Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness and Safety of Insulin Delivery and Glucose Monitoring Methods for Diabetes Mellitus

I. Background and Objectives for the Systematic Review

Burden of Diabetes and Its Classification

Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycemia resulting from: defects in insulin secretion from the pancreatic beta cells; insulin action at the level of skeletal muscle, liver, and fat; or both. The resultant hyperglycemia, if untreated, can lead to long-term complications, including microvascular complications (i.e., retinopathy, nephropathy, and peripheral and autonomic neuropathy) and macrovascular complications (i.e., coronary heart disease, cerebrovascular disease, and peripheral arterial disease).[1] The prevalence of diagnosed diabetes in the United States is currently 7.7 percent[2] and is expected to increase to nearly 10 percent by 2050, at which time an estimated 39 million people will have diabetes in the United States.[3,4] Thus, a large segment of the population requires glucose-lowering therapies to maintain normal glucose levels (normoglycemia) and prevent diabetes complications.

Type 1 Diabetes Mellitus

Type 1 diabetes, which accounts for 5 to 10 percent of all diabetes cases, is characterized by autoimmune destruction of pancreatic islet cells that results in an inability to produce insulin and a need for daily insulin administration to sustain life.[1] Individuals with type 1 diabetes require insulin to prevent life-threatening ketosis, to maintain normoglycemia without inducing significant hypoglycemia, and to maintain normal/ideal body weight and promote normal growth and development in children.[1]

Type 2 Diabetes Mellitus

Type 2 diabetes is the result of a combination of insulin resistance and impaired insulin secretion by the beta cells of the endocrine pancreas.[1] Typically, insulin resistance predominates early, and insulin secretion decreases over time. However, the relative contribution of each of these factors to the disease course varies by patient. Eventually, the impairment in insulin resulting from beta cell dysfunction can lead to insulin deficiency, necessitating insulin therapy. Type 2 diabetes accounts for 90 to 95 percent of diabetes cases in the United States.[1]

Diabetes Mellitus in Pregnancy

In pregnant women with pre-existing type 1 or type 2 diabetes, poor glycemic control is associated with poorer pregnancy outcomes. Hyperglycemia early in pregnancy is associated with fetal anomalies, and hyperglycemia later in pregnancy can be associated with macrosomia, delivery complications, stillbirth, and neonatal hypoglycemia.

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Importance of Tight Glycemic Control and Associated Risks in Diabetes

Tight glycemic control with intensive insulin therapy has been shown to reduce the risk of the microvascular and macrovascular complications of diabetes.[5-8] Throughout the duration of pregnancy, tight glycemic control is recommended to avoid maternal, fetal, and neonatal complications.[9]

While tight glycemic control lowers the risk of diabetic complications, it is not without risks. Intensive insulin therapy is associated with an increased risk of hypoglycemia and glycemic instability,[7] which can lead to compromised quality of life. Severe hypoglycemia, which can be life threatening, is defined as an episode that requires another person to assist in treatment to resolve symptoms. Nonsevere hypoglycemia may be symptomatic, but individuals are able to correct it without assistance from others. Both types of hypoglycemic episodes can be a source of significant distress and anxiety to patients and a barrier to achieving tight glycemic control. With long-standing diabetes complicated by recurrent hypoglycemia, unawareness of hypoglycemia can result, putting patients at risk for severer hypoglycemic episodes.[10] Finally, intensive insulin therapy can also lead to weight gain, due to more efficient fuel utilization and/or overtreatment of hypoglycemic episodes.[11,12]

Methods To Achieve Tight Glycemic Control and Minimize Risk: Advances in Insulin Delivery (Conventional vs. Intensive Insulin Therapy)

Insulin therapy has evolved over the last 25 years to more closely mimic normal pancreatic physiology. In the past, conventional insulin therapy consisted of one to two injections of intermediate-acting insulin mixed with short-acting insulin before breakfast and dinner. Because of the pharmacokinetics of these older insulins, tight control was difficult to achieve and often was accompanied by significant hypoglycemia due to their prolonged duration of action. This difficulty led to the development of more physiological basal and meal-time (prandial) insulins that, when used together, mimic normal pancreatic function (peakless basal insulin secretion, rapid release of insulin in response to meals, and rapid resolution of the prandial insulin peak). In addition, the development of continuous subcutaneous insulin infusion via a pump (CSII) provided another means to deliver insulin in a more physiological manner. Thus today, intensive insulin therapy is delivered as at least three daily insulin injections (i.e., multiple daily injections, or MDI) or by the use of the external CSII.

Methods To Achieve Tight Glycemic Control and Minimize Risk: Advances in Glucose Monitoring

Self-Monitoring of Blood Glucose

Following publication of the Diabetes Control and Complications Trial,[11] self-monitoring of blood glucose (SMBG) by fingerstick replaced the assessment of glucose by urine dipstick to allow more specific and timely feedback on the degree of hyperglycemia. SMBG is the most

widely used technique, whereby patients check their blood glucose with fingersticks. This allows patients to evaluate their individual response to therapy and assess whether blood sugar targets have been achieved. SMBG is accepted as part of effective diabetes treatment and has been shown to be effective, especially for patients who are being treated with insulin injection or pump therapy.[13] This type of self-monitoring is also useful for patients who may not be on insulin therapy as a guide to adjust therapy, but there are fewer data on this population. In patients with type 2 diabetes, Welschen and colleagues[14] found a 0.4 percent reduction of hemoglobin A_{1c} (HbA_{1c}) with SMBG usage when compared with no usage. As patients also were receiving diet, exercise, and health education in addition to medications, it is not entirely clear that the effect was due to use of SMBG.[14] The challenge of this technique is associated pain that affects adherence to this technique and is a barrier to tight glycemic control. Therefore, continuous glucose monitoring systems have been developed in recent years.

Continuous Glucose Monitoring System: Retrospective and Real-Time

A continuous glucose monitoring (CGM) system is a device that records blood sugar levels throughout the day and night with a significantly decreased need for fingerstick measurements. Real-time continuous glucose monitoring (rtCGM) was first approved by the U.S. Food and Drug Administration in 2005. This equipment consists of a transcutaneous glucose sensor that is connected to a transmitter and receiver. CGM systems can be used in real time, retrospectively, and prospectively.[15] Some show graphical representation of glucose levels, and some have adjustable alarms for alerts of high and low glucose values. Sensor-augmented pumps are also available.[16] A CGM system, in conjunction with intensive insulin treatment, can be a useful tool to lower HbA_{1c} values in adults who are ≥25 years of age and have type 1 diabetes. Success in lowering HbA_{1c} depends on adherence to ongoing use of the device.[17] These devices are useful in detecting fluctuating blood sugars and trends in changing blood sugars, which are important in adjusting medications. Technologies for these devices are continuously improving.

rt-CGM differs from retrospective CGM in that it provides blood glucose feedback data to the patient while he or she is wearing the device and does not need to be downloaded and evaluated after data collection unlike retrospective CGM. This advantage of rt-CGM has resulted in it being the preferred method of CGM in the clinical setting. As a result, the focus of our review will be on studies examining rt-CGM.

Knowledge Gaps: Comparative Effectiveness of Insulin Delivery and Glucose Monitoring in Specific Diabetic Populations

Type 1 Diabetes Mellitus

Comparison of multiple daily injections to continuous subcutaneous insulin infusion. The majority of the evidence from comparisons of MDI to CSII in patients with type 1 diabetes indicates improved glycemic control with CSII use in adults, although its impact on other clinical outcome measures are unclear.[18,19] In children with type 1 diabetes, the benefit of CSII for glycemic control and clinical outcomes has not been established. Thus, there is still uncertainty regarding the benefit of CSII in the very young with type 1 diabetes. Another population in whom the benefits of rt-CGM are unclear is older patients with type 1 diabetes. In all of these

populations, CSII may be associated with uncontrolled hyperglycemia because of device malfunction and with the potential risk of local infection at the catheter site. The benefits and risks of intensive insulin therapy with CSII, therefore, have not clearly been established, though they are crucial in determining the cost-effectiveness of this expensive technology.

Comparison of SMBG to rt-CGM. Presently, there are conflicting reports of the effect of rt-CGM on glycemic control, hypoglycemia frequency, or other clinically relevant outcomes in individuals with type 1 diabetes. To date, no systematic reviews or meta-analyses comparing the effects of rt-CGM to SMBG have been published, although this information would be valuable for clinicians to understand the potential added utility of this new technology and to determine its cost-effectiveness. In addition, several other factors appear to be especially relevant, including the age of the patient, the effect of adherence to rt-CGM on potential benefits, and the potential interaction with the mode of insulin delivery (CSII vs. MDI).

Type 2 Diabetes Mellitus

Comparison of MDI to CSII. While the literature suggests that CSII with the insulin pump, when compared with MDI, lowers HbA_{1c} more in individuals with type 1 diabetes,[18] the comparative effectiveness of insulin pump therapy and MDI has not been assessed as systematically in patients with type 2 diabetes. While some studies suggest that CSII is comparable to MDI in attaining adequate glycemic control,[18] other studies found a lower HbA_{1c} in patients treated with CSII.[20-23]

Comparison of SMBG to rt-CGM. To our knowledge, a systematic review of the comparative effectiveness of rt-CGM and SMBG on glycemic control, hypoglycemia frequency, and other clinically relevant outcomes has not been performed in individuals with type 2 diabetes.

Diabetes in Pregnancy

Comparison of MDI to CSII. We found one systematic review of randomized controlled trials (RCTs) published in 2007 that compared CSII to MDI in pregnant women who had pre-existing type 1 or type 2 diabetes.[24] The resulting review included only 60 women with 61 pregnancies. There was a statistically significant increase in mean birth weight associated with CSII when compared with MDI, which was not viewed by the authors as clinically significant. There were insufficient data to permit conclusions about other outcomes, such as perinatal mortality, major and minor fetal anomalies, hypoglycemia, hyperglycemia, and admission to the neonatal intensive care unit for treatment of hypoglycemia. It is, therefore, important to provide an updated synthesis of the literature in this area.

The evidence base for the comparison of MDI to CSII in pregnant women with pre-existing type 2 diabetes is small and has not been evaluated by a systematic review. This topic is increasingly important as the prevalence of type 2 diabetes has been increasing dramatically in younger populations, including women of child-bearing age.

Comparison of SMBG to rt-CGM. rt-CGM is a new technology whose benefit has not been clearly established in pregnant women with pre-existing type 1 or type 2 diabetes, although the

theoretical utility of this tool in improving neonatal outcomes is great. A systematic review of the literature is required to assess the quality and completeness of the current knowledge base.

Summary

Our systematic review will help to address the clinically relevant question of whether the mode of intensive insulin therapy (MDI vs. CSII) results in better glycemic control, less hypoglycemia, improved quality of life, and improved clinical outcomes in individuals with type 1 diabetes, type 2 diabetes, and pre-existing diabetes in pregnancy. We will also determine whether these outcomes differ by the type of strategy used for blood glucose monitoring (SMBG vs. rt-CGM) in those same populations. Finally, based on the studies available in the literature, we will attempt to determine if there is an interaction between types of intensive insulin-delivery methods and blood glucose-monitoring systems on our outcomes of interest. As these effects may differ by age, we will stratify available data by the age of the study populations. Answers to these questions will facilitate clinical decisionmaking regarding appropriate modes of insulin delivery and glucose monitoring for various populations of individuals with diabetes so that therapeutic options can be selected that result in improved process, intermediate, and clinical outcomes.

II. The Key Questions

Our draft Key Questions (KQs) were posted for public comment in October 2010 (see Appendix 1). Based on the public comments, we made the following changes to the KQs:

1) We will not include pregnant women with gestational diabetes in the review. There is a range of glucose abnormalities among women with gestational diabetes, and many women with gestational diabetes are not on intensive insulin therapy. Insulin pump therapy and CGM are more relevant to pregnant women with pre-existing diabetes. The population for this review will include patients with type 1 diabetes, patients with type 2 diabetes who are on insulin therapy, and pregnant women with pre-existing diabetes.

2) We will see if there are any studies that focused on older adults (age >65 years). Currently, there is no upper age limit on our proposed study populations, so we should be able to examine this group if data are available. Therefore, the age categories considered for this review will be very young children, adolescents, and adults, including older adults (age >65 years).

3) KQ3 was made a subquestion of KQ 2.

There were several other relevant comments about the KQs and the protocol. These comments and our responses are summarized below.

1) We plan to abstract the following data to use in our analysis when available: measurement of adherence, MDI delivery method (pen vs. vial or syringe), study

design, information about device use (e.g., analyses based on adherence to wearing the device, training of patient/staff, generation/model of devices), study participant characteristics, adjustment to insulin therapy, definitions of hypoglycemia, definitions of diabetes, assessment of quality of life, rt-CGM alarm threshold, and study length and followup time.

2) Because insulin regimens may change over time, it may be difficult to determine if the current delivery method is responsible for the long-term outcomes. Therefore, we will abstract data on the length of use of current technology, changes in the mode of insulin delivery over time, and changes in the type of insulin used over time if available.

3) The list of process measures and intermediate outcomes will not change. Some of the suggested outcomes were either beyond the scope of the review (e.g., changes in carbohydrate counting, diet, and physical activity) or only applied to a particular insulin-delivery device or blood glucose-monitoring technique (e.g., time spent in the hypoglycemic range).

The finalized KQs are:

KQ 1

In patients receiving intensive insulin therapy, does mode of delivery (multiple daily injections [MDI] vs. continuous subcutaneous insulin infusion [CSII]) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus? (Process measures, intermediate outcomes, and clinical outcomes of interest are summarized below in Table 1.) Do these effects differ by:

a. Type 1 or type 2 diabetes status?
b. Age: very young children, adolescents, and adults, including older adults (age >65 years)?
c. Pregnancy status: pre-existing type 1 or type 2 diabetes?

KQ 2

In patients using intensive insulin therapy (MDI or CSII), does the type of glucose monitoring (real-time continuous glucose monitoring [rt-CGM] vs. self-monitoring of blood glucose [SMBG]) have a differential effect on process measures, intermediate outcomes, and clinical outcomes (see Table 1) in patients with diabetes mellitus (i.e., what is the incremental benefit of rt-CGM in patients already using intensive insulin therapy on process and outcome measures)? Do these effects differ by:

a. Type 1 or type 2 diabetes status?
b. Age: very young children, adolescents, and adults, including older adults (age >65 years)?
c. Pregnancy status: pre-existing type 1 or type 2 diabetes?

d. Intensive insulin delivery: MDI or CSII?

Table 1. Summary of process measures and intermediate and clinical outcomes

Process Measures	Intermediate Outcomes	Clinical Outcomes
• Ratio of basal to bolus insulin • Frequency of adjusting insulin therapy • Adherence to insulin therapy/sensor use • Frequency of professional or allied health visits	Primary • Hemoglobin A_{1c} Secondary • Hyperglycemia • Weight gain • Hypoglycemia frequency	Microvascular* • Retinopathy • Nephropathy • Neuropathy Macrovascular* • Coronary heart disease • Cerebrovascular disease • Peripheral arterial disease Severe hypoglycemia Quality of life Fetal outcomes† Maternal pregnancy outcomes • C-section rates

*We will only include objective assessments of microvascular and macrovascular outcomes (i.e., we will be excluding patient self-reported microvascular and macrovascular outcomes).
†Fetal outcomes include gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, and admission to a neonatal intensive care unit.

For each KQ we will identify:

- **Population(s):**

  Adults, adolescents, and children with type 1 or type 2 diabetes mellitus and pregnant women with pre-existing diabetes treated with insulin therapy.

  1. We will use age ranges prescribed by the Juvenile Diabetes Research Foundation[17] (<8 years [very young children], 8–14 years [children], 14–25 years [adolescent], and >25 years [adults]); however, our final definitions will be guided by those used in the literature that is reviewed.
  2. If available, we will examine data among populations of older adult (>65 years).

- **Interventions:**

  The interventions of interest are CSII (see Appendix 2 for a list of insulin pumps and models) and rt-CGM (see Appendix 3 for a list of monitors).

  1. We will not be including the following devices because they are no longer used in the United States:

     a. GlucoWatch continuous glucose meter

b. Insulin pumps with regular insulin

- **Comparators:**

  All studies must have a concurrent comparison group.

  1. CSII would be compared with MDI, which will be defined as at least three injections of basal and rapid-acting insulin per day.
  2. rt-CGM would be compared with SMBG, which will be defined as at least three fingersticks per day.

- **Outcomes measures for each KQ:**

  1. Process measures

     a. Ratio of basal to bolus insulin
     b. Frequency of adjustments to insulin therapy
     c. Adherence to insulin therapy/sensor use
     d. Frequency of professional or allied health visits

  2. Intermediate outcomes

     a. HbA_{1c}
     b. Hyperglycemia
     c. Weight gain
     d. Hypoglycemia frequency

  3. Clinical outcomes

     a. Objective assessments of microvascular outcomes (retinopathy, nephropathy, and neuropathy)
     b. Objective assessments of macrovascular outcomes (coronary heart disease, cerebrovascular disease, and peripheral arterial disease)
     c. Severe hypoglycemia
     d. Quality of life
     e. Fetal outcomes (gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, and admission to a neonatal intensive care unit)
     f. Maternal pregnancy outcomes (cesarean section rates)

- **Timing:**

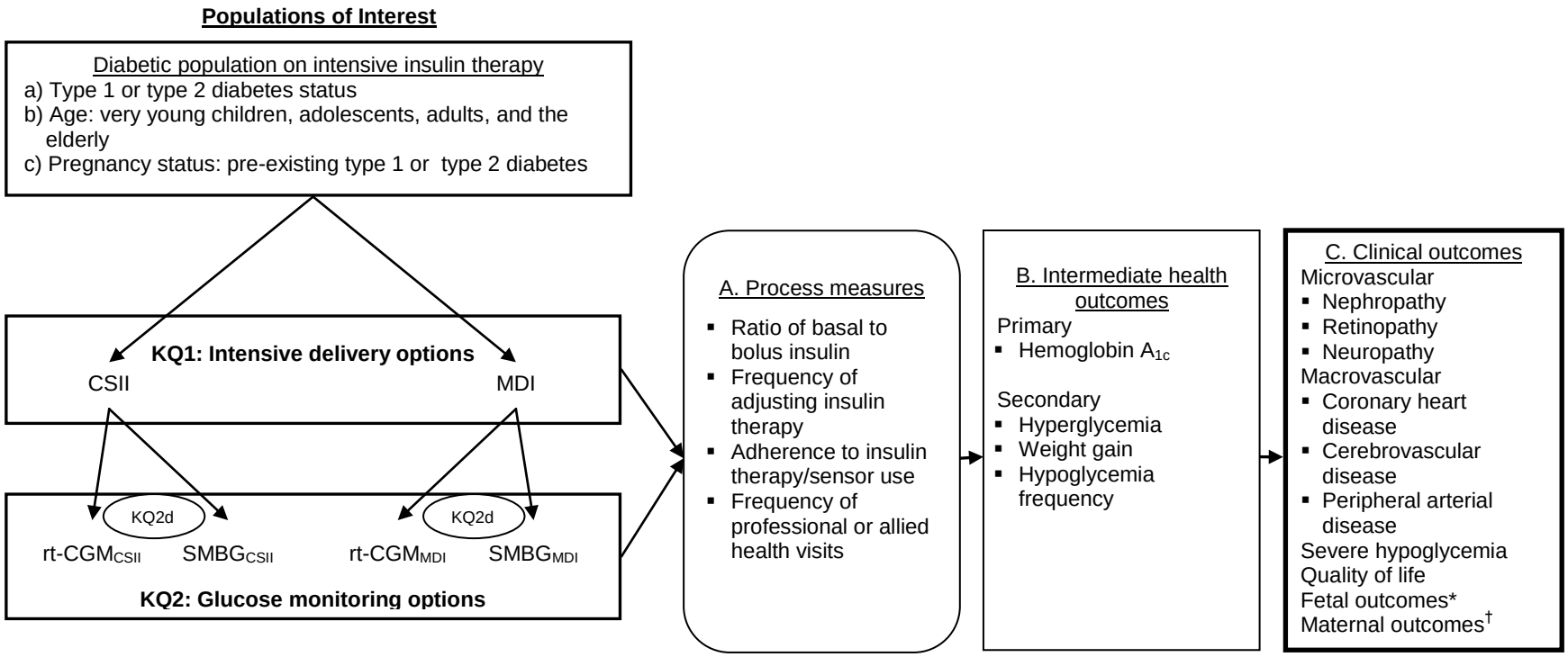
  Usage of a device for at least 24 hours.

- **Settings:**

Outpatient setting.

III. Analytic Framework

Figure 1. Analytic framework for multiple daily injections or insulin pump therapy with or without continuous glucose monitoring for diabetes



Abbreviations: CSII = continuous subcutaneous insulin infusion; KQ = key question; MDI = multiple daily injections; rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose.

*Fetal outcomes include gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, and admission to a neonatal intensive care unit.

†Maternal outcomes include cesarean section rates.

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IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

The inclusion/exclusion criteria are presented in Table 2.

Table 2. Inclusion and exclusion criteria

Population and condition of interest	• All studies will include human subjects exclusively. • We will include studies of adults, adolescents, and children with a formal diagnosis of diabetes mellitus and pregnant women with pre-existing diabetes. ○ Acceptable diagnoses will include type 1 diabetes and type 2 diabetes. Patients with latent autoimmune or pancreatomy will be considered to have type 1 diabetes. Those with steroid-induced or transplant-induced diabetes will be considered to have type 2 diabetes. ○ We will exclude pregnant women with gestational diabetes. Patients with maturity onset diabetes of the young will also be excluded, as the diagnosis is difficult to make without genetic testing and intensive insulin therapy is often not required. ○ We will use age ranges prescribed by the Juvenile Diabetes Research Foundation[17] (<8 years [very young children], 8–14 years [children], 14–25 years [adolescent], and >25 years [adults]); however, our final definitions will be guided by those used in the literature that is reviewed.
Interventions	• We will include studies that evaluate CSII and rt-CGM. ○ We will exclude implantable insulin pumps and retrospective CGM devices, as these are no longer used clinically. ○ We will exclude studies in which regular insulin was used in the insulin pump. ○ We will exclude studies evaluating the GlucoWatch continuous glucose monitor, as it is no longer used in the United States.
Comparisons of interest	• We will include studies that compare subcutaneous insulin infusion to either placebo or MDI, which will be defined as at least three injections per day. • We will include studies that compare rt-CGM to either placebo or SMBG, which will be defined as at least three fingersticks per day. • We will exclude studies of premixed insulin, because patients who use a premixed insulin are rarely considered for intensive insulin therapy with CSII. • We will exclude studies that do not have a concurrent comparison group.
Outcomes	• We will include studies that evaluate one of the following outcomes: ○ Process measures – Ratio of basal to bolus insulin – Frequency of adjusting insulin therapy – Adherence to insulin therapy/sensor use – Frequency of professional or allied health visits ○ Intermediate outcomes – HbA1c – Quality of life – Hyperglycemia – Weight gain – Hypoglycemia frequency ○ Clinical outcomes – Objective assessments of microvascular outcomes (retinopathy, nephropathy, and neuropathy) – Objective assessments of macrovascular outcomes (coronary heart disease, cerebrovascular disease, and peripheral arterial disease) – Severe hypoglycemia – Fetal outcomes (gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, and admission to a neonatal intensive care unit)

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	– Maternal pregnancy outcomes (cesarean section rates)
Type of study	• We will exclude articles with no original data (reviews, editorials, and commentaries). We will also exclude studies published in abstract form only. • We will exclude case reports, case series, and cross-sectional studies. • We will include both randomized controlled trials and observational studies that evaluate microvascular, macrovascular, maternal, or fetal outcomes. For all other outcomes, we will include only randomized controlled trials. • We will not place any restrictions on sample size or language. • Because we will be excluding studies of outdated technologies, we will exclude studies published before 1994, the 1st year that insulin analogues were used.
Timing and Setting	• We will exclude studies in which patients used an insulin device for <24 hours. • We will include studies that were conducted in an outpatient setting.

Abbreviations: CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; rtCGM = real-time continuous glucose monitoring.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

We searched the following databases for primary studies: MEDLINE®, EMBASE®, and the Cochrane Central Register of Controlled Trials. We developed a search strategy for MEDLINE, accessed via PubMed, based on an analysis of medical subject headings (MeSH) and text words of key articles identified a priori. Our search strategy for MEDLINE is:

((“Diabetes Mellitus”[mh] OR Diabet*[tiab] OR hyperglycem*[tiab] OR hyperglycaem*[tiab]) AND (“Insulin Infusion Systems”[mh] OR “continuous subcutaneous insulin”[tiab] OR CSII[tiab] OR “insulin pump”[tiab] OR “insulin pumps”[tiab] OR “pump therapy”[tiab] OR “pump treatment”[tiab] OR “artificial pancreas”[tiab] OR (“Monitoring, Ambulatory”[mh] AND (glucose[tiab] OR insulin[tiab] OR glycem*[tiab] OR glycaem*[tiab])) OR “CGM”[tiab] OR (“continuous glucose”[tiab] AND (monitor*[tiab] OR sensing[tiab] OR sensor*[tiab])))) NOT (animal[mh] NOT human [mh])

In addition, we will search ClinicalTrials.gov and review the data from the U.S. Food and Drug Administration for any additional information. We will also review the reference lists of each included article, relevant review articles, and related systematic reviews for additional relevant studies.

The search will be updated during the peer review process.

C. Data Abstraction and Data Management

Two independent reviewers will conduct title scans. For a title to be eliminated at this level, both reviewers will need to indicate that the study was ineligible. If the reviewers disagree, the article will be advanced to the next level, which is abstract review.

The abstract review phase was designed to identify studies reporting the effects of CSII therapy and rt-CGM devices on process measures, intermediate outcomes, and clinical outcomes. Abstracts will be reviewed independently by two investigators and will be excluded if both

investigators agree that the article meets one or more of the exclusion criteria (see the inclusion and exclusion criteria listed in Table 2). Differences between investigators regarding the inclusion or exclusion of abstracts will be tracked and resolved through consensus adjudication.

Articles promoted on the basis of the abstract review will undergo another independent parallel review to determine if they should be included in the final qualitative and quantitative systematic review and meta-analysis. The differences regarding article inclusion will be tracked and resolved through consensus adjudication.

We will use a systematic approach to extract all data to minimize the risk of bias in this process. We will create standardized forms for data extraction, which will be pilot tested. By creating standardized forms for data extraction, we seek to maximize consistency in identifying all pertinent data available for synthesis.

Each article will undergo double review by the study investigators for data abstraction. The second reviewer will confirm the first reviewer's abstracted data for completeness and accuracy. Reviewer pairs will be formed to include personnel with both clinical and methodological expertise. A third reviewer will audit a random sample of articles selected by the first two reviewers to ensure consistency in the data abstraction of the articles. Reviewers will not be masked to the authors of the articles, their respective institutions, nor the journals in which their articles were published.

For all articles, the reviewers will extract information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, gender, race, type of diabetes, duration of diabetes, socioeconomic status, education level, comorbidities, nutrition patterns, and exercise patterns), eligibility criteria, interventions (including device model, MDI delivery method, rt-CGM alarm threshold, length of use of current technology, changes in insulin delivery mode over time, changes in the type of insulin used, and training of patients/staff), adherence to wearing a treatment device, outcome measures, definitions, and the results of each outcome, including measures of variability. For the outcome of hypoglycemia, we will differentiate between biochemical and symptomatic hypoglycemia. For the outcome of cesarean delivery, we will abstract information regarding the indication for cesarean delivery. For studies evaluating maternal and fetal outcomes, we will abstract information about when CSII or MDI is initiated in relation to the pregnancy (i.e., prenatal, 1st trimester, or 2nd trimester).

All information from the article review process will be entered into a DistillerSR database (Evidence Partners Inc., Ottawa, Canada) by the individual completing the review. Reviewers will enter comments into the system whenever applicable. The DistillerSR database will be used to maintain the data and to create detailed evidence tables and summary tables.

D. Assessment of Methodological Quality of Individual Studies

Article quality will be assessed differently for RCTs and observational studies during the final qualitative and quantitative review. For RCTs, the dual, independent review of article quality will be based on the Cochrane Collaboration's Risk of Bias Tool.[25] For nonrandomized observational studies, we will use the Downs and Black quality assessment tool.[26] Additionally, we plan to use selected items from the McHarm Tool to assess adverse events.[27] We will supplement these tools with additional quality-assessment questions based on recommendations in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter, *Methods Guide*).[28] For both the RCTs and the nonrandomized studies, the overall study quality will be assessed as:

- **Good (low risk of bias).** These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- **Poor (high risk of bias).** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

E. Data Synthesis

We will conduct meta-analyses when there are sufficient data (at least three studies) and studies are sufficiently homogenous with respect to key variables (population characteristics, study duration, and insulin delivery device).

For continuous outcomes, we will calculate a weighted mean difference by using a random-effects model with the DerSimonian and Laird formula.[29] For dichotomous outcomes, we will calculate a pooled effect estimate of the relative risk between the trial arms of RCTs, with each study weighted by the inverse variance, by using a random-effects model with the DerSimonian and Laird formula for calculating between-study variance.[29]

Heterogeneity among the trials in all the meta-analyses will be tested by using a standard chi-squared test with a significance level of alpha ≤0.10. Heterogeneity will also be examined among studies by using an I^2 statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance.[30] A value greater than 50 percent may be considered to have substantial variability. If we find substantial heterogeneity, we will attempt to determine potential reasons for this by conducting metaregression analyses.

Publication bias will be examined by using Begg's test[31] and Egger's test,[32] including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes for which meta-analyses are conducted.

STATA statistical software (Intercooled, version 9.2, StataCorp, College Station, TX) will be used for all meta-analyses.

Studies that are not amenable to pooling will be summarized qualitatively.

F. Grading the Evidence for Each Key Question

At the completion of our review, we will grade the strength of evidence based on the quantity, quality, and consistency of the best available evidence, addressing KQs 1 and 2 by adapting an evidence grading scheme recommended in the *Methods Guide*.[28,33] We will apply evidence grades to the bodies of evidence about each intervention comparison for each outcome. We will assess the risk of bias of individual studies according to study design characteristics, such as confounding and selection and information biases. We will assess the strength of the best available evidence by assessing the limitations to individual study quality (using individual quality scores), consistency, directness, precision, publication bias, and the magnitude of the effect.

We will classify evidence pertaining to KQs 1 and 2 into four basic categories: 1) "high" grade (indicating high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of the effect); 2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of the effect and may change the estimate); 3) "low" grade (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and 4) "insufficient" grade (evidence is unavailable).

G. Assessing Applicability

We will assess the applicability of studies in terms of the degree to which the study population (age, race, sex, and baseline HbA_{1c}), interventions (titration schedule), outcomes, and settings (followup interval) are typical for the treatment of individuals with diabetes who are receiving treatment in a usual care setting. We are limiting the interventions in the review to those that are most applicable to the current population of patients with diabetes (i.e., those interventions that are currently used in the U.S. population).

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VI. Definition of Terms

CGMS = continuous glucose monitoring system
CSII = continuous subcutaneous insulin infusion
DCCT = Diabetes Control and Complications Trial
HbA_{1c} = hemoglobin A_{1c}
MDI = multiple daily injections
RCT = randomized controlled trial
rt-CGM = real-time continuous glucose monitoring
SMBG = self-monitoring of blood glucose

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

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Appendix 1. Draft Key Questions

KQ1: In patients with diabetes using intensive insulin therapy, what is the comparative effectiveness of multiple daily injections (MDI) versus continuous subcutaneous insulin infusion (CSII) on process measures, intermediate outcomes, and clinical outcomes? Process measures, intermediate outcomes, and clinical outcomes of interest are summarized below in Table 1. Do these effects differ by:

1a. Type 1 or Type 2 diabetes status?
1b. Age: very young children, adolescents, and adults?
1c. Pregnancy status: gestational diabetes (GDM) and pre-existing Type 1 and Type 2 diabetes?

KQ2: In patients with diabetes using intensive insulin therapy (stratified by MDI or CSII), what is the comparative effectiveness of real-time continuous glucose monitoring (rt-CGM) versus self-monitoring of blood glucose (SMBG) on process measures, intermediate outcomes, and clinical outcomes (see Table 1)? Do these effects differ by:

2a. Type 1 or Type 2 diabetes status?
2b. Age: very young children, adolescents, and adults?
2c. Pregnancy status: GDM and pre-existing Type 1 and Type 2 diabetes?

KQ3: In patients with diabetes using rt-CGM, what is the comparative effectiveness of MDI versus CSII on process measures, intermediate outcomes, and clinical outcomes (Table 1)? Do these effects differ by:

3a. Type 1 or Type 2 diabetes status?
3b. Age: very young children, adolescents, and adults?
3c. Pregnancy status: GDM and pre-existing Type 1 and Type 2 diabetes?

Table 1. Summary of process measures and intermediate and clinical outcomes

Process Measures	Intermediate Outcomes	Clinical Outcomes
• Ratio of basal to bolus insulin • Frequency of adjusting insulin therapy • Adherence to insulin therapy/sensor use	Primary • Hemoglobin A_{1c} Secondary • Quality of life • Hyperglycemia • Weight gain • Hypoglycemia frequency	Microvascular • Retinopathy • Nephropathy • Neuropathy Macrovascular • Coronary heart disease • Cerebrovascular disease • Peripheral arterial disease Severe hypoglycemia Fetal outcomes* Maternal pregnancy outcomes • Antenatal hospital stay (% requiring admission, length of stay) • Cesarean section rates

*Fetal outcomes include gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, and admission to a neonatal intensive care unit.

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Appendix 2. List of insulin pump models

Manufacturer	Model	Decision Date	Features
Abbott			
	Insulin Pump	12/23/05	Insulin pumps are indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin.
	Aviator	1/11/08	The Aviator insulin pump shares the same intended use and indications for use as the predicate device, the Abbott Diabetes Care infusion pump. Both the Aviator infusion pump and the predicate pump have two microprocessors to control and monitor drug delivery. The user interface on the Aviator was enhanced as a result of user needs.
	Freestyle Aviator	2/20/09	Insulin pump and BGM system-insulin infusion pump (Aviator) and wireless remote controller (Aviator companion). Aviator companion provides an alternate user interface to the Aviator pump which is useful when pump is hidden under clothing.
Animas			
	Model IR 1000	2/10/00	Subcutaneous delivery of insulin at programmable basal and bolus rates.
	Model IR 1000 LR	05/29/02	Insulin infusion pump and software for histories, basal rate program, and pump settings.
	Model IR 1200	10/16/03	The system will deliver a prescribed dosage of insulin as a single programmable bolus or at multiple programmable basal rates. The system will also provide set-up information, dosage history, alarms, error and warning messages, device status, and self test capabilities.
	Model IR 1250	12/10/04	Insulin delivery system, basal and bolus programmable options, computer software (Mac or PC available), minor differences between this and 1200 series, including food item-insulin pairings.
Cane			
	Microjet Quark model U-100	12-12-01	Pump for insulin infusion therapy.
Cardiac Pacemakers, Inc.			
	Betatron IV insulin infusion system	2-23-90	No summary information.
Deltec/Smiths Medical			
	Deltec Cozmo® TM Insulin Infusion Pump (Model1700) and Accessories	8-13-02	Compared to: MiniMed Model 508 Insulin Pump, MiniMed 3.0-ml Reservoir, Deltec CADD-Diplomat System,and MiniMed Corn-StationTM Communication System.
	Deltec Cozmo® Insulin infusion pump w/ CoZmonitor® Glucose monitor	5-27-04	Insulin infusion pump and glucose monitor.

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Appendix 2. List of insulin pump models

Manufacturer	Model	Decision Date	Features
	Deltec Cozmo® Insulin Infusion Pump model 1800 w/ CoZmonitor®	12-1-06	Insulin infusion pump and glucose monitor.
Disetronic/ Roche			
	H-TRON™ V 100 insulin infusion pump	4-12-97	No summary information.
	H-TRON™plus V 100 insulin infusion pump	9-15-97	Functionally equivalent to previous model.
	DAHEDI insulin infusion pump	6-15-99	Basic infusion insulin pump.
	D-TRON™ insulin infusion pump	12-30-99	Equivalent to H-Tron Plus V100.
	D-TRON™ insulin infusion pump	8-2-02	Slight modifications.
	D-TRON™plus insulin pump	9-11-02	Slight modifications for D-TRON.
	D-TRON™plus modification	10-29-02	Slight modifications for D-TRONplus.
	D-TRON™plus modification	12-1-04	Slight modifications for D-TRONplus.
	ACCU-CHECK® Spirit	3-18-05	Infusion insulin pump.
	ACCU-CHEK® Spirit modification	6-15-06	Minor modifications.
Insulet			
	iXL™ Diabetes management system	12-19-03	Equivalent to Medtronic MiniMed. Insulin pump.
	iXL™-11 DMS	1-3-05	Insulin pump and blood glucose measurement system.
Mendigo			
	Solo™ insulin patch pump	7-3-09	Same as prior models, insulin pump.
	Solo™ MicroPump insulin-delivery system	1-25-10	Identical to prior Solo patch pump.
Medtronic Minimed			

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Appendix 2. List of insulin pump models

Manufacturer	Model	Decision Date	Features
	Model 506 external insulin pump	7-2-90	Insulin infusion pump.
	Infusion pump Model MMT-507	4-30-96	Insulin infusion pump.
	Insulin pump model 505	4-8-97	Insulin infusion pump, simplified software.
	Model 507C	8-15-97	Slight modification to model 507.
	Model 508	6-8-99	Insulin infusion pump.
	Paradigm® model 512 Insulin pump and BD Paradigm link Glucose monitor	6-17-03	Bolus and basal insulin pump and linked glucose monitor.
	Paradigm ®Model 511	7-19-04	Insulin infusion pump.
	Model MMT-712E	1-31-06	Insulin infusion pump.
	MMT- 512, MMT-712, MMT-515, and MMT-715	4-25-08	Continuous delivery insulin pumps.
NiliMedix			
	ADI	6-6-08	Ambulatory insulin infusion pump.
Nipro			
	Glucopro infusion pump	6-24-02	Equivalent to Disetronic H-Tron plus v100.
	Amigo ®	5-9-05	Insulin infusion pump.
	Amigo ®	12-14-07	Equivalent to Animas IR 1250.
Pharma-Plast			
	Pharma-Plast insulin infusion set	6-21-89	Insulin infusion pump.
Sooil			
	DANA Diabecare®	8-14-00	Insulin infusion pump (basal and bolus).
	DANA Diabecare® II	8-2-02	Software modifications to previous DANA.
	DANA Diabecare® IIS	2-2-07	Slight modifications to previous II.

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Appendix 3. List of continuous glucose monitors

Manufacturer	Model	Decision Date	Features
Abbott			
	FreeStyle Navigator®	3-12-08	18+ CGM system, alarms
	FreeStyle Navigator® supplements	4-2-08; 5-15-08; 5-21-08; 6-2-08; 8-6-08; 8-25-08; 10-8-08; 3-6-09; 4-9-09; 4-13-09; 5-8-09; 6-24-09; 8-21-09; 9-21-09; 9-25-09; 10-29-09; 11-20-09; 1-11-10; 1-19-10; 7-9-10	Minor modifications to original
Dexcom			
	STS® Continuous Glucose Monitor	3-24-06	Detects trends and tracks patterns in adults (18+); indicated for use as an adjunctive device to complement, not replace, standard glucose monitoring devices; aids in detection of hyperglycemia and hypoglycemia, facilitates both acute and long-term therapy adjustments
	STS® supplements; Seven plus system	5-31-07; 8-12-06; 9-1-06; 9-22-06; 12-26-06; 1-23-07; 2-26-07; 3-15-07; 4-10-07; 5-25-07; 10-22-07; 11-13-07; 1-11-08; 5-15-08; 7-16-08; 12-3-08; 2-13-09; 5-5-09; 9-17-09; 9-23-09; 12-4-09; 1-28-10; 6-9-10; 7-15-10; 8-25-10; 9-9-10	Various updates/modifications to the STS Continuous Glucose Monitor system
Medtronic Minimed			
	Continuous Glucose Monitoring System	6-15-99	Continuously records interstitial glucose levels; supplements, does not replace standard at home glucose monitors. Can download the information gathered through computer software
	Guardian® Telemetered Glucose Monitoring system	2-20-02; 6-25-02; 9-5-02	Continuous Glucose Monitor

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Appendix 3. List of continuous glucose monitors

Manufacturer	Model	Decision Date	Features
	Guardian® Real Time Continuous Glucose Monitoring System	1-7-04	Hypo- and hyperglycemia alerts; up to 21 days stored data.
	Paradigm® Real Time System	7-18-05; 8-24-05	No summary information.
	Guardian® Real Time	4-7-06	Slight modifications to enable continuous glucose monitor to communicate with insulin pump directly.
	Paradigm® RT	6-14-06	Modifications to monitor and transmitter; can manually enter calibration.
	Guardian® RT	10-16-06	Approval for use in Puerto Rico.
	Paradigm® RT and Guardian® RT	3-8-07	Pediatric use approved (ages 7–17 years) and adults (ages 18+ years).
	Minimed RT transmitter, CGM system	4-18-08; 8-21-09; 11-5-09; 12-1-09; 3-20-10; 4-5-10; 6-3-10; 9-9-10	Slight modifications.
	Continuous Glucose Monitoring System	4-23-08	Slight modifications.
		7-17-08; 8-28-08; 10-2-08; 10-3-08; 11-14-08; 11-20-08; 3-16-09; 6-16-09; 6-19-09; 8-13-09; 8-21-09; 10-1-09; 10-28-09; 10-29-09; 3-26-10; 6-10-10 8-23-10	Slight modifications.