Second-Line Therapy for Patients with Diabetes Inadequately Controlled on Metformin: Addendum to Project Protocol — August 14, 2009

This document briefly describes modifications to the *COMPUS Project Protocol for Second-Line Therapy for Patients with Diabetes Inadequately Controlled on Metformin* (www.cadth.ca/media/pdf/compus_2nd_line_T2DM_Protocol_e.pdf). All modifications are listed according to the relevant sections in the Project Protocol.

Section 5.1.3

Additional antidiabetes agents to be studied:

- liraglutide (a GLP-1 analogue)
- saxagliptin (a DPP-4 inhibitor).

Section 6.1.2 (a) Selection criteria

Clarification:

- Primary studies will be included if second-line agents are compared as add-ons to metformin monotherapy regardless of treatment history before metformin monotherapy. This includes studies that employ a metformin monotherapy run-in period before the addition of second-line agents.

Section 6.1.2 (i) Data synthesis and analysis

Changes to the planned analysis:

- All data from head-to-head, direct treatment comparisons that form a closed network will be synthesized at the drug class level (e.g., sulfonylureas, thiazolidinediones). For glycosylated hemoglobin (A1C), body weight, and hypoglycemia outcomes, separate mixed treatment comparison (MTC) analyses will be conducted in which sulfonylureas and thiazolidinediones will be disaggregated to the level of individual agents.
- Weight loss agents (i.e., orlistat and sibutramine) are primarily used to lower body weight rather than to manage hyperglycemia. The populations enrolled in studies involving these agents are, therefore, likely to differ from studies of other agents. Hence, these agents will be excluded from MTC analysis, although any direct comparisons of weight loss agents versus placebo or other antidiabetes treatments will be reported.
- Study arms that use fixed, low doses of second-line therapies will be removed from the reference case MTC meta-analysis. Doses lower than the defined daily doses from the World Health Organization will be considered low doses. Where the defined daily dose is not available, doses lower than the lowest recommended maintenance doses in product monographs will be defined as low doses.
- The reference case analysis will exclude data from extension phases for all outcomes other than safety and long-term complications.
- The deviance information criterion statistic will be used to assess the goodness-of-fit of all models, including subgroup and sensitivity analyses. The deviance information criterion statistic provides a measure of model fit that penalizes model complexity.

Low-value deviance information criterion statistics indicate better-fitted models; models with a deviance information criterion statistic decrease of two or more units indicate a significantly better model.[1-3]

Section 6.1.2 (j) Sensitivity and subgroup analyses

Additional sensitivity analyses:

- Low-dose treatment arms and studies (as defined under "Changes to the planned analysis" above) removed from the reference case analysis will be included in a MTC that accounts for dose differences across studies by disaggregating each class-level node into three separate nodes: titrated dose, fixed low dose, and fixed medium to high dose.
- Removal of studies less than one year in duration.
- Removal of studies and study arms testing antidiabetes agents that are not currently approved in Canada.
- Replacement of data from core studies with extension phase data where only the former was included in the reference case analysis.
- Removal of studies in which subjects were treated with less than 1,500 mg of metformin daily before initiation of second-line therapy (replaces subgroup analysis based on metformin dosing at baseline — see "Removed subgroup analyses" below). Where reported, mean daily dose of metformin will be used to conduct this analysis; otherwise, the protocol dose defined under study methods will be used.

Removed sensitivity analyses:

- Removal of studies in which inadequate control on metformin was defined by an A1C threshold of less than 7%. This sensitivity analysis is unnecessary in light of the planned meta-regression to adjust for differences in baseline A1C across studies (see Section 6.1.2 (k) below).
- Removal of studies that used fixed, sub-maximal doses of second-line therapies. This analysis will be replaced by the additional sensitivity analysis involving low-dose treatment arms defined above.

Removed subgroup analyses:

- Because none of the included randomized controlled trials used maximal metformin doses (2.55 g daily) before initiating second-line therapy, this subgroup analysis will be replaced by a sensitivity analysis in which studies will be removed if subjects are treated with less than 1,500 mg daily (see "Additional sensitivity analyses" above).

Section 6.1.2 (k): Addressing differences in "study-level" characteristic(s) across studies within and between pair-wise contrasts (additional section)

We will explore differences in study-level characteristics between trials to identify heterogeneity (variation in treatment effects between trials within a pair-wise contrast) and inconsistency (variation in treatment effects between pair-wise contrasts). Box plots and summary tables will be generated to help illustrate differences across trials with respect to the following study-level characteristics:

- Baseline A1C (for A1C MTC)
- Duration of diabetes (for A1C MTC)

- Baseline weight or body mass index (for weight MTC).

We will perform meta-regression to test the effect of adjusting for these covariates on MTC results. Similar to the sensitivity and subgroup analyses, the deviance information criterion statistic will be used to assess the goodness-of-fit of each meta-regression model considered.

Second-line therapy for patients with diabetes inadequately controlled on metformin: Addendum to Project Protocol –October 16, 2009

This document briefly describes modifications to the COMPUS Project Protocol for Second Line Therapy in Patients with Diabetes inadequately controlled on metformin: www.cadth.ca/media/pdf/compus_2nd_line_T2DM_Protocol_e.pdf. Section 6.2 of the protocol has been replaced with the following more detailed description of COMPUS' proposed approach to assessing cost effectiveness.

6.2 Methods

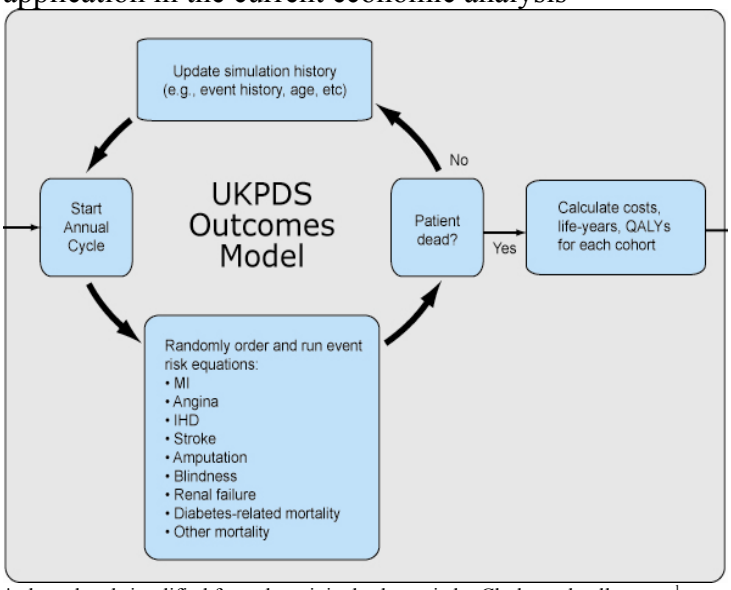
6.1 Type of Evaluation

An incremental cost-utility analysis of 2nd line antidiabetes therapies in patients with type 2 diabetes who have failed metformin monotherapy will be conducted.

6.2 Model Structure and Validation

The incidence of diabetes-related complications over the expected remaining lifetime of a hypothetical patient cohort will be forecasted using the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model®.[1] The model estimates risks for developing seven diabetes-related complications based upon data obtained from 3,642 patients with type 2 diabetes who were enrolled in the United Kingdom Prospective Diabetes Study. Model projections have been validated against published clinical and epidemiological studies.[2]

Figure 1. Schematic of United Kingdom Prospective Diabetes Study Model and its application in the current economic analysis



*adapted and simplified from the original schematic by Clarke and colleagues.[1]
MI = myocardial infarction; IHD =ischemic heart disease; QALYs = quality-adjusted life years

6.3 Population

When available, patient characteristics of simulated patients were derived from RCTs included in the systematic review and MTC meta-analysis (for internal validity). Otherwise, patient characteristics were derived from Sensitivity analyses will be performed where demographic characteristics of simulated patients are modified to reflect those in the Canadian clinical setting (for external validity).[3]

Table 1: Patient characteristics of simulated patients

Parameter	Estimate	Reference
Risk Factors		
Age(y)	56.1 (9.7)	RCTs in MTC
Duration of diabetes (y)	6.7 (5.1)	RCTs in MTC
Weight (kg)	89 (15)	RCTs in MTC
Height (m)	1.69 (0.15)	RECORD Trial[4]
BMI	31.2 (5.1)	RCTs in MTC
Gender	54% Male	RCTs in MTC
Ethnicity	98% Caucasian	RECORD Trial[4]
HbA1C(%)	8.30 (0.9)	RCTs in MTC
Smoking	Current=16% Past=49% Never=35%	RECORD Trial[4] , Ferrannini[5], DIGEM trial[6]
Chol (mmol/l)	4.5 (0.98)	RECORD Trial[4]
LDL (mmol/l)	3.3 (0.9)	RECORD Trial[4]
HDL (mmol/l)	1.2 (0.3)	RECORD Trial[4]
SysBP (mmHg)	139 (16)	RECORD Trial[4]
History of diabetes related complications*		
History of Ischemic heart Disease	9%	DICE Study[3]
History of CHF	5%	DICE Study[3]
History of Amputation	0%	DICE Study[3]
History of Blindness	0%	Ontario[7] and Alberta Diabetes Atlases[8]
History of Renal Failure	0%	Ontario[7] and Alberta Diabetes Atlases[8]
History of Stroke	4%	DICE Study[3]
History of MI	9%	DICE Study[3]
History of Atrial Fibrillation	4%	DICE Study[3]
History of PVD	3%	Ostgren 2004[9], Go 2001[10]

* Time since pre-existing event estimated based upon data from Ontario Diabetes Economic Model.[11]

6.4 Time horizon

As recommended by CADTH guidelines,[12] the reference case analysis will be conducted over a lifetime time horizon (i.e., 40 years). Because clinical outcomes were based upon extrapolated data using surrogate outcomes (i.e. A1C), results for time horizons of 10 and 25 years will also be reported.

6.5 Clinical Evidence

6.5.1 Meta-analysis of randomized controlled trials

Treatment effects (A1C, overall hypoglycemia, weight) will be derived from our random-effects mixed treatment comparisons (MTC) meta-analysis of randomized controlled trials. Additional details on our MTC meta-analysis are reported in the Clinical Review Methods Sections of the Project Protocol and this Addendum. Sensitivity analyses will be conducted to determine whether use of other clinical effect estimates (e.g., direct pair-wise estimates, fixed vs. random-effects MTC, effect estimates from dose-stratified model) impact cost-effectiveness estimates.

6.5.2 Modeling of adverse effects

Most RCTs included in the meta-analysis are unlikely to have adequate sample size or be of sufficient duration to capture incidence rates of infrequent adverse events that may of be of economic importance. These include:

- severe hypoglycemia in patients using insulin secretagogues or insulin
- congestive heart failure in patients using thiazolidinediones
- pancreatitis in patients using DPP-4 inhibitors
- fractures in patients using thiazolidinediones
- Other adverse effects identified in our search of the literature for studies of safety (e.g., large RCTs, observational studies, safety reviews)

Rather than pool results from smaller RCTs, we will derive event rates and treatment effects for the above adverse events from large observational studies and randomized controlled trials. Since these outcomes are not included in the UKPDS Outcomes Model® (with the exception of congestive heart failure), they will be added to the economic analysis via separate sub-models constructed using @Risk (Palisade Corporation, Ithaca, New York, USA).

The increased risk of hypoglycemia in patients using insulin secretagogues or insulin will be included in the reference case analysis. The baseline event rates for mild to moderate hypoglycemia will be derived from patients who did not use sulfonylurea in the RECORD trial,[4] the longest trial included in our meta-analysis. Effect estimates for each drug class derived from our MTC meta-analysis for overall hypoglycemia will be multiplied by the baseline event rates observed in the RECORD trial.[4] Rates of severe hypoglycemia among patients using insulin, insulin secretagogues and those not using insulin or insulin secretagogues will be derived from a population-based study by Leese et al.[13] This study[13] was the only one which provided event rates stratified by pharmacotherapy (metformin, SU, insulin) and provided healthcare resource utilization data. We will also conduct additional sensitivity analyses where rates of mild/moderate and severe hypoglycemia are derived from other large RCTs[14,15] and observational studies.[16]

One of the thiazolidinediones, rosiglitazone, has been reported to increase the risk of ischemic heart disease (IHD),[17] although recent evidence from the RECORD,[4] which was powered to detect cardiovascular outcomes, reported no increase in risk. Modeling an increased risk for this outcome in the UKPDS model is challenging since it is predicted

by a number of surrogates (e.g., A1C, cholesterol), all of which influence multiple outcomes within the UKPDS Outcomes Model®. Based on the recent RCT evidence,[4] and due to the lack of a satisfactory modeling approach, thiazolidinediones will be assumed to incur no additional risk of IHD in the reference case analysis. We will, however, incorporate an increased risk [HR, 2.10 (95% CI, 1.35 to 3.27) and rate difference was 2.6 per 1000 person years (95% CI, 1.1 to 4.1)] of congestive heart failure in patients using TZDs, along with an increased risk of fractures in a sensitivity analysis, based upon data from the RECORD trial.[4] We will artificially increase the risk of congestive heart failure among patients using TZDs by increasing the body mass index among this patient-population. CHF is the only sub-model in the UKPDS Outcomes Model that is influenced by BMI and therefore the only outcome that will be affected by the BMI increase.[1] The increased fracture risk associated with TZDs will be added to the economic analysis via a separate sub-model constructed using @Risk (Palisade Corporation, Ithaca, New York, USA).

A large, recently published cohort study[18] reported no difference in risk of acute pancreatitis for initiators of DPP-4 inhibitor sitagliptin (RR, 1.0, 0.5-2.0) when compared to those using metformin or glyburide. We will therefore not apply an increased risk of acute pancreatitis in patients taking the DPP4-inhibitors in the reference case analysis. We will, however, run a sensitivity analysis where we assume an increase risk of acute pancreatitis because DPP4-inhibitors are newer agents and their safety profile may still be emerging. Some of the RCTs in our meta-analysis reported an increase in gastrointestinal symptoms among patients using α-glucosidase inhibitors.[19,20] Nevertheless, we did not apply a quality of life decrement for this outcome in our reference case analysis because: (i) this outcome was not identified by CERC as a critical outcome of interest; and (ii) we have not, with the exception of hypoglycemia in patients using insulin secretagogues, applied decrements for adverse events for other classes of oral anti-diabetes drugs. We will, however, run a sensitivity analysis to ensure robustness of cost-effectiveness results to inclusion of this parameter in the model. This sensitivity analysis will apply an increased risk (56% vs. 29%)[19,20] of gastrointestinal symptoms among patients using metformin plus α-glucosidase inhibitors compared with those using metformin monotherapy and apply a utility decrement (-0.0288) as per Sullivan et al.[21] The increased risk of gastrointestinal complications associated with α-glucosidase inhibitors will be added to the economic analysis via a separate sub-model constructed using @Risk (Palisade Corporation, Ithaca, New York, USA).

6.6 Perspective

The perspective of this analysis will be that of a Canadian Ministry of Health.[12] Therefore, only direct costs to the Canadian Health Care System will be considered. [12]

6.7 Valuing Outcomes

The primary outcome measure in our analysis will be the quality-adjusted life year (QALY), which captures both quantity and quality of life. Patients with type 2 diabetes will be assumed to have an EQ-5D score of 0.753.[21,22] Quality weights for included long-term diabetes-related complications will be obtained from a U.S. catalogue of EuroQol 5-

dimension (EQ-5D) scores (when available).[21,22] Otherwise, utility scores will be obtained from a study by Clarke and colleagues.[23]

Table 1: Utility decrements for modeled health states

	Utility decrement (year 1)	Utility decrement in subsequent years (Year ≥ 2)
Ischaemic Heart Disease	-0.0412	-0.0240
Mycardial infarction	-0.0409	-0.0120
Heart Failure	-0.0635	-0.0180
Stroke	-0.0524	-0.0400
Amputation*	-0.28	-0.28
Blindness	-0.0498	-0.0498
Renal Failure*	-0.2630	-0.2630

*Utility decrements were not available from the US catalogue;[21,22] therefore, they were obtained from a study by Clarke et al[23] which utilized the EQ-5D instrument.

There is limited evidence that examines to the impact of hypoglycemia and fear of hypoglycemia on health-related quality of life.[24] Moreover, widely-cited evidence[25] in this area is of low quality.[24] For the reference case analysis, patients experiencing mild to moderate hypoglycemia will be assumed to have a transient reduction in health-related quality of life (HRQoL).[26] Patients will be assumed to move from having no problems to a health state characterized by moderate anxiety, with or without depression, and having some problems with performing usual activities, thus resulting in a disutility of 0.167 during the episode.[27] Each mild to moderate hypoglycemic episode will be assumed to last for 15 minutes, which coincides with the 15/15 rule: 15 grams of carbohydrate followed by 15 minutes of waiting.[28] Thus, each episode will be associated with a annual decrement of 0.000004767 QALYs.[27] In contrast, those having a severe hypoglycaemic episode will have a transient reduction in HRQoL followed by a chronic decrement in HRQoL due to fear of future hypoglycaemic episodes.[24] We will apply the same decrement which was applied in a recently published report[24] by the National Institute of Clinical Excellence (NICE), where an annual decrement of 0.01 was applied for each severe hypoglycaemic event. The estimates used by NICE[24] are less pronounced than those reported in an industry-sponsored study by Currie and colleagues.[25] NICE considered estimates generated by Currie and colleagues[25] at length; however, due to methodological limitations, they felt that estimates by Currie and colleagues were overstated.[24] Nevertheless, we will conduct sensitivity analyses where we explore the impact of using utility decrements by Currie and colleagues.[25] We will also conduct a sensitivity analysis where we only assume a transient reduction in HRQoL for severe hypoglycaemic episodes (i.e., no chronic decrement in HRQoL for fear of future events).

Utility scores for other adverse events (e.g., gastrointestinal symptoms, pancreatitis, fractures) explored in sensitivity analyses will be derived from the published literature.[21,22,29]

6.8 Resource Use and Costs

6.8.1 Price and dose of 2nd line anti-diabetes drugs

Unit costs for drugs will be obtained from the Ontario Public Drug Program (when available).[30] Otherwise, prices will be obtained from other public drug programs in Canada.[31-34] For the reference case analysis, we will apply the price of the lowest cost alternative (LCA) for each drug class (e.g., price of generic glyburide for sulfonylureas, generic pioglitazone for TZDs) plus a 10% mark-up and $7.00 pharmacy fee per 90 day supply. With the exception of metformin (max dose), we will assume that patients use the average defined daily dose (DDD) for each treatment, as defined by the World Health Organization. Sensitivity analyses will be conducted to explore how choice of agent within each class (e.g., gliclazide vs. glyburide; pioglitazone vs. rosiglitazone) and the assumed dose (e.g., average dose vs. max dose) of each agent impacts cost-effectiveness results.

6.8.2 Price and frequency of blood glucose test strip use across agents

Patients using certain 2nd line antidiabetes agents (e.g., insulin secretagogues, insulin) typically use more blood glucose test strips than those using other agents. For the reference case analysis, average daily utilization of blood glucose test strips for each agent will be derived from a recent utilization study in Ontario (Table 2).[35] We will apply a cost of $0.72 per test strip plus a pharmacy fee of $7.00 per 100 test strips. No mark-up was applied because test strips are not eligible for mark-up in the Ontario Public Drug Program. We will also conduct additional sensitivity analyses where the price of test strips is varied and where we assume that patients using non-hypoglycemia-inducing oral glucose lowering drugs do not use any test strips and those using hypoglycemia-inducing oral glucose lowering drugs and insulin use 1.16 and 2.08 test strips per day, respectively (Table 2).

Table 2. Average daily utilization of blood glucose test strips in 2008 by seniors in the OPDP, according to type of oral antidiabetes drug

Therapy	Daily use	SD
Insulin users	2.08	1.71
Hypoglycemia-inducing oral glucose lowering drugs	1.16	0.94
Non-hypoglycemia-inducing oral glucose lowering drugs	0.94	1.19

6.8.3 Change in treatment regimen over time

For the reference case, we will assume that patients remain on their second-line therapy over their remaining lifetime (i.e. 40 year time horizon). We have opted for this approach because: (i) all clinical and economic benefits are solely attributable to the second-line agents in question, rather than subsequent agents used after failure of second-line therapy; and (ii) the UKPDS Outcomes Model was not designed to explore variation in treatment sequences over time. Nevertheless, the reference case analysis does not capture the reality of actual clinical practice, in which the an increasing number of patients with type 2 diabetes require insulin therapy as the disease progresses.[3] As a result, cost-savings that may be realized due to delaying the initiation of insulin therapy (which is more expensive than other therapies) will not be captured. To address this limitation, we will run a sensitivity analysis where all patients were assumed to initiate insulin NPH

once they reach an A1C value greater than or equal to 9.0%. For this sensitivity analysis, patients initially follow identical treatment pathways, and then diverge once metformin monotherapy fails and initiation of a second-line agent is required (Step 3 in Table 3 and where patients enter model). Progression to insulin therapy occurs after a predefined time period governed by when A1C values exceeds 9.0%.[3] A1C effect estimates for basal insulin are derived from our MTC meta-analysis. Further sensitivity analyses will also be conducted where we assume that newer agents (i.e., DPP4-I, TZD) delay on the onset of insulin initiation, relative to older agents (SU, meglitinides, α-glucosidase inhibitors).

Table 3. Treatment algorithm for hypothetical patient cohort(s) in sensitivity analysis

Treatment step	Metformin	Comparator(s)
1	Diet and exercise	Diet and exercise
2	Metformin monotherapy	Metformin monotherapy
3 (Enter cohort)*	Metformin (max dose) plus placebo	Metformin (max dose) plus comparator
4†	Add-on insulin NPH after inadequate glycemic control (i.e., A1C≥9.0%) with 2nd line therapy	Add-on insulin NPH after inadequate glycemic control (i.e., A1C≥9.0%) with 2nd line therapy

6.8.4 Cost of diabetes-related complications

Resource utilization and costs associated with managing long-term diabetes-related complications will be obtained from the Ontario Ministry of Health and Long-term Care (Table 4).[11] Inpatient, outpatient, and emergency room visits, prescription drug claims, long-term care, and home care costs for managing diabetes-related complications will be included in the model.[11] Costs will be inflated to 2009 Canadian dollars using the Health Component of the Canadian Consumer Price Index.

Table 4: Management costs of diabetes-related complications states

	Fatal	Non-Fatal	In subsequent years
Ischaemic Heart Disease	$0	$5,588	$3,226
Mycardial infarction	$9,363	$17,853	$2,792
Heart Failure	$0	$16,332	$4,579
Stroke	$8,811	$24,318	$3,374
Amputation	$0	$37,723	$5,166
Blindness	$0	$2,988	$2,129
Renal Failure	$0	$24,204	$10,985

* The average annual cost for patients without diabetes-related complications who are using metformin monotherapy was $1,944,[11] while those using 2nd line therapy had an annual cost of $$1,944[11] plus the additional cost of second-line therapy and blood glucose test strips
† Inflated to 2009 Canadian dollars using the health component of the Consumer Price Index (CPI)
C$, Canadian dollars

Resource utilization associated with managing a severe hypoglycaemic episode will be based upon a study by Leese et al.[13] (Table 5) and the National Institute of Clinical Excellence.[24] Management costs will be based upon costing data from the Alberta Case Costing Database (Table 5).[36] For the reference case, we will assume that episodes of mild to moderate hypoglycaemia have no impact on health service resource use.[24]

Table 5: Costs related to a severe hypoglycaemic episode.

	Unit cost	% receiving	Weighted
Glucagon	$93.69	90%	$84.32
Consultation with ambulance services only	$600	34%	$204.07
Consultation with primary/emergency care only[36]	$208	7%	$14.59
Consultation with primary/emergency care and ambulance service	$809	52%	$420.49
Direct or indirect hospital admission	$4,302	28%	$1,204.67
Average cost per severe hypoglycaemic episode			**$1,928.14**

Management costs for adverse events explored in sensitivity analyses will be derived from published Canadian sources.[4,11,36]

6.9 Discount Rate

Both costs and QALYs were discounted at a rate of 5%, as recommended by CADTH guidelines.[12] Sensitivity analyses will be conducted where discount rates are varied between 0% and 5%.

6.10 Handling Uncertainty and Variability

A non-parametric bootstrapping* method,[37,38] in which 999 bootstrap iterations of 100 patients, will be used to estimate the mean life expectancy, quality-adjusted life-expectancy, and costs for each treatment arm. Net-benefits cost-effectiveness acceptability curves will be generated based on the proportion of bootstrap iterations with the highest net-monetary benefit[39] across a range of willingness-to-pay thresholds:

One, two and multi-way sensitivity analyses will be performed to examine robustness of results to changes in parameters and model assumptions. Specifically, we will assess how variation in the following parameters impacts cost-effectiveness estimates:

i. treatment effects (e.g., A1C, overall hypoglycemia, BMI)
ii. source of treatment effects (e.g., MTC meta-analysis, direct pair-wise meta-analysis, MTC model which adjusts for dose),
iii. price of agents (price of lowest cost alternative vs. price of newer agents available within class),
iv. application of class vs. agent clinical effect estimates (e.g., price of glyburide and SU class effect estimates vs. price of glyburide and glyburide-specific effect estimates)
v. average daily test strip frequency,
vi. price of blood glucose test strips,
vii. patient characteristics (e.g., baseline A1C, duration of diabetes)
viii. increase in costs associated with managing long-term diabetes related complications
ix. time horizon (i.e., 10 years, 25 years, 40 years),

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

x. changes in treatment regimen over time (i.e., patients are assumed to initiate insulin when baseline A1C hits 9.0%)
xi. discount rate (i.e., 0% and 3%),
xii. rates of adverse events (e.g., mild to moderate hypoglycemia, severe hypolycemia)
xiii. application of transient disutilities for hypoglycaemic episodes versus chronic disutilities associated with fear of future hypoglycemiac episodes
xiv. inclusion of a utility decrement for gastrointestinal discomfort in patients using α-glucosidase inhibitors
xv. inclusion of an improvement in HRQoL associated with weight loss
xvi. inclusion of adverse events in model (e.g., fracture risk for TZDs, pancreatitis for DPP4-inhibitors, gastrointestinal discomfort in patients using α-glucosidase inhibitors)
xvii. variation in third line agent (e.g., biphasic or mixed insulin) used after patients are inadequately controlled (i.e., A1C≥9%) on 2nd line therapy agent
xviii. variation in time to initiation of insulin therapy across agents (e.g., newer agents delay the onset of insulin initiation relative to older agents)

6.11 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.

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