13	(dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab.	58
14	(apo-metformin or apotex or genmetformin or glucophage or glumetza or novo-	77

#	Searches	Results
	metformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab.	
15	(Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab.	52
16	(Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmgg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or Dimethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab.	62
17	(657-24-9 or 1115-70-4).rn.	13,435
18	or/11-17	13,680
19	Treatment Failure/	37,978
20	"Add on Therapy"/	4,064
21	or/19-20	41,909
22	18 and 21	492
23	((fail or failed or failing or failure or inadequately or poorly controlled or resistance or resistant or intolerance or intolerant or contraindications or contraindication or suboptimally controlled or refractory) adj4 metformin).ti,ab.	325
24	22 or 23	775
25	10 or 24	1,584
26	meta-analysis.pt.	0
27	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/	52,739
28	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.	18,704
29	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.	2,306
30	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.	3,942
31	(data synthes* or data extraction* or data abstraction*).ti,ab.	7,375
32	(handsearch* or hand search*).ti,ab.	1,647
33	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.	4,184
34	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.	1,112
35	(meta regression* or metaregression* or mega regression*).ti,ab.	622
36	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	67,485
37	(medline or Cochrane or pubmed or medlars).ti,ab,hw.	35,616
38	(cochrane or health technology assessment or evidence report).jw.	2,829
39	(meta-analysis or systematic review).md.	0
40	or/26-39	101,861

#	Searches	Results
41	25 and 40	142
42	limit 41 to (english language and yr="1990 - 2009")	133

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 1; 2009	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature and Hand Searches

Dates for Search:	March 2009
Keywords:	Metformin failure, lines of therapy, second line therapy, diabetes

This section lists the main agencies, organizations, and websites searched; it is not a complete list.

Health Technology Assessment Agencies

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS), Quebec
http://www.aetmis.gouv.qc.ca

Canadian Agency for Drugs and Technologies in Health (CADTH)
http://www.cadth.ca

Health Technology Assessment International (HTAi)
http://www.htai.org

International Network of Agencies for Health Technology Assessment (INAHTA)
http://www.inahta.org

NHS Health Technology Assessment /National Coordinating Centre for Health Technology Assessment (NCCHTA), Department of Health, R&D Division
http://www.ncchta.org

NHS National Institute for Health and Clinical Excellence (NICE)
http://www.nice.org.uk

University of York NHS Centre for Reviews and Dissemination (NHS CRD)
http://www.york.ac.uk/inst/crd

The Wessex Institute for Health Research and Development, Succinct and Timely Evaluated Evidence Review (STEER)
http://www.wihrd.soton.ac.uk/

Agency for Healthcare Research and Quality (AHRQ)
http://www.ahrq.gov/

Department of Veterans Affairs Research & Development, general publications
http://www.research.va.gov/resources/pubs/default.cfm

VA Technology Assessment Program (VATAP)
http://www.va.gov/vatap/

ECRI
http://www.ecri.org/

Search Engines

Google
http://www.google.ca/

APPENDIX 3: AMSTAR* — Systematic Review Quality Assessment Tool

Project: Test Strips	Statement:	Author:
Title:		
Reviewer:		Date:
RefMan #:		**Total Score: /11**

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ **Yes** ☐ **No** ☐ **Can't answer** ☐ **Not applicable**
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ **Yes** ☐ **No** ☐ **Can't answer** ☐ **Not applicable**
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms should be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ **Yes** ☐ **No** ☐ **Can't answer** ☐ **Not applicable**
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language, etc.	☐ **Yes** ☐ **No** ☐ **Can't answer** ☐ **Not applicable**
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ **Yes** ☐ **No** ☐ **Can't answer** ☐ **Not applicable**
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ **Yes** ☐ **No** ☐ **Can't answer** ☐ **Not applicable**
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ **Yes** ☐ **No** ☐ **Can't answer** ☐ **Not applicable**
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ **Yes** ☐ **No** ☐ **Can't answer** ☐ **Not applicable**
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ **Yes** ☐ **No** ☐ **Can't answer** ☐ **Not applicable**
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ **Yes** ☐ **No** ☐ **Can't answer** ☐ **Not applicable**
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both terms of the systematic review and the included studies.	☐ **Yes** ☐ **No** ☐ **Can't answer** ☐ **Not applicable**

*Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews.[29]

APPENDIX 4: Forms for Existing Systematic Reviews

Appendix 4–1: General Information of All Included Systematic Reviews and Meta-analyses

Author / Year	Source of Publication	Organization	Source of Funding	Number of Studies Included in SR	Type of Studies Included in SR	Quality Score
SR1						
SR2						
…						
SRn						

SR = systematic review.

Appendix 4–2: Key Information of Good-Quality Systematic Reviews and Meta-analyses Included

Author / Year	Search Period	Data-base	Restric-tion (e.g., language)	Availa-bility of Search Strategy	Popu-lation	Inter-vention	Compa-rator	Out-come	Research Question	Key Results / Meta-analysis	Subgroup Analysis / Data Description	Quality Score
SR1												
SR2												
…												
SRn												

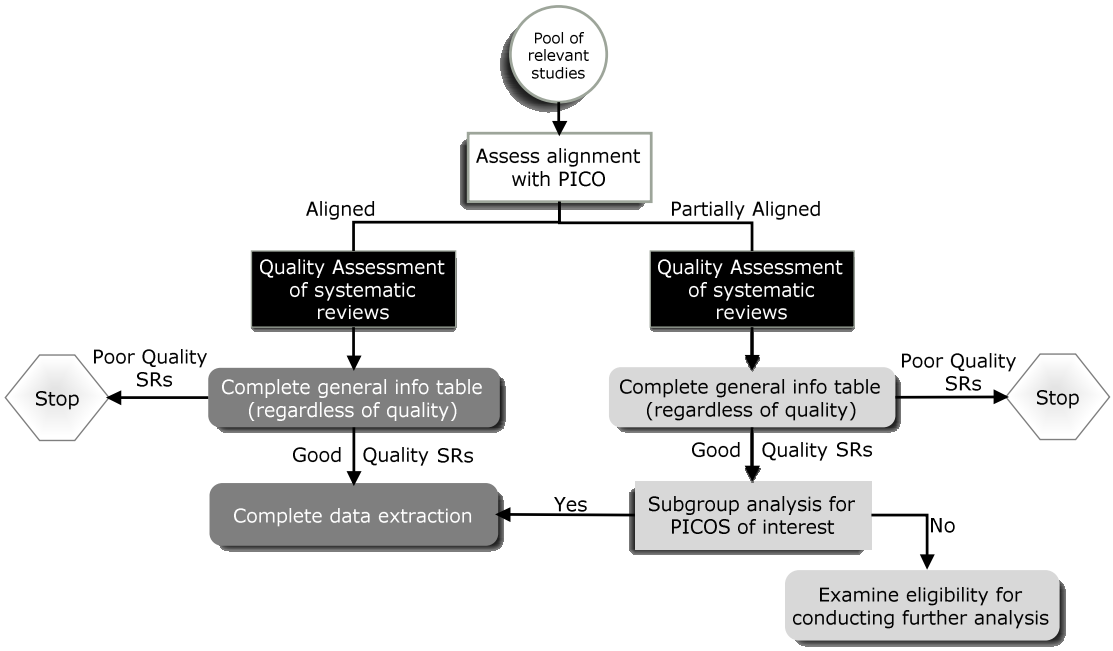
SR = systematic review.

Appendix 4–3: Comparative List of Primary Studies Included in Good-Quality Systematic Reviews and Meta-analyses Passing Applicability Assessment

Primary Studies Included		High-Quality Systematic Reviews Included						
Author	Publication Year	SR1 (author, year)	SR2	SR3	SR4	SR5	…	SRn
Study 1		•						
Study 2								
Study 3		•						
…								
Total no. of studies included		2						
Types of studies included		RCTs						

RCT = randomized controlled trial; SR = systematic review.

Appendix 4–4: Overview of Process for Assessing the Applicability of Existing Systematic Reviews and Meta-analyses



PICO = Patient, Intervention, Comparison and Outcome; SRs = systematic reviews.

Appendix 4-5: Summary of the Applicability of Good-Quality Existing Systematic Reviews and Meta-analyses Included

Author /Year	COMPUS Recommendations	Rationale				Additional Comments
		Relevancy	Quality	Search Date	Degree of Effort to Update SR	
SR1						
SR2						
...						
SRn						

COMPUS = Canadian Optimal Medication Prescribing and Utilization Service; SR = systematic review.

APPENDIX 5: SIGN 50* — Randomized Controlled Trial Quality Assessment Tool

Project: Test Strips		Statement #:		Author:
Title:				
Reviewer:		Date:		**RefMan #:**
SECTION 1: Internal validity				
In a well conducted RCT study…		In this study this criterion is:		
1.1	The study addresses an appropriate and clearly focused question.	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.2	The assignment of subjects to treatment groups is randomised	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.3	An adequate concealment method is used	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.4	Subjects and investigators are kept 'blind' about treatment allocation	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.5	The treatment and control groups are similar at the start of the trial	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.6	The only difference between groups is the treatment under investigation	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.7	All relevant outcomes are measured in a standard, valid and reliable way	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?			
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
1.10	Where the study is carried out at more than one site, results are comparable for all sites	☐ Well covered ☐ Adequately addressed	☐ Poorly addressed ☐ Not reported	☐ Not applicable ☐ Not addressed
Section 2: OVERALL ASSESSMENT OF THE STUDY				
2.1	How well was the study done to minimise bias? Code ++, +, or –		-	
SECTION 3: OTHERS				
3.1	How was this study funded? *List all sources of funding quoted in the article, whether government, voluntary sector, or industry.*			

* *SIGN 50: A guideline developers' handbook.*[30]

APPENDIX 6: Data Extraction Fields Contained in the Pre-designed Data Extraction Form

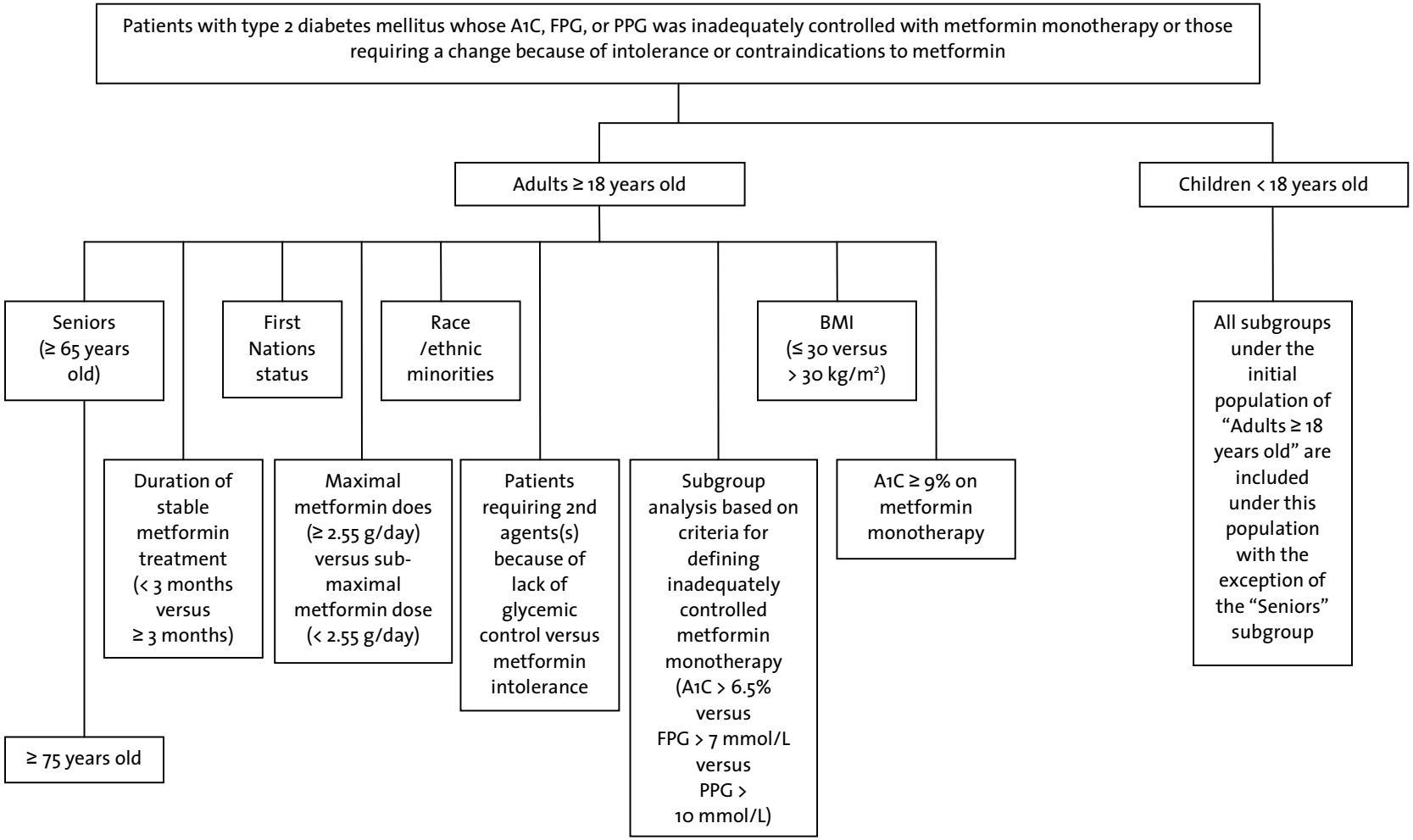
Characteristics of studies and patients

- Reference Manager ID
- Author
- Publication year
- Publication status (full article / abstract)
- Country
- Sponsor/funding
- Type of study
- Subgroup
- Inclusion/exclusion criteria
- Intervention and comparator (dosing, frequency, and duration)
- Randomized sample size
- Dropout rate
- ITT or non-ITT
- Age
- Male/total patients
- Ethnicity
- Duration of diabetes
- History of diabetes-related complications
- Smoking history
- Metformin dosage at baseline
- Duration of stable metformin therapy
- Contamination with other oral antidiabetes drugs
- Metformin failure (inadequate control, intolerance, contraindication)
- Criteria for metformin failure (A1C > 6.5%, FPG > 7 mmol/L, two-hour postprandial glucose > 10 mmol/L)
- Definition of overall, severe, and nocturnal hypoglycemia

Outcome information

- **A1C, Weight /BMI** (number of patients, mean, and standard deviation (SD) / standard error (SE) at baseline and end of treatment; difference of mean with SD/SE from baseline to end of treatment)
- **Overall /severe/nocturnal hypoglycemia, pancreatitis — for incretin agents only, upper extremity fractures / macular edema — for TZDs only** (number of patients, time period, mean of the number of episodes/patient / time period, SD/SE, number of patients who had at least one episode / time period)
- **Diabetes-specific health-related quality of life / generic health-related quality of life, patient satisfaction with diabetes care / diabetes treatment** (instruments, number of patients, mean, and SD/SE at baseline and end of treatment; difference of mean with SD/SE from baseline to end of treatment)
- **Serious adverse events and complications** — congestive heart failure, ischemic heart disease, all-cause mortality, nephropathy, neuropathy, peripheral vascular disease, retinopathy, stroke / transient ischemic attack (definition, number of total patients, number of patients with events).

APPENDIX 7: Evaluation Structure for Second-Line Therapy in Patients with Diabetes Inadequately Controlled on Metformin



A1C = glycosylated hemoglobin; BMI = body mass index; FPG = fasting plasma glucose; PPG = post-prandial plasma glucose.

APPENDIX 8: Sample GRADE Evidence Profile

Number of Studies	Quality Assessment						Summary of Findings					Importance of Outcome
							No. of Patients		Effect		Quality of Evidence	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Intervention	Comparator	Relative (95% CI)	Absolute		
Outcome 1												
Outcome 2												
Outcome 3												

CI = confidence interval.

APPENDIX 9: Proposal from Brogan Inc. to Study Current Utilization of Second-Line Antidiabetes Drugs in Canada

Objective
The objective of the study will be to identify patients who are not adequately controlled on metformin monotherapy and stratify them based on demographic (age, sex, region) and utilization patterns.

The following items will be reported:
- A 3-year study cohort described below
- The total number of metformin monotherapy patients in the cohort
- The median of the daily dose from the last metformin monotherapy claim for each sub-group of the cohort, and the total median across the entire cohort.

Time Period
The analysis will cover a four-year period beginning January 1, 2005 and ending December 31, 2008.
One study cohort will be tracked as follows:
- Index Period for patient identification (see Outline and Delivery): Jan. 1, 2005 to Dec. 31, 2005.
- One-year time window (for each patient) to verify that patients are new-to-therapy: e.g., Jan. 1, 2004 to Dec. 31, 2004. (I.e. Patient must have no claims for any drug on the Target Drug List for 12 months prior to the follow-up period.)
- Three-year follow-up period (for each individual patient) for core analysis: Jan. 1, 2006 to Dec. 31, 2008

Data Source
Data used in the analysis will come from Brogan Inc.'s public and private claims-level database warehouse. Public data will be reported for Ontario only. Private drug plan data will be reported by region.

Note: Brogan Inc. presents aggregated data in all reports to prevent the indirect identification of individuals. Information in the cells where there are 5 or fewer observations will be suppressed and indicated with a value of 3. The reports will not contain any personal information.

Target Drugs
Target drugs for this study shall be separated into groups, and combination therapy, based on therapeutic subclass. Only glitazones and insulins will be further broken down into sub-groups (see below):

1. Metformin – all brand and generic variants of metformin HCl
2. Glitazones
   a. Pioglitazone
   b. Rosiglitazone
3. Insulins – all generic and brand insulins
   a. Very rapid-acting and rapid-acting insulin analogue
   b. Long-acting human insulin analogue
   c. Short-acting human insulin
   d. Intermediate-acting human insulin
   e. Long-acting human insulin
   f. Multi-phasic human insulin
   g. Multi-phasic insulin analogue
4. DPP-4 Inhibitors
5. Sulfonylureas

6. Alpha-glucosidase inhibitors
7. Lipase inhibitors
8. Meglitinides
9. Combination OAD drugs
10. Other OAD drugs

Outline and Delivery

Note: New-to-therapy metformin patients will be identified during the first year and tracked for up to three years. Their claims will be analyzed from initiation of metformin therapy up to the earlier of (a) the point of inadequate control (failure of therapy) or (b) the end of the study period.

For the purposes of this study, "inadequately controlled on metformin monotherapy" will be defined as the first instance of an add-on or switch to an additional diabetes management therapy from the target drug list (see above). Switches and add-ons will be determined based on Brogan Inc.'s proven RxDynamics methodology, using a 90-day window after failure of metformin monotherapy.

Patients who terminate metformin monotherapy before the end of three years, but neither add-on nor switch to additional therapies will be excluded from the study.

Patients will then be stratified by age, sex, geographical region (PDP data only), and course of therapy taken after inadequate control on metformin monotherapy. Summary statistics will be reported for each strata, including average and median metformin monotherapy length (standard deviation and interquartile range), number of patients, and percentage of patients relative to the total.

Median Daily Dose

Daily dose will be determined by each patient's last claim of metformin monotherapy, prior to an add-on or switch. The median of this calculation will be reported for each strata below, as well as for the overall 3-year cohort.

Final delivery of this analysis will be a spreadsheet aggregating data by age group, sex, and course of therapy (ODB and PDP data), and geographical region (PDP data only). The breakdown for aggregation will be as follows:

Age Groups

- <15
- 15-24
- 25-44
- 45-64
- 65 or older

Regions[3]

- West
- Ontario
- Quebec
- East

Sex

- Male
- Female

Post-Metformin-Monotherapy Utilization (see target drug list classification schema above)

- Add-on
- Switch

[3] Patients will be broken down by province if there is sufficient data for statistically meaningful results. Otherwise, geographic region will be used.

APPENDIX 10: Moderator's Guide for Focus Groups — Health Professionals

Moderator's Guide - Prescribers

This moderator's guide will be used for focus groups and/or interviews with medical specialists, family physicians and nurse practitioners.

1.0 Introduction

1.1 Before we start, I would like to explain a few things about this study and today's focus group.

- The group will last 60 to 90 minutes.
- There will be observers from CADTH behind the mirror, who are observing so they can see and hear your comments first-hand and learn as much as possible from the study.
- The group will be audio-recorded to allow for a more detailed report; audio files will remain the property of the research firm and will be erased after 12 months.
- Participation in the group is strictly voluntary and participants need not answer any question that makes them feel uncomfortable.
- The identity of participants will be kept confidential in all aspects of the study and in the final report.
- The study is being undertaken by the Canadian Agency for Drugs and Technologies in Health (CADTH) – a not-for-profit agency funded by the federal and provincial governments and mandated by them to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies.
- This study is focusing on the diabetes management topic area.

1.2 Are there any questions or concerns related to this study?

2.0 Second-Line Therapy

I'd like to start by asking you some questions about your opinions and current practice regarding second-line therapy after a patient's metformin therapy has failed.

2.1 For approximately what percentage of patients with type 2 diabetes do you prescribe metformin monotherapy as initial antihyperglycemic therapy? What prompts to opt for this treatment?

2.2 What criteria do you use to determine whether treatment with metformin monotherapy is successful? What constitutes failure of metformin monotherapy?

Probe for: Do you always use the A1c as a surrogate for evaluating treatment efficacy?
Probe for: If so, why? If not, what other markers do you use (i.e. fasting blood glucose, post-prandial blood glucose) and why do you prefer these?

2.3 What is the maximal dose and duration of metformin you will normally try before deciding to add or switch to a second agent?

Probe for: Is a second agent added to metformin, or is metformin discontinued once the second agent is started? Why do you prefer this approach?

2.4 What class of second-line agents do you normally use when adding to, or switching from, metformin?

2.5 Are there particular circumstances under which you would opt for a newer oral antihyperglycemic class (i.e., TZDs or DPP-4 inhibitors) instead of using an agent from an older class (e.g., sulfonylureas) as second-line therapy?

2.6 What are your thoughts on the relative merits of the oral agents? Are there particular oral agents you feel are better than others in terms of:

Overall **efficacy**?
The risk of **weight gain**?
The risk of **hypoglycemia**?
The **cost of therapy** and the patient's drug coverage?
The **patient preference**?

2.7 Under what circumstances do you opt to add or switch to insulin as a second-line therapy instead of an oral agent?

Probe for: preferences regarding prandial (bolus), basal, basal-bolus combinations, or premixed insulins as second-line therapy

2.8 Generally speaking, do you feel your patients are able to access appropriate second-line therapies when these therapies are required? If not, what do you perceive as barriers?

Probe for: Formulary restrictions, cost, adherence issues, self-management/burden of care/caregiver issues?

2.9 What would you say are the primary sources of information you use to guide your choice of second-line therapies in type 2 diabetes?

Probe for: Information from **pharmaceutical companies**
Probe for: **CDA** Guidelines

2.10 What are your thoughts regarding the available evidence to guide choice of second-line agents? Are there any issues, uncertainties or controversies you would like to see more information on? If yes, please explain.

2.11 What is your preferred method of receiving information on second-line treatments?

Probe for: Written materials, workshops, lectures, journal articles

3.0 Key Messages Related to SMBG

I'd now like to change topics a little. We'll stay on the topic of diabetes but switch to self-monitoring of blood glucose using test strips. This is a topic that CADTH has been studying for some time now, and their findings have led them to create a series of key messages to inform prescribers and other care providers when it comes to counselling patients on the use of test strips to self-monitor their blood glucose. I will share these key messages with you in just a minute, but first let me ask you a few questions about diabetes management.

3.1 What role does self-monitoring of blood glucose have in managing your patient's diabetes?

3.2 What is your current practice regarding SMBG?

Now I'd like to share CADTH's key messages that have been developed to inform patients, prescribers and others on the use of test strips to self-monitor blood glucose and give you a chance to tell me what you think of them.

<Moderator distributes copies of key messages and allows three minutes to read.>

3.3 What is your first reaction to these messages? How do you feel when you read them?

3.4 Do these messages contain information or positions that are new to you? Do they run counter to the way you currently prescribe self-monitoring of blood glucose?

3.5 How clear/persuasive are these messages? As a whole, are they convincing enough to get you to rethink your current position on self-monitoring of blood glucose? Why or why not? What can be done to improve them?

3.6 How important is it to you that these key messages are supported by evidence? Specific references?

3.7 In your opinion, what would be the most effective way to communicate these key messages? How can we get these messages in front of prescribers, pharmacists, diabetes educators and patients in a way that will get their attention, be credible and be persuasive?

Probe: Source – radio; newspaper; tv; Dr.'s office; social media; etc.

3.8 In your opinion, are there any barriers that would prevent you from aligning your practice with these key messages? What obstacles might you encounter?
Do you have suggestions for solutions to these obstacles?
Probe: strategies; ideas; how to get key influencers to buy in

3.9 Do you have suggestions for doctors on how to change their practice?

How would you change *your* practice? How long would it take? What support would you need? (e.g. email; posters; pamphlet; grand rounds; etc.)

3.12 If you were to change your practice to align with these messages, what might be the reaction from your patients? How would this kind of change affect them and why?

4.0 Conclusion

4.1 Does anyone have any final thoughts or comments on either second-line therapies for treating patients with type two diabetes, or on the key messages presented about self-monitoring of blood glucose? Anything you'd like to add to the discussion that hasn't come up yet?

Thanks very much for your participation today. I appreciate your time and your thoughts and remind you to see the receptionist on your way out to pick up your thankyou incentive.

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Moderator's Guide - Influencers

This moderator's guide will be used for focus groups and/or interviews with pharmacists and diabetes educators.

1.0 Introduction

1.1 Before we start, I would like to explain a few things about this study and today's focus group.

- The group will last 60 to 90 minutes.
- There will be observers from CADTH behind the mirror, who are observing so they can see and hear your comments first-hand and learn as much as possible from the study.
- The group will be audio-recorded to allow for a more detailed report; audio files will remain the property of the research firm and will be erased after 12 months.
- Participation in the group is strictly voluntary and participants need not answer any question that makes them feel uncomfortable.
- The identity of participants will be kept confidential in all aspects of the study and in the final report.
- The study is being undertaken by the Canadian Agency for Drugs and Technologies in Health (CADTH) – a not-for-profit agency funded by the federal and provincial governments and mandated by them to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies.

  This study is focusing on the diabetes management topic area.

1.2 Are there any questions or concerns related to this study?

2.0 Second-Line Therapy

I'd like to start by asking you some questions about your opinions regarding second-line therapy after a patient's metformin therapy has failed.

2.1 What are your thoughts on the relative merits of the oral agents used to treat patients with type two diabetes? Are there particular oral agents you feel are better than others in terms of efficacy, convenience or side-effect profile?

2.2 In your opinion, are there any advantages or disadvantages to using newer oral antihyperglycemic agents like a TZD or DPP-4 inhibitor as compared to using an older agent like a sulfonylurea as a second-line therapy once metformin has failed?

2.3 For Diabetes Educators Only:

What are your thoughts on using insulin in patients with type two diabetes, who have failed metformin? Under what situations (if any) should insulin be chosen rather than an oral agent as second-line therapy?

Probe for: preferences regarding prandial (bolus), basal, basal-bolus combinations, or premixed insulins as second-line therapy

2.4 In your opinion, what are the most important factors that should be considered when a prescriber is choosing a second-line therapy?

Probe for: How important is the risk of **weight gain**?
Probe for: How important is the risk of **hypoglycemia**?
Probe for: How important is the **cost of therapy** and the patient's drug coverage?
Probe for: How important is **patient preference**?

2.5 Generally speaking, do you feel patients with diabetes are able to access the appropriate second-line therapies they require? If not, what do you perceive as barriers?

Probe for: Formulary restrictions, cost

2.6 What are the primary sources of information you use to obtain guidance on the choice of second-line therapies in type 2 diabetes?

Probe for: Information from **pharmaceutical companies**
Probe for: **CDA** Guidelines

2.7 What are your thoughts regarding the available evidence to guide choice of second-line agents? Are there any issues, uncertainties or controversies you would like to see more information on? If yes, please explain.

2.8 What is your preferred method of receiving information on second-line treatments?

Probe for: Written materials, workshops, lectures, journal articles

3.0 Key Messages Related to SMBG

I'd now like to change topics a little. We'll stay on the topic of diabetes but switch to self-monitoring of blood glucose using test strips. This is a topic that CADTH has been studying for some time now, and their findings have led them to create a series of key messages to inform prescribers and other care providers when it comes to counselling patients on the use of test strips to self-monitor their blood glucose. I will share these key messages in just a minute, but first let me ask you a few questions about diabetes management.

3.1 What is your current practice regarding SMBG?

3.2 What role does self-monitoring of blood glucose have in managing your patient's diabetes?

CADTH has been working on a study of self-monitoring of blood glucose (SMBG) for time now and the results of their review of clinical- and cost-effectiveness has led them to draft a series of five key messages to inform prescribers, other care providers and patients with diabetes. Now I'd like to share CADTH's key messages on the use of test strips to self-monitor blood glucose and give you a chance to tell me what you think of them.

<Moderator distributes copies of key messages and allows three minutes to read.>

3.5 What is your first reaction to these messages? How do you feel when you read them?

3.6 Do these messages contain information or positions that are new to you? Do they run counter to the way you currently prescribe self-monitoring of blood glucose?

3.7 How clear/persuasive are these messages? As a whole, are they convincing enough to get you to rethink your current position on self-monitoring of blood glucose? Why or why not? What can be done to improve them?

3.8 How important is it to you that these key messages are supported by evidence? Specific references?

3.9 In your opinion, what would be the most effective way to communicate these key messages? How can we get these messages in front of prescribers, pharmacists, diabetes educators and patients in a way that will get their attention, be credible and be persuasive?
Probe: Source – radio; newspaper; tv; Dr.'s office; social media; etc.

3.10 In your opinion, are there any barriers that would prevent [pharmacists] / [diabetes educators] (depending on which focus group) from aligning their practice with these key messages? What obstacles might they encounter? Do you have suggestions for solutions to these obstacles?
Probe: strategies; ideas; how to get key influencers to buy in

3.11 Do you have suggestions for [pharmacists] / [diabetes educators] (depending on which focus group) on how to change their practice?

How would you change *your* practice? How long would it take? What support would you need? (e.g. email; posters; pamphlet; grand rounds; etc._

3.12 If [pharmacists] / [diabetes educators] (depending on which focus group) were to change their practice to align with these messages, what might be the reaction from patients? How would this kind of change affect patients and why?

4.0 Conclusion

4.1 Does anyone have any final thoughts or comments on either second-line therapies for patients with type two diabetes, or on the key messages regarding self-monitoring of blood glucose? Anything you'd like to add to the discussion that hasn't come up yet?

Thanks very much for your participation today. I appreciate your time and your thoughts and remind you to see the receptionist on your way out to pick up your thank-you incentive.

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APPENDIX 11: Moderator's Guide for Focus Groups — Patients

Moderator's Guide - Patients

This moderator's guide will be used for focus groups involving patients with type two diabetes.

1.0 Introduction

1.1 Before we start, I would like to explain a few things about this study and today's focus group.

- The group will last 60 to 90 minutes.
- There will be observers from CADTH behind the mirror, who are observing so they can see and hear your comments first-hand and learn as much as possible from the study.
- The group will be audio-recorded to allow for a more detailed report; audio files will remain the property of the research firm and will be erased after 12 months.
- Participation in the group is strictly voluntary and participants need not answer any question that makes them feel uncomfortable.
- The identity of participants will be kept confidential in all aspects of the study and in the final report.
- The study is being undertaken by the Canadian Agency for Drugs and Technologies in Health (CADTH) – a not-for-profit agency funded by the federal and provincial governments and mandated by them to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies.

This study is focusing on the diabetes management topic area.

1.2 Are there any questions or concerns related to this study?

2.0 Second-Line Therapy

I'd like to start by asking you some questions about your opinions regarding medications to control your blood glucose levels.

2.1 What medications do you currently use to control your blood glucose levels? How long were you on metformin and what prompted your doctor to suggest either addition of other agents or switch in therapy?

2.2 How did you feel when your doctor told you that you were going to need another medication to control your blood glucose levels?

2.3 Did you have any concerns when your doctor prescribed medication to lower your blood glucose?

Probe for: Were you concerned that some medications might be better or worse than others?
Probe for: Were you concerned about whether some drugs might make you gain more weight?
Probe for: Were you concerned that some drugs might make it more likely that you experience hypoglycaemia?

2.4 Do you feel your doctor took these concerns into account when prescribing blood glucose-lowering medications?

Probe for: Did you request that a particular medication be prescribed for you? If so, why?
Probe for: Did your doctor fulfill your request? Why or why not?

2.5 Have you looked for information on blood glucose-lowering medications in the past? If so, where did you find good information? What are the best sources out there?

Probe for: Specific websites, organizations, friends and family, advertising

2.6 Do you feel you have enough information on medications to lower your blood glucose levels? If not, how would you like to receive more information and from whom?

2.7 Do you feel you are receiving the blood glucose-lowering medications you need? If not, what might be preventing you from receiving the medications you need?

3.0 Key Messages Related to SMBG

I'd now like to change topics a little. We'll stay on the topic of diabetes but switch to self-monitoring of blood glucose using test strips. This is a topic that CADTH has been studying for some time now, and their findings have led them to create a series of key messages to inform prescribers and other care providers and their patients on the use of test strips to self-monitor blood glucose. I will share these key messages with you in just a minute, but first let me ask you a few questions about diabetes management.

3.1 How do you currently monitor your blood glucose, when, and how many times on an average day?

3.2 How important is this? To you? To your health care provider? Why?
Probe for rationale: Health care provider says so; I feel more in control; it does work to control blood glucose)

CADTH has been working on a study of self-monitoring of blood glucose (SMBG) for time now and the results of their review of clinical- and cost-effectiveness has led them to draft a series of five key messages to inform prescribers, other care providers and patients with diabetes. Now I'd like to share CADTH's key messages on the use of test strips to self-monitor blood glucose and give you a chance to tell me what you think of them.

<Moderator distributes copies of key messages and allows three minutes to read.>

3.3 What is your first reaction to these messages? How do you respond when you see them?

Probe for: What difference would it make to you if you didn't have to test as often? (e.g. less in control of diabetes; not a problem: I do other things to manage my diabetes)

3.4 Do these messages contain information that is new to you or that conflicts with the way you currently feel about monitoring your blood glucose?

Probe for: does this information conflict with the advice you receive from health care providers?

3.5 How clear/persuasive are these messages? As a whole, are they convincing enough for you to rethink your current views on monitoring your blood glucose? Why or why not? What can be done to improve them?

3.6 In your opinion, what would be the most effective way to communicate these key messages? How can we get these messages to people with type two diabetes in a way that will get their attention, be credible and be persuasive?

Probe: Source – radio; newspaper; tv; Dr.'s office; social media; etc.

4.0 Conclusion

4.1 Does anyone have any final thoughts or comments either about medications to control blood glucose, or about the key messages on self-monitoring blood glucose? Anything you'd like to add to the discussion that hasn't come up yet?

Thanks very much for your participation today. I appreciate your time and your thoughts and remind you to see the receptionist on your way out to pick up your thank-you incentive.

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APPENDIX 12: Change Request Form

Project Change Request Form	
Project Code	
Project Title	
Requestor	
Request Date	
Change Request Description and Rationale	
Change Request Impact	
Approval from Director, Topics and Research	
Approval Date	