The New England Comparative Effectiveness Public Advisory Council

Public Meeting – October 29, 2014

Controversies in the Management of Patients with Type 2 Diabetes

Public Comments and Response – December 2014

Authored by:

Response to Public Comments

The purpose of the New England Comparative Effectiveness Public Advisory Council (CEPAC) is to aid patients, physicians and policymakers in New England in the application and use of comparative effectiveness information to improve the quality and value of health care in the region. In partnership with the Institute for Clinical and Economic Review (ICER), CEPAC is tasked with producing actionable information to aid regional policymakers in the medical policy decision-making process.

ICER has produced an evidence review and policy analysis in response to increasing stakeholder interest in the management of type 2 diabetes. For transparency, all comments received during the public comment period for the draft report and public meeting are included in this response document. Comments related to program decisions, process, or other matters not pertaining specifically to the project scope or evidence assessment are acknowledged through inclusion only.

This document responds to comments from the following parties:

- Richard Chapell, CORE-US Outcomes Research; Merck & Co., Inc.
- Kathleen R. Gans-Brangs, PhD, Senior Director, Medical Policy and Quality; AstraZeneca LP, US Medical Affairs
- Stephen Habbe, Advocacy Director, Northeast; American Diabetes Association
- Mary Jane Milner, RN, CDE, CDOE
- Julia C. Prentice, Ph.D., Associate Director, HCFE; Assistant Professor, Boston University School of Medicine;
- Neeti Trivedi, PharmD, Manager, Medical Information, Medical Information & Services; Janssen Scientific Affairs, LLC
- Tami Wisniewski, MPH, Senior Director, Health Economics and Outcomes Research, Clinical, Medical, and Regulatory Affairs; Novo Nordisk, Inc.
- Andrew Zebrak, Executive Director, Government Affairs and Public Policy; Boehringer Ingelheim Pharmaceuticals, Inc.

	Comment 1	Response
Richard Chapell, CORE-US Outcomes Research; Merck & Co., Inc.		
1.	We believe that the economic model, as presented, does not accurately represent the Medicaid population in New England or the prices paid by Medicaid for diabetes treatment. It oversimplifies the realities of long-term treatment of type 2 diabetes, and omits important outcomes that could have a major influence on long-term costs…	*Thank you for your comments and references.. A sensitivity analysis has been added to the report that is reflective of the demographics, clinical characteristics, and costs in a Medicaid Type 2 diabetes population. We have clearly noted the limitations of our analysis with respect to certain outcomes such as hypoglycemia.*
2.	The estimated prices of non-insulin medications do not correspond with our observations and experience, nor do they correspond with estimates published by Analysource (http://www.analysource.com/). In particular, we have not observed that DPP-4 inhibitors are more expensive than GLP-1 agonists. Since this differential drives many of the conclusions of the model, we request that the report acknowledge the well-known fact that published wholesale prices may not reflect what payers actually pay, and actual prices may be lower than estimated. We further request that some sensitivity analyses be applied to the model to show how it behaves when different assumptions regarding pricing are applied. Obviously, the states know what they pay, and such an analysis would enable them to ensure that the model results truly apply to them.	*Unfortunately, Analysource is a proprietary, fee-based service that does not appear to include any information that is freely available to the public.* *We are unsure about your comments on DPP-4 inhibitors vs. GLP-1 agonists. Our model suggests lower acquisition costs as well as lower lifetime strategy costs for DPP-4s in comparison to GLP-1s.* *Our Medicaid analysis (described in comment 1) involves alternative pricing.*
3.	The simulation was based on a hypothetical cohort of 100 patients for each analysis. We would recommend a larger cohort that truly represents the diversity of T2DM patients in New England. The validity of the baseline profiles may need to be further examined. For example, the baseline HbA1c appeared to be high, 8.30% and 8.61%, for 2nd and 3rd line respectively. Average age is young, especially for a Medicaid population. Cholesterol is lower than we normally observe in our treatment populations. For these reasons, we question whether the model can be generalized to the New England Medicaid population.	*No changes to the report. Cohort size was as recommended in the UKPDS model user guide, as were numbers of Monte Carlo and bootstrap iterations.* *Our new Medicaid analysis makes alternative assumptions regarding diversity, age, HbA1c levels, smoking status, and other variables.*
4.	Given high baseline HbA1c and efficacy estimates (based on CADTH's meta-analysis) in the range of 0.69%-0.96% for 2nd line and 0.72%-1.15% for 3rd line, the majority of patients (in the US setting as the analyses intended) would be projected to not be at goal for the remaining lifetime simulated. While projected life expectancies (~11 years) and QALYs (~8.4 years) appeared to be in the range similar to results from other models, this may be, in part, a result of low average age at baseline. Failure to attain treatment goal would likely result in further modifications to treatment, a probability that is not taken into account by the model.	*No changes to the report. Much of the context set in the report revolves around a move away from a uniform HbA1c goal. In addition, the UKPDS model incorporates a natural rise in HbA1c over time, so we are unsure what concerns you have regarding "not being at goal" for a particular duration.* *Modeling treatment modification would overly complicate a model such as this and reduce clarity regarding what the focus of each strategy is. Our*

		approach is described as a limitation, but we note that the vast majority of diabetes models have the same limitation.
5.	The model assumes patients will remain on the same treatment for the remaining lifetime. This is likely to underestimate the lifetime cost for patient on low-cost drugs (e.g. SU, NPH) and overestimate the lifetime cost for patient on more expensive drugs, such as DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors.	*No changes to the report. Please see comment #4 above.*
6.	The UKPDS OM allowed a different initial HbA1c drop for each treatment but assumed a same HbA1c time profile thereafter for all the treatment. This is at odds with the observed natural history of type 2 diabetes. HbA1c tends to rise over time, even in treated, adherent patients. As a result, the model evaluated only the impact of the initial efficacy of a treatment over the remaining lifetime but not the potential difference in durability. Compounded by assuming one treatment for the remaining lifetime, the projections on lifetime diabetes-related complications and life expectancy are questionable. True costs are likely to be higher.	*No changes to the report. The UKPDS model includes extrapolations that approximate a natural rise in HbA1c over time, a feature which has now been clarified in the report.*
7.	Finally, the model did not take into account differential effects of treatments on body weight and hypoglycemia. Both of these factors decrease utility and can lead to additional treatment costs. By omitting these factors, the model ignores the potential benefits of newer treatment options	*No changes to the report. To clarify, the model incorporates changes in body weight and the clinical effects of this in the UKPDS (heart failure). We also included a sensitivity analysis that involved additional disutility from obesity. We note the limitation of not including hypoglycemia's effects explicitly in the model.*
8.	…we disagree with the statement on Page 9 that "Links have also been established between DPP-4 inhibitors and pancreatitis…" The review cited (Cernea, 2011) makes no mention of pancreatitis in relation to DPP-4 inhibitors. All discussion of pancreatitis involves GLP-1 agonists. A more accurate summary of the current thinking on incretin-based drugs and pancreatitis comes from the recent joint statement of the FDA and EMA (Egan et al., 2014, New England Journal of Medicine 370: 794-7)…	*Revised citations as suggested.*
9.	Several recently-approved drugs have been omitted from the review. Please consider listing GLP-1 agonists Albiglutide (Tanzeum) and Dulaglutide (Trulicity) as well as the DPP-4 inhibitor Alogliptin (Nesina).	*Revised as suggested.*
10.	Page 9: The description of the mechanism of action of DPP-4 inhibitors centers on GLP-1. Please note that DPP-4 inhibitors block degradation of both GLP-1 and GIP. Moreover, DPP-4 inhibitors act in a glucose-dependent manner.	*Revised as suggested.*
11.	Page 12: Please change the sentence "The high price of new oral medications, including DPP-4 inhibitors and GLP-1 receptor agonists, also contribute to the escalating costs of diabetes disease management." to read "The high price of newer medications, including DPP-4 inhibitors, GLP-1 receptor	*Removed the term "oral" as to be inclusive of GLP-1s. Consideration of SGLT2 inhibitors as a newer medication are outside the scope of this review, however.*

	agonists and SGLT2 inhibitors; may also contribute to the escalating costs of diabetes disease management." To list some, but not all new medications introduces bias.	
12.	Page 12: Please do not refer to the Medtronic insulin pump as an "artificial pancreas". We believe that this is inaccurate and misleading.	*Revised language to refer to Medtronic 530g system, not the insulin pump as a stand-alone device.*
13.	Page 36: Please consider deleting the draft paragraph on this page. One of the agents discussed, taspoglutide, has been discontinued and will not be marketed.	*No changes to the report. Because we did not make intra-class comparisons, all study agents were eligible for inclusion in the evidence review.*
14.	Page 38: Please consider including the following sitagliptin vs glimperide study: Arechavaleta R et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab 2011 Feb;13(2):160-8.	*No changes to the report. This study was included in the CADTH review used as a basis for the report.*
15.	Also the following sitagliptin vs. glipizide study, described in two publications: Nauck et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes, Obesity Metabol 2007 Mar;9(2):194-205. Seck et al. Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. International Journal of Clinical Practice 2010 Apr;64(5):562-576.	*No changes to the report. These studies were included in the CADTH review used as a basis for the report.*
16.	Presentations of Tables 8 and 10 are unconventional. When more than two treatments are compared, they are normally organized in such a way that the agents are presented in order of either QALY or Cost so that incremental cost-effectiveness ratios may be calculated properly, with dominated strategies identified. Please consider reorganizing the tables in a more user-friendly format. Including an efficiency frontier graph might also be helpful in fully communicating your findings.	*No changes made to the report.*
17.	Typos, Grammar and Minor Points of Clarity	*All typos and grammatical errors have been corrected where appropriate.*
18.	Page 12: Please consider deleting the first paragraph under Emergent Treatment Options since it is not possible to predict if or when these compounds will receive FDA approvals.	*No changes to the draft report. The purpose of this section is to provide an overview of current developments in treatment approaches, and not to comment on potential availability.*
19.	Page 13: We believe that the sentence "However, data on their efficacy compared to other oral antidiabetic agents are lacking (Vasilakou, 2013). " is inaccurate. Please consider deleting. Please change "glucose suspend feature," to "threshold suspend feature," Glucose is not suspended. Insulin pumping is suspended if blood glucose falls below a preset threshold.	*Revised as suggested.* *Revised as suggested.*

20.	Page 14: The table states that DPP-4 inhibitors decrease the liver's release of glucagon. It is the pancreas that releases glucagon. Please revise. Please use consistent language describing hypoglycemia risks for DPP-4 inhibitors and GLP-1 receptor agonists. Please add "or insulin" to the statement (unless taken with sulfonylurea) Hypoglycemia is listed as a potential adverse event for DPP-4s but not GLP-1s. Since risks are similar for both classes, please either list or omit for both. Please change the title of Table 1 to acknowledge that the table does not include non-insulin medication. We suggest changing "characteristics of non-insulin medications" to "characteristics of select non-insulin medications"	*Revised as suggested.* *Revised as suggested.* *Revised as suggested.* *Revised as suggested.* *Revised as suggested.*
21.	Comments regarding changes from "DPP-4 or GLP-1 agent" to "DPP-4 inhibitor or GLP-1 receptor agonist"	*Revised as suggested.*

	Comment 2	Response
Kathleen R. Gans-Brangs, PhD, Senior Director, Medical Policy and Quality; *AstraZeneca LP, US Medical Affairs*		
1.	Despite the importance of hypoglycemia, weight gain, and risk of major adverse cardiovascular events for patients, the economic model considered does not appear to reflect hypoglycemia, the base-case model does not appear to consider weight gain, and risk of major adverse cardiovascular events does not appear to be included…	*Thank you for your comments and references. No changes to the report. The exclusion of hypoglycemia is noted as a limitation, the base-case model does consider the clinical effects of changes in body weight (a sensitivity analysis also considers weight-related disutility), and the UKPDS model has specific risk equations for all major cardiovascular events of interest.*
2.	In regard to hypoglycemia, the report may want to consider a broader societal perspective. Hypoglycemia can adversely impact a patient's quality of life, social functioning, and work productivity. Moreover, hypoglycemia may indirectly impact patient adherence, and the risk of hypoglycemia may impact the willingness of providers and patients to set aggressive HbAlc targets. Even if the model is applied to a more narrow payer perspective, these latter two factors (adherence and HbAlc goal-setting} may adversely impact real-world HbAlc reduction in ways not manifest in clinical trials nor incorporated into the economic model.	*No changes to the report. The effects of hypoglycemia on clinical outcomes and productivity are mentioned in several sections of the report. Models for CEPAC use a payer perspective to reflect the regional health-system and coverage implications of the panel's recommendations.* *While issues of adherence and reluctance to set aggressive HbA1c goals are real clinical issues, we are sure the commenter recognizes that these are nuanced and therefore nearly impossible to model.*
3.	The report acknowledges the SGLT2 inhibitor class as a new emerging treatment option; however, it mentions that data on their efficacy compared to other oral antidiabetic agents is lacking. Head to head studies comparing SGLT2 inhibitors to other classes of antidiabetic therapies have been conducted including active comparator studies of dapagliflozin vs metformin XR (24-week data) and glipizide (up to 4-year data)…	*Removed statement stating there is a lack of head-to-head studies for SGLT2 inhibitors.*
4.	Page 3: … while the cost of diabetes medications and supplies has increased with the growing prevalence of diabetes, it has not increased as a proportion of the total cost of managing diabetes.	*No changes made to the report.*
5.	Page 7: Recommend revising copy to "GLP-1 Receptor Agonist" per the prescribing information. Recommend including the SGLT2 inhibitor class into the "Pharmacological options" portion of the draft document as it is an approved treatment option for patients with T2DM and mentioned in the AACE guidelines.	*Revised as suggested.* *No changes made to the report. Inclusion of SGLT2 inhibitors are outside the scope of this review.*
6.	Page 8: In addition to the limitations of using sulfonylureas due to hypoglycemia in general, please note that in patients with renal and hepatic impairment hypoglycemia may be prolonged.	*No changes made to the report*

	Recommend that the report list Bydureon® (exenatide extended release for injectable suspension) with its effects on satiety from Garber et al to support mention of weight loss further down in the paragraph. Please include glucagon suppression in the presence of glucose per the mechanism of action for GLP-1 Receptor Agonists. Recommend removing the statement from Cornea et al and replace with a statement reflecting the most recent update from FDA on pancreatitis. Recommend removing the statement from Cornea et al and replace with a statement reflecting the most recent update from FDA on pancreatitis.	*Revised as suggested.* *Revised as suggested.* *Included additional citation.*
7.	Page 9: Saxagliptin is indicated as add-on to insulin: per Onglyza® (saxagliptin) full prescribing information section 14.2 Combination Therapy Add-on Combination Therapy with insulin (with or without metformin)	*Revised as suggested.*
8.	Page 10: The report notes that sulfonylureas (SUs) are associated with a modest increase in stroke, acute Ml, or death compared with alternative treatments. Additional publications from 2014 continue to investigate this topic…	*Included additional citations.*
9.	Page 12: AZ recommends language per the Farxiga® Full Prescribing of paragraph Information: SGLT2 inhibitors work to block reabsorption of filtered glucose by the kidney.	*Revised as suggested.*
10.	Page 14, Table 1: The table containing SU, DPP-4i and GLP-1 RA, lists an advantage of sulfonylureas as "most significant reduction in HbA1c levels." Please note that a clinical trial of saxagliptin have found it non-inferior to glipizide when added to metformin… Comment on Main Mechanism of Action for DPP-4i: Please consider revising per Onglyza full prescribing information Glucagon is released by alpha cells in the pancreas. Comment on Potential Risk/Adverse Events for DPP-4i: Please suggest adding the following text per the Onglyza Full Prescribing Information: low risk of hypoglycemia when used as monotherapy; risk of hypoglycemia is evident with use of an insulin secretagogue (e.g., SU) or insulin… Recommend the following language to emphasize weight loss seen in clinical studies: Weight loss; lowers risk of hypoglycemia (unless taken with sulfonylurea).	*Took out mention of reduction of A1c levels as a benefit to be consistent with language for GLP-1s and DPP-4s.* *Revised as suggested.* *Revised as suggested.* *Took out hypoglycemia as potential adverse event* *Revised as suggested.*
11.	Pages 19-21: Recommend including the SGLT2 inhibitor class coverage within Tables 3 and 4 these tables. Please include the following information: ME: Bydureon four 2mg GLP-1 vials/0.65 ml syringe or pen for 7 days…	*See response #5.* *No changes to the draft report. QL dosing not included as part of Maine Preferred Drug List.*

12.	Page 24: Report states: Patients with an initial HbAlc of >7.5% can also be considered for dual therapy as first-line treatment. Suggest that the context should read greater than or equal to 7 .5% per guidelines. Page 24: Delete use of "oral" from clinical guidelines when also referring to GLP-1 receptor agonists	*Revised as suggested.* *See response #11 in comment 1.*
13.	Comments on pages 25: Recommend including the recommendations regarding initial triple therapy for patients with HbAlc of >9.0% in addition to the recommendation for HbAlc <8% for initial triple therapy.	*No change made to the report*
14.	Typos, Grammar and Minor Points of Clarity	*Changes made where appropriate*
15.	Page 29: Recommend including a summary of the Goring et al reference to include the SGLT2 inhibitors as a second or third line option for the treatment of T2DM.	*See response #5.*
16.	Page 36: …non-severe hypoglycemia can present a burden to patients by interfering with: social activities, work productivity, quality of life, adherence, treatment satisfaction, HbAlc targets, and balance. These factors can lead to increased costs (e.g., falls) or result in diminished real-world effectiveness of treatments associated with hypoglycemia by impacting adherence and HbAlc targets. Please note that in addition to clinical trial evidence, saxagliptin is associated with a lower risk of hypoglycemia than sulfonylurea treatment in the real-world.	*No changes made to the report. ICER acknowledges that nonsevere hypoglycemia poses a burden on patients but is rarely presented in clinical trials as having a significant impact on clinically relevant outcomes.*
17.	Page 36: Recommend adding summary of saxagliptin head to head study vs. glipizide add-on to metformin. (Goke et al) to the section on DPP-4 Inhibitors.	*No changes made to the report. This study was included in the CADTH review used as a basis for the report.*
18.	Page 38: The CADTH report cites clinicaltrials.gov as the reference for the SAVOR study.	*No changes made to the report. This comment is outside the scope of this review.*
19.	Page 40: Sulfonylureas result in significantly increased overall hypoglycemia and increased severe hypoglycemia along with significantly increased weight with similar HbAlc reduction with the use of SU compared with use of DPP-4i in patients with T2DM.	*No changes to the report. We are unsure whether this is a suggested rewording, but all of these issues are highlighted on pages 36-39.*
19.	Page 42: In the section on GLP-1 Receptor Agonist as second-line pharmacotherapy, AZ recommends adding a summary of the head to head study Bydureon vs. Byetta in this section (Blevins et al).	*No changes made to the report. This study was included in the CADTH review used as a basis for the report.*
20.	Page 46: In addition to economic models assessing cost-effectiveness, real-world cost and resource use comparisons have been conducted. This comparison found the DPP-4i saxagliptin was associated with lower rates of all-cause hospitalizations, and emergency department visits, as well as lower all-cause and diabetes-related medical costs compared with sulfonylurea treatment. These results were recently replicated in a different insurance claim database, and similar	*No changes to the report. As noted in this section, we chose to focus on independently-conducted evaluations by academic groups and/or government agencies.*

	results were found comparing DPP-4is as a class to sulfonylureas.	
21.	Page 46: Please consider an economic model that incorporates hypoglycemia, weight gain in the base case, a societal perspective, and the durability of diabetes medications.	*No changes to the report. Please see previous comments regarding each of these considerations.*
22.	Pages 51-56: Treatment effects included in this model were limited (e.g., model only considered HbA1c and body weight). This narrow perspective may underestimate the cost-effectiveness of GLP-1 Receptor Agonists. For example, in a cost-utility analysis by Davies and colleagues (2012) comparing liraglutide vs. glimepiride, systolic blood pressure, weight and cholesterol were the key drivers of cost-effectiveness, with a relatively small contribution from HbA1c.	*No changes to the report. We considered the intermediate clinical outcomes of primary interest in available RCTs.*
23.	Page 56: Table 8 shows cost estimates to be greater for GLP-1 Receptor Agonists, which differs from previous economic evaluations. For example, Sullivan et al (2009) used the CORE model to project and compare long-term outcomes of morbidity and mortality, and costs of complications of type 2 diabetes mellitus from a randomized controlled trial of patients receiving liraglutide versus glimepiride immunotherapy.	*No changes to the report. We cannot comment on different assumptions and a different model. In addition, our estimates of treatment effects came from a network meta-analysis of multiple studies, not a single RCT.*
24.	Pages 62-63: Per the pivotal studies for the new oral and injectable antidiabetic agents, please consider revising the language to reflect data that there are lower rates of hypoglycemia associated with the newer antidiabetic agents compared with sulfonylureas and NPH insulin is a very significant clinical benefit in patients with diabetes.	*No changes to the report. These differences are already noted in other sections.*

	Comment 3	Response
Stephen Habbe, Advocacy Director, Northeast; American Diabetes Association		
1.	According to the Association's Standards of Care, some patients cannot be clearly classified as having type 1 or type 2 diabetes. Clinical presentation and disease progression vary considerably in both types of diabetes. Occasionally, patients diagnosed with type 2 diabetes may present with ketoacidosis. Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia and occasionally with diabetic ketoacidosis. However, difficulties in diagnosis may occur in children, adolescents, and adults, with the true diagnosis becoming more obvious over time.	*Thank you for your comments and references. No changes have been made to the report. Although type 2 diabetes may present as clinically similar to type 1 due to its progressive nature, we are only considering literature that evaluates treatment approaches specifically as they apply to populations with type 2 form.*
2.	The Association's Standards of Care stress a patient-centered approach to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences. As such, second and third line therapies may differ depending upon patient circumstances and need.	*No changes made to the report. It is not our intention to limit treatment options for type 2 diabetes, but rather to objectively assess the available evidence, including the potential benefits/harms in subpopulations.*
3.	…the Association's position statements and Standards of Care offer options, not single mandates in order to preserve patient-centeredness and avoid a one-size-fits all approach. Therefore, any recommendations made by the Council should encourage additional treatment options be available to patients based on clinical circumstances.	*No changes made to the report. ICER's role is to objectively report the available evidence for CEPAC's deliberation of comparative effectiveness and value of the interventions being considered. It is neither group's intention to ignore or supplant patient-centered treatment recommendations in the clinical guidelines.*

	Comment 4	Response
Mary Jane Milner, RN, CDE, CDOE		
1.	… I feel that it would benefit your entire process to have council members who have more direct clinical patient expertise with diabetes education. There seemed to be some inconsistency in knowledge about certain medications, insulin pumps and CGMS possessed by some members of the CEPAC Council.	*Thank you for your comments and references. We have added language to the background of the report to clarify that CEPAC members are not selected for their expertise in the topic being addressed, but rather to provide an objective view of the evidence.*
2.	…in the studies comparing NPH to Long-Acting Analogs they were giving the NPH insulin at night only and that is not how NPH is typically given. It is used typically used twice a day. The hypoglycemia tracked in the studies for the NPH was notably higher than the Analogs and you would need to double the amount of hypoglycemia if you use it twice a day. As most clinicians know, NPH peak time is very unpredictable making it one of the most difficult insulin to use. I feel that protocols should not be based on data collected for studies that use insulin in a manner which is not typical for that particular insulin.	*Regarding the state of the evidence, we have acknowledged that the available studies utilized dosing methods that may not be typical in a clinical setting. We have added observational studies to this section of our evidence review to provide context that is reflective of "real-world" experience and outcomes.*
3.	There seemed to be a huge amount of either misinformation or lack of education as to what insulin pumps can do and who they may benefit. I heard discussions on how insulin pump companies change their infusion sets or reservoirs just in order to make patients upgrade to the next and newest model of their insulin pump, driving cost upwards…	*No changes made to report. Evaluation of changes in insulin pump technology is outside the scope of this review.*
4.	To dismiss CGMS as experimental I believe is short sighted as I know there are many Type 2 patients with hypoglycemic unawareness that would benefit greatly having a device that would allow them to treat themselves when the device they are wearing alarms at a safe predetermined BG level…The diabetes education that is delivered today in any ADA or AADE certified facility is always evidenced based however, after hearing details of the parameters on study candidate selection I'm not convinced that these studies always are representative of a typical Type 2 diabetic patient.	*No changes made to the report. CEPAC's role is to objectively determine whether the evidence is sufficient to assess comparative clinical effectiveness of the interventions being addressed. If evidence is lacking or methodologically poor, those considerations are factored into their understanding of the value of those approaches.*

	Comment 5	Response
Julia C. Prentice, Ph.D., Associate Director, HCFE; Assistant Professor, Boston University School of Medicine		
1.	…there is emerging evidence based on large observational studies that SUs increase the risk of poor long-term health outcomes. The main limitation of observational studies is that treatment selection may be associated with unobserved patient risk (i.e. selection bias) but these recent studies have employed innovative methodologies to control for selection bias. Using propensity scores to match patients on observed characteristics, Roumie et al. (2012) found veterans who initiated a SU compared to metformin were at a significantly increased risk of cardiovascular events and death.	*Thank you for your comments and references. No changes made to the report. A more recent study by Roumie et al which reached the same conclusions is included in the evidence review.*
2.	My colleagues and I recently predicted long-term outcomes for veterans initiating SUs compared to thiazolidinediones (TZDs) as a second-line agent after metformin…	*No changes made to the report. Because this study has not yet been published in a peer-reviewed journal, we cannot consider it for inclusion in the evidence review.*
3.	Meta-analyses of randomized controlled trials and guidelines have repeatedly concluded that there is not enough evidence on long-term outcomes to make conclusions about the most effective second line agent. By necessity, observational studies are required to investigate long-term risks as the medications are being used in clinical settings. The emerging data from these recent studies suggests that SUs can cause serious adverse outcomes and they should not be recommended as the preferred second-line treatment for type 2 diabetes.	*No changes made to the report. The lack of long-term studies for all oral antidiabetic agents recommended for second-line treatment is discussed at several points in the report.* *We also note that, while data are now becoming available on the potential harms of sulfonylureas, most authoritative guideline statements have not yet been changed.*

	Comment 6	Response
Neeti Trivedi, PharmD, Manager, Medical Information, Medical Information & Services; Janssen Scientific Affairs, LLC		
1.	The document states "the mission of CEPAC is to provide objective, independent guidance on how information on comparative effectiveness can best be used across New England to improve the quality and value of health care services." Based on this objective it is important to consider all available therapeutic treatment options which include SGLT2 inhibiters…	*Thank you for your comments and references. See response #5 in comment 2.*
2.	Under the category of newer drug classes mentioned in the first paragraph, consider listing SGLT2 inhibitors since they are considered as a second-line option recognized by AACE guidelines: https://www.aace.com/files/aace_algorithm.pdf.	*See response #5 in comment 2.*
3.	Section 2.2: When discussing additional management options in the 2nd paragraph, please consider listing SGLT2 inhibitors since they are considered as a second-line option recognized by AACE guidelines: https://www.aace.com/files/aace_algorithm.pdf . Consider broadening the scope of this September 2014 evidence review to include SGLT2 inhibitors as part of the discussion of the available second- and third-line medications. Otherwise, please acknowledge in this section that SGLT2 inhibitors have recently emerged as a newer class of antidiabetic drugs and consider evaluating this class in a future evidence review; please refer readers to page 12 of this review which lists SGLT2 inhibitors as Emerging Treatment Options. … For full utility of this analysis, it would be optimal to include all current management options that providers and payers are being faced with considering and weighing for optimal patient care...	*See response #5 in comment 2.*
4.	Please consider adding SGLT2 inhibitors to the list of potential combination treatment options. Additionally, please consider the following published studies in your review: o Wilding J, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. *Int J Clin Pract*. 2013;67(12):1267-1282. o Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care*. 2013;36(9):2508-2515. o Fulcher G, Matthews D, Perkovic V, et al. Canagliflozin in subjects with type 2 diabetes mellitus inadequately controlled on sulfonylurea monotherapy: A CANVAS substudy. Poster presented at: The 73rd Scientific Session of the American Diabetes Association (ADA), June 21-25, 2013, Chicago, IL.	*See response #5 in comment 2.*
5.	Page 12: The mechanism of action of SGLT2 inhibitors should be more correctly stated as: SGLT-2 inhibitors reduce reabsorption of filtered glucose and lowers the RTG, thereby increasing urinary glucose excretion (UGE). (Invokana PI)	*Revised as suggested*

6.	Please note, Vasilakou et al. does not state that these data are lacking. On the contrary, Vasilakou et al. cites 13 studies (N=5175) in which SGLT2 inhibitors are compared with other antidiabetic agents, including a published study which compared metformin + glimepiride vs. metformin + Canagliflozin. Data exists on head to head efficacy for Cana in two head to head trials vs Sitagliptin (Januvia) DPP-IV and one head to head study vs sulfonylurea. For the purposes and declared referent comparison, the Canagliflozin head to head study versus sulfonylurea should be considered in this current evaluation (Cefalu 2013; Leiter 2014)….	*See response #3 in comment 2.*
7.	Add-on to metformin and glimepiride: At week 52, both the 100 mg and 300 mg doses of Canagliflozin were non-inferior to glimepiride for reductions in A1C, with the 300 mg dose demonstrating statistical superiority. Both doses of Canagliflozin also showed significantly greater reductions in body weight and significantly lower incidences of hypoglycemic events than glimepiride (Cefalu 2013). At week 104, both doses showed reductions in A1C and body weight and lower incidences of hypoglycemic events than glimepiride (Leiter 2014).	*See response #5 in comment 2.*
8.	Inclusion of SGLT2s in summary tables and clinical guidelines	*See response #5 in comment 2.*
9.	Page 35: In addition to evaluating mean change in HbA1C, change in body weight, and rate of overall hypoglycemia, please consider evaluating changes systolic blood pressure (SBP) as an outcome of interest, as SBP is a reported outcome in the currently approved SGLT2 Inhibitors Prescribing Information. One study evaluated the efficacy and safety of Canagliflozin as compared with those of placebo (26 weeks) and Sitagliptin in patients with T2DM inadequately controlled on immediate-release metformin alone (N=1284). Both the 100 mg and 300 mg doses of Canagliflozin, as compared with placebo, significantly improved A1C, FPG, and 2-hour PPG at week 26. (Lavalle-González FJ, et al 2013) A second study evaluated the efficacy and safety of Canagliflozin as compared with those of glimepiride as add-on therapy in patients with T2DM inadequately controlled on metformin alone (N=1450). The mean maximum daily dose of glimepiride was 5.6 mg, and ≥4 mg/day of glimepiride was taken by 82% of patients. More patients in the glimepiride group (11%; 51/482) than in the Canagliflozin 100 mg (7%; 32/483) or 300 mg groups (5%; 24/485) received pioglitazone glycemic rescue therapy before week 52. The LSM change in body weight from BL to week 52 was -3.7 kg with Canagliflozin 100 mg, -4.0kg with Canagliflozin 300 mg and 0.7 kg with glimepiride (for both Canagliflozin doses: P<0.0001 vs glimepiride). (Cefalu et al 2013)	*See response #5 in comment 2.*
10.	Page 37 – 41: Under the Treatment added-on to metformin tab in Figure 4, consider adding results for SGLT2 inhibitors for completeness. Otherwise, please consider deleting results for meglitinides, TZDs, and AGIs to be consistent with section 2.2, specifically page 7 which explains the scope of this review is limited to DPP-4 inhibitors, sulfonylureas, GLP-1 agonists and insulin. Under the Treatment added-on to metformin and a sulfonylurea tab in Figure 5, consider adding results for SGLT2 inhibitors for completeness. Otherwise, please consider deleting results for	*See response #5 in comment 2.*

	meglitinides, TZDs, and AGIs to be consistent with section 2.2, specifically page 7 which explains the scope of this review is limited to DPP-4 inhibitors, sulfonylureas, GLP-1 agonists and insulin.	
11.	Page 46-47: Economic evaluations were based on dollars per QALY gained and incremental QALYs. While a valid and useful evaluation, a more practical cost-efficiency evaluation might be considered by calculating the total cost in one year per efficacy percentage (as determined by the percentage of patients achieving A1C<7%)… An economic evaluation for third-line pharmacotherapy for Type 2 diabetes was conducted and presented at the 50th Annual Meeting of the European Association for the Study of Diabetes (Thompson 2014). The Economic and Health Outcomes Model of T2DM was used to simulate the effectiveness of Canagliflozin 300 mg plus metformin and sulfonylurea versus sitagliptin 100 mg plus metformin and sulfonylurea in individually hypothetical patients over 40 years. The hypothetical patients experienced 0.04 more QALYs when treated with Canagliflozin 300 mg versus sitagliptin 100 mg when both were used in combination with metformin and sulfonylurea. Improved BMI profile (larger decrease with Canagliflozin 300 mg compared to sitagliptin 100 mg) and improved survival over time had the largest impact on the QALYs. Likewise, an economic evaluation was conducted using the Economic and Health Outcomes Model T2DM comparing the second-line treatment options of Canagliflozin 100mg and 300mg versus glimepiride titrated to maximal tolerated doses both as add-on to metformin (patients failing on metformin alone). The simulation modeled outcomes over 30 years. The mean discounted QALYs of 9.20 in the Canagliflozin arm and 8.15 in the glimepiride arm, a difference of 1.06 QALYs, reflects differences in weight, the need for earlier initiation of insulin and the development of macrovascular disease. The incremental cost per QALY gained for Canagliflozin 100 mg and 300 mg versus glimepiride (mean dose of 5.6 mg) were $18,380 and $14,436, respectively. Additional cost offsets as well as QALY gains were estimated, reflecting the substantially lower risk of hypoglycemia events and weight loss associated with Canagliflozin.	*No changes made to the report. We chose to report outcomes of consistent interest for clinicians and policymakers, using data available from RCTs.* *We cannot comment on presented but unpublished studies.* *There is no reference listed for this study. Results do vary from model to model based on parameters, assumptions, and costs.*
12.	Page 49: In light of the current drug treatment options that must be considered by providers and patients, this review should expand the scope to include all drug options which include the multiple drugs in the new category of SGLT2 inhibitors…	*See response #5 in comment 2.*
13.	Page 50: Current FDA-approved treatment options include SGLT2 inhibitors (Canagliflozin, dapagliflozin and empagliflozin) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. .	*See response #5 in comment 2.*
14.	Page 52-53: Severe hypoglycemia may be considered a complication that may incur substantial costs if the patient requires medical assistance and/or hospitalization. This may need to be incorporated into the model.	*No changes to the report. We note this exclusion as a limitation.*
15.	Page 61: As this evaluation stands, a major limitation is the lack of inclusion of the SGLT2 inhibitor class. There are three drugs currently approved for use by the FDA in this category. The SGLT2inhibitor class is a drug treatment option that is an active consideration by providers and patients in second and third-line pharmacotherapy for Type 2 Diabetes.	*See response #5 in comment 2.*

16.	Many other important considerations beyond costs should be kept in mind. In a patient-centered healthcare delivery environment which encourages patient engagement, insulin may not always match patient needs or preferences. As this analysis illustrates that the newer oral agents may offer modest clinical improvements over sulfonylureas and may be of interest for the provider patient partnership.	*Contextual considerations such as this were part of the Policy Roundtable discussion, which is now included as Section 7 of the report.*

	Comment 7	Response
Tami Wisniewski, MPH, Senior Director, Health Economics and Outcomes Research, Clinical, Medical, and Regulatory Affairs; Novo Nordisk, Inc.		
1.	We would like to clarify that in its 2008 Guidance for Industry, the FDA recommended the implementation of non-inferiority designs when comparing newer insulins with approved standard regimens in order to focus attention on key secondary attributes of insulin, primarily risk of hypoglycemia. Though this guidance was published in 2008 and the Cochrane Review was conducted in 2006, it is possible that these preferences for study design were already communicated between the FDA and Industry sponsors, thus explaining why there is little evidence in the literature to support superiority of one regimen over another based on HbA1c control via RCTs… we recommend that the clinically relevant outcomes considered should be equal ability to treat to HbA1c target, followed by evaluation of clinically meaningful and statistically significant differentiation of key secondary attributes like hypoglycemia, weight outcomes, and long term micro- and macro-vascular complications.	*Thank you for your comments and references. No changes made to the report. We recognize that these non-inferiority studies are meant to show comparability between agents; however, we mean to present all clinically relevant end-points as they are reported in the available literature.*
2.	…we respectfully disagree with ICER to limit one of the primary outcomes of interest to severe hypoglycemic events only (pg. 31). While we understand that severe hypoglycemia is most relevant when considering the perspective of a state Medicaid agency due to the increased costs associated with such events, there is evidence to suggest that mild to moderate hypoglycemia does have a negative impact on patients… We recommend that ICER consider severe hypoglycemic events and total hypoglycemic events as primary outcomes of interest for this review as consideration of total hypoglycemic events more readily incorporates the patient perspective.	*No changes made to the report. ICER acknowledges that nonsevere hypoglycemia poses a burden on patients but is rarely presented in clinical trials as having a significant impact on clinically relevant treatment outcomes.*
3.	In the Cochrane Review (2006) referenced on pg. 32, 9 RCTs are evaluated, 7 of which included administration of NPH only at bedtime, compared to glargine dosed at breakfast or bedtime… While we are not aware of evidence demonstrating what proportion of patients with T2DM on NPH insulin utilize a twice daily regimen, it is important to realize that intensification to a twice daily regimen with NPH is one option recommended by the American Diabetes Association for patients who do not attain fasting blood glucose levels within target at pre-dinner measurement. Thus, it is important to distinguish that the effects on hypoglycemia seen with insulin analogues compared to NPH may be dependent on the dosing regimen.	*ICER acknowledges that the available studies utilized dosing methods that may not be typical in a clinical setting. We have added observational studies to this section of our evidence review to provide context that is reflective of "real-world" experience and outcomes.*
4.	While ICER recognizes the importance of the impact of hypoglycemia on people with diabetes by including the rate of severe hypoglycemia as an endpoint of the primary outcomes of interest (pp. 31) in the clinical assessment, this importance is not translated to the economic modelling, where all hypoglycemic events, even severe events, are excluded. ICER further recognizes severe hypoglycemic events are greater for	*No changes to the report. We note this as a limitation of our modeling effort.*

	SU's (pg.35, 36, 37 and Table 1 pg. 14) but does not include the negative effect in modelling. We are concerned that this further contributes to disproportionate favoring of the SU arms in the model both in terms of costs and utilities.	
5.	ICER states the perspective of the economic model is that of a Medicaid State Agency. Thus, it seems that results should be considered within the context of a T2DM Medicaid population.	*As noted previously, a sensitivity analysis has been added that uses demographics, clinical characteristics, and costs that are more reflective of a Medicaid population.*
6.	All Typos and Minor Points of Clarification	*Revised as suggested where appropriate.*
7.	The time horizon and treatment duration is not clearly stated. Please clarify and describe rationale for selection of the time horizon. The timeframe from which effectiveness results are derived would be helpful for interpretation as these results are used as a basis for extrapolation to a lifetime.	*The report has been clarified to note that a lifetime time horizon was used. In the absence of comparative data on adherence between regimens, we assumed perfect treatment adherence, as most other models in this area have.*

	Comment 8	Response
Andrew Zebrak, Executive Director, Government Affairs and Public Policy; *Boehringer Ingelheim Pharmaceuticals, Inc.*		
1.	BI recommends that ICER re-examine its economic evaluation (Chapter 6, Page 46), which suggests that sulfonylureas may be an appropriate second- and third-line medication for the general type 2 diabetes patient population when compared to other agents such as DPP-4's and GLP-1's.	*Thank you for your comments and references. No changes made to the report.*
2.	Treatment of severe hypoglycemia can result in additional costs. BI requests clarification on whether ICER addressed the impact of hypoglycemic episodes on patient morbidities (including those that may not be initially attributed to hypoglycemic excursions, such as cognitive sequelae) , the attendant costs of these morbidities (e.g., emergency room visits) and the costs of the weight gain common in patients prescribed sulfonylureas when determining treatment cost effectiveness.	*No changes made to the report. The effects of weight gain are clearly described in the methods description of Section 6, and the exclusion of hypoglycemia as an outcome is clearly described as a limitation.*
3.	Another important aspect to consider relates to medication adherence in the interventions included as part of this evidence review. Adherence is known to play a primary role in controlling type 2 diabetes, as poor medication adherence can lead to symptom exacerbation and poor patient outcomes. Real-world evidence has suggested that DPP-4 inhibitors outperform other medications in this capacity…	*No changes made to the report. ICER and CEPAC acknowledge that adherence may impact treatment outcomes but is rarely evaluated in clinical trials. Additionally, observational studies have addressed the difficulty in identifying and quantifying the impact of improved adherence on clinically relevant end-points.*
4.	The recommendations presented by ICER do not appear to reflect nuances or considerations of how the guidelines are practically applied in the current clinical standard of care. Guidelines cited by ICER, such as those released by the American Diabetes Association and the American Association of Clinical Endocrinologists, issue patient-focused recommendations, most notably A1c goals, that take into consideration individual patient characteristics.	*No changes made to the report. ICER's role is to objectively report the available evidence for CEPAC's deliberation of comparative effectiveness and value of the interventions being considered. It is neither group's intention to ignore or supplant patient-centered treatment recommendations in the clinical guidelines.*
5.	…according to UnitedHealthcare's 2014 Prescription Drug List lists, there only three official formulary tiers; specifically Tradjenta and Onglyza are listed under Tier 2 (with supply limits) while Januvia is included under Tier 3 with indications that it may only be available under Tier 4 or purchased through mail order pharmacies in *some* plans.23 BI recommends that the report clearly note these distinctions, as it does in other rows of Table 4. BI also recommends thorough review of all source documents to ensure the accuracy and clarity of similar data provided in this report.	*Revised as suggested.*