Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness*

Draft review available for public comment from August 15, 2011 to September 9, 2011.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Quality of report	Good	Thank you for your comments!
Peer Reviewer 2	Quality of report	Superior	Thank you for your comments!
Peer Reviewer 1	General comments	This is a comprehensive and clinically important review of the efficacy of insulin pump therapy in types 1 and 2 diabetes. The key questions are appropriate, explicitly stated, and addressed directly in the review.	Thank you for your comments!
Peer Reviewer 2	General comments	The key questions are appropriate, as are the populations. From the reviewer's perspective the key comparisons would be CSII vs MDI and rt-CGM vs not in T1 patients (adult and pediatric).	We agree that this would be an appropriate comparison and this study has not been conducted yet. We indicate in the discussion that this is an important area of future research.
Peer Reviewer 4	General	Rating: Fair; however, we recognize the enormity of this task and the huge amount of work that went into producing this document	Thank you for your comments!
Peer Reviewer 4	General	Regarding the General Comments, Introduction, Methods, Results, and Discussion/Conclusion, we believe that the authors achieve the desired objectives to some extent, but with qualifications as listed below. The report is clinically meaningful. We agree with the conclusions regarding outcomes in subjects with type 2 diabetes and in pregnant women.	Thank you for your comments!
Peer Reviewer 4	General	We would be willing to review revisions after January 1, 2012; the revisions should be summarized separately, and then identified in the document by highlighting the changes in red.	Thank you very much for the offer. However, we will follow AHRQ's requirements for submitting the final report.
Reviewer 5	General	1 definitely clinically meaningful 2 Target audience not very clearly defined 3 Key questions are appropriate	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Response
Reviewer 6	General	The report is clinically meaningful and provides useful information. Both target population and audience are explicitly defined. And the key questions are appropriate and explicitly stated. However, the report is so dense that it is hard to follow in some places, even with the excellent use of frequent headers. I think a reader will have to be extremely motivated to read this report. Otherwise they will only read the summary.	We appreciate that the report is dense with details and have tried to emphasize the key points in an organized fashion in the Executive Summary.
Peer Reviewer 3/TEP	Comments to editors	The entire review was performed on-line prior to the due date, only to have the site crash when I submitted it. I have left comments for editors on the website, but will not use it again for a manuscript review as it is both poorly designed to accept word documents and has demonstrated its instability. This version of the review is less comprehensive than the original, simply because my time is limited and my frustration level is high. My comments to the authors are not colored by this, but the depth and quality of this review is less than I would have hoped to provide (and did in the original!).	We are very sorry to hear of the difficulties you had with the reviewing software. We will alert ARHQ to this problem.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3/TEP	General comments	This is a well written and comprehensive review of two separate clinical issues in diabetes care; specifically comparisons of therapeutic modalities in the setting of intensive insulin therapy, and the intensity of monitoring of glucose during such therapy. The authors appear to have employed traditional systematic review techniques and meta-analytical methodologies, but have lost their focus on the clinical issues. For example, the data are not generalizable, as the initiation, instruction, monitoring and therapeutic changes implied for both CSII and rt-CGM are limited to expert centers and highly motivated and intelligent individuals or families with diabetes. Second, there is an inherent ascertainment bias in all studies of rt-CGM when it comes to hyperglycemia and hypoglycemia, as there is considerably more data available compared to SMBG. Third, they ignore the temporal changes in diabetes therapy and targets which differentiate this from prior reviews and the potential impact on meta-analyses of older versus more recent papers. Finally, the authors need to expand their Future Research to address the “clinically relevant end-points” to provide guidance for future power calculations to determine the feasibility and practicality of undertaking the study. For example, determining microvascular and macrovascular endpoints in studies of these interventions is not feasible.	We agree that these are all excellent points that have now been addressed in the revised discussion. We have added the following statements to the discussion: "Our data are not generalizable to non-specialty settings or all patients with diabetes mellitus as the initiation, instruction, monitoring, and therapeutic changes for CSII and rt-CGM use if often limited to expert settings and highly motivated patients and families. All studies of rt-CGM are subject to ascertainment bias because there are more hypoglycemia and hyperglycemia data than with SMBG alone. Finally, because it is not feasible to perform double-blinded RCTs, there is potential to bias reporting of quality of life outcomes in favor of CSII and rt-CGM if patients believe them to be superior a priori." We believe that the temporal changes in therapy and how that explains how our review differs from prior reviews is now addressed in the revised discussion section on CSII versus MDI. We have added the following statement to the "Future Research" section regarding clinical outcomes: "There is also a need for well-designed prospective, observational studies to determine the comparative effectiveness of CSII versus MDI and rtCGM versus SMBG on clinically relevant long-term micro- and macrovascular outcomes. Such studies would also provide guidance on effect sizes for future power calculations to determine whether it is even feasible and practical to undertake RCTs examining these outcomes."
Peer Reviewer 3/TEP	General comments	This is a well written and comprehensive review of two important aspects of diabetes care	Thank you for your comments!

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3/TEP	General comments	The organization is excellent, with initial delineation of unique demographic groups by type of diabetes, age and presence of pregnancy. Goals of therapy differ in these groups, so their analysis is necessarily separate. This later point deserves greater explanation in the Introduction and will help to explain the paucity of data in those over the age of 60. The authors need to describe the clinical indications for both intensive insulin therapy and intensive glucose monitoring, and how the goals of therapy have changed over time as this may impact the interpretation of the data	We agree that the goals of therapy are different for different groups with diabetes. We have added a statement to the "Importance of Tight Glycemic Control and Associated Risks in Diabetes" on less stringent glycemic goals in certain elderly individuals with diabetes. We have also added a section under "Knowledge Gaps" entitled "Clinical Decision-Making and Indications" to describe the indications for intensive insulin therapy and intensive glucose monitoring. We believe that discussion of how intensive insulin therapy and intensive glucose monitoring have evolved over time is already discussed in the introduction in "Methods to Achieve Tight Glycemic Control and Minimize Risks."
JDRF/Aaron Kowalski	General	JDRF applauds AHRQ on its efforts to develop evidence-based reports and technology assessments that assist payors, physicians and individuals with T1DM in their decision-making towards achieving optimal glycemic control and appreciates AHRQ's inclusion of research suggested by JDRF and other stakeholders earlier in the process. We would like to reiterate AHRQ's findings regarding the value of real time CGM (rt-CGM) and also of sensor-augmented pump therapy (rt-CGM with CSII) in improving the clinical outcomes and lives of people with type 1 diabetes. It is critical that access to these technologies remain broadly available to reduce the rate of complications, improve quality of life and significantly lower healthcare costs for all stakeholders. While we agree with AHRQ's finding that pump therapy improves the quality of life for individuals with T1DM we believe that the scope of clinical benefits are inadequately addressed due to the exclusion of earlier studies using regular human insulin. We recommend that these papers be reconsidered for inclusion in your draft	Thank you for your comments. While we agree that earlier studies that used regular insulin in the insulin pump were scientifically valid, their results are less relevant today as only rapid-acting analogs are used in the pump. We still believe that the most relevant comparisons are the ones used currently in clinical practice. In our comparative effectiveness review we sought to include technologies which are relevant to current real-world practice. For this reason we included pumps using rapid-acting analogs rather than regular insulin. The papers referenced while helpful do not meet our inclusion criteria.

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		document as these remain scientifically valid comparisons of CSII vs MDI.We also take this opportunity to include a very recent reference1 on the usage and effectiveness of the low glucose suspend feature of the Medtronic Veo insulin pump. The integration of this feature in a system that combines rt-CGM and CSII represents an important first milestone towards developing artificial pancreas systems. These systems would ultimately enable tighter control over the management of glucose levels than is possible using sensor-augmented pump therapy. A recent study2 by Michael O'Grady and other researchers at University of Chicago and Harvard predicted that the development of an artificial pancreas could save Medicare almost $2 billion over the next 25 years.	
JDRF/Aaron Kowalski	publications cited	Pratik Agrawal et al. Usage and Effectiveness of the Low Glucose Suspend Feature of the Medtronic Paradigm Veo Insulin Pump. Journal of Diabetes Science and Technology Volume 5, Issue 5, September 2011; Michael J. O'Grady et al. Changes in Medicare Spending for Type 1 Diabetes with the Introduction of the Artificial Pancreas. O'Grady Health Policy LLC June 9, 2011	Our review was focused on the two current technologies--CSII and rt-CGM. We agree that this recent technology is important in extending the effectiveness of the sensor-augmented pump in the future. A full discussion/review of approaches to closed-loop technology is beyond the scope of our systematic review.

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Roche diagnostics	search strategy	In general, the search strategy seems to be appropriate with regard to the questions to be answered. Still, we found the following limitations: The cut-off point for the search is October 2010. Given almost one year elapsed since then AHRQ may want to consider an updated search. Given the strategy AHRQ did not explicitly search for SMBG, but only for “diabetes” combined with either “insulin infusion systems” or “continuous glucose monitoring”. It only used the MeSH term „Monitoring, Ambulatory“1 which is quite general. Furthermore, within Medline the MeSH term is not consistently applied for glucose monitoring and very seldom for SMBG.	The Executive Summary and abstract have been modified to reflect the updated search through July 2011.
Roche diagnostics	Search/objectives	It may be assumed that both aspects will be covered by most studies, but there can be cases where the study is restricted to only hypoglycemia	We reviewed the articles that you had suggested. None of them met our exclusion criteria.
Roche diagnostics	Search/objectives	99 PubMed and 62 Embase hits we found by adding “Hypoglyc(a)em*” to the search terms. AHRQ excluded in the Embase search publications about certain drugs which do not have much relation to diabetes: „OR 'budesonide'/exp OR 'budesonide' OR 'methylprednisolone'/exp OR 'methylprednisolone' OR 'prednisolone'/exp OR 'prednisolone' OR 'prednisone'/exp OR 'prednisone' OR '6- methylprednisolone':ab,ti OR budesonide:ab,ti OR corticosteroid*:ab,ti OR glucocorticosteroid*:ab,ti OR prednisolone:ab,ti OR prednisone:ab,ti)“ The reason for exclusion of these drug terms appears not to be clear. AHRQ may want to revisit this topic and may want to decide to run an updated search. The purpose of the double use of the term “NOT ([animals]/lim NOT [humans]/lim)” was not clear to us.	See response to comment above. There was an error in the search string as presented in the appendix, and this has been fixed.
Roche diagnostics	inclusion/exclusion criteria	In general, AHRQ used a different study selection approach than other systematic	While observational studies do provide some evidence regarding comparative effectiveness, it is

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		reviews like Cummins et al. (4), Misso et al. (5) and and Pańkowska et al. (6). In comparison, this leads to a significantly reduced body of medical evidence. It seems that AHRQ follows a goal of high internal validity in it's inclusion and exclusion criteria. A significant emphasis is given randomized clinical trials. Observational evidence is only accepted for unless micro- or macro vascular outcomes and maternal or fetal outcomes, thus for outcomes that apparently need time to develop and are therefore difficult to capture in clinical trials. Despite its aim in the methods guide cited above, until now AHRQ does not given any reason for choosing this approach. Therefore, Roche Diagnostics would appreciate if AHRQ could give reasons for this choice. Furthermore, developing a clear rationale for including non-randomized studies would enhance the quality of the report.Beyond that we acknowledge that assessing the quality of studies like RCTs and observational studies is an integral part of HTA. Still, we kindly ask to consider if limiting the observational evidence base to studies that only accept micro- or macro vascular outcomes and maternal or fetal outcomes without giving a reason is appropriate for learning health care system in the era of comparative effectiveness:"Research using observational data already occurs frequently, and has for a long time. Using such data for research is clearly consistent with the Institute of Medicine's evolving concept of a "learning healthcare system" in which healthcare delivery continuously benefits as real-world evidence accumulates". In this context Dreyer al. state: "Although methodological challenges and a lack of accepted principles to assess the quality of nonrandomized	our opinion that, if adequate randomized CT data are available, that this type of data is far superior as it is less subject to confounding by unmeasured variables and other biases.

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		studies of comparative effectiveness have limited the practical use of these investigations, even imperfect studies can contribute useful information if they are thoughtfully designed, well conducted, carefully analyzed, and reported in a manner that addresses concerns from skeptical readers and reviewers." and "… the interpretation of these observational studies requires weighing of all available evidence, tempered by judgment regarding the applicability of the studies to routine care."(8) Because of the advantage of potential longer follow-up in observational studies, they can avoid typical pitfalls of short duration trials like patients not becoming proficient in pump usage. Moreover, they can generate useful data about training requirements for pump users or patient satisfaction in terms of continuation rates.(4) The Czech National Register documents outcomes after switching to CSII: Patient groups of type 1 and 2 diabetes "achieved substantial reduction of HbA1c. Safety evaluation showed that fewer patients with T2 diabetes were affected by adverse events. According to that CSII treatment for patients with T2 diabetes is similarly effective with a slightly better safety profile."	

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Roche diagnostics	inclusion/exclusion criteria	Especially, considering adherence data from RCTs only is questionable because one misses insights important information about acceptance and success factors of insulin delivery in real- life, e.g. within a pediatric population or adolescents: “Extensive screening by a multidisciplinary diabetes team prior to initiation of CSII regimen results in relatively lower discontinuation rates and a higher chance of maintaining optimal glycemic control (HbA1C < 8%) compared to previous studies." And "Adolescents currently prescribed CSII therapy evidenced key differences from their counterparts using multiple daily injections (MDI) in insurance status, diabetes management behavior, and family functioning related to diabetes. Efforts to understand the role of family factors in the maintenance of CSII therapy with clinical indicators of CSII use may inform treatment effectiveness. They emphasized the difficulties of school-age children receiving pre-lunch insulin injections and the stress thereby induced in these children and their parents.	We acknowledge that information may not be adequately captured in the published literature. We have cited that as a limitation.
Roche diagnostics	inclusion/exclusion criteria and regular insulin	We would like to specifically ask for clarification with regard to inclusion and exclusion of studies using regular insulin. While studies using regular insulin for insulin pumps were excluded when using methods of insulin delivery methods no longer used in clinical practice as stated on page ES-7, the procedure with regard to studies using regular insulin for MDI regimens appears less clear. It is stated on page 72 that the review only includes studies using rapid-acting insulin analogs and not regular insulin in the CSII and MDI intervention groups. However, studies using regular insulin for insulin boluses are included in the review, and “regular insulin was used for MDI” does	We decided to limit to rapid analogues in that this is what is generally used in clinical practice. There was a time period when rapid acting insulin analogues were used in the pump but regular insulin were used in MDI and we decided that inclusion of these studies was more appropriate than excluding them. In theory, this comparison should favor the rapid acting CSII, particularly in terms of HbA1c, hypoglycemia outcomes, and quality of life.

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		not appear in the exclusion report (Appendix C). There is no obvious scientific rationale for excluding studies using regular insulin for CSII but not for MDI. In both regimens, rapid-acting insulin analogs might support better postprandial glucose control, for instance by reducing the risk of early postprandial hyperglycemia and late postprandial hypoglycemia related to better matching of insulin action with glucose absorption after meals with high glycemic index. Modern insulin pumps may be able to compensate pharmacokinetic properties of insulin to some extent by offering a choice of different bolus types. When using multi-wave boluses (also called dual-wave boluses) consisting of an immediately delivered and an extended part for meals with prolonged nutrient absorption, the pattern of insulin delivery when using rapid- acting insulin analogs can be modified to achieve a duration of insulin action observed when using regular insulin. In contrast, only standard, immediately delivered, insulin boluses can be administered in MDI therapy. While in the United States, only rapid-acting analogs are currently approved for use in insulin pumps, in some other territories, regular insulin are available for use in insulin pumps.The share of rapid-acting analogs has been increasing during the last decade for both CSII and MDI therapy, with the share of rapid-acting analogs higher in CSII therapy.	
Roche diagnostics	exclusion	"Other reasons for exclusion" for the study by Home 1982 could be specified to a larger extent.	We excluded all studies published prior to 1994, the year when insulin analogues were introduced. Since regular insulin is no longer used in insulin pumps, we decided to exclude all studies that did not use an insulin analogue in the pump.

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Roche diagnostics	exclusion	Why is applying "No comparison with placebo or usual care" to Nosadini 1988 a valid exclusion criteria?	We excluded all studies published prior to 1994, the year when insulin analogues were introduced. Since regular insulin is no longer used in insulin pumps, we decided to exclude all studies that did not use an insulin analogue in the pump.
Roche diagnostics	exclusion	Furthermore, we provide a comparison of the studies the systematic reviews by Misso et al. (Table 1) and Cummins et al. (Table 2) include in comparison to the draft by AHRQ. Especially those studies for which AHRQ does not give explicit exclusion reasons may be to be considered for inclusion into the AHRQ draft comparative effectiveness review.	We have summarized in a table, separate from the report, the reasons that articles included in the Misso systematic review were not included in ours. We have also summarized this in the discussion. The review by Misso included observational studies and studies utilizing regular insulin in the CSII whereas our review excluded these studies.
Roche diagnostics	exclusion/general	compares our figures (forest plots, etc) to Misso in regards to their inclusion of more observational studies	We have excluded observational studies due to their inherent biases as stated previously.
Medtronic/Francine Kaufman	General	We fully support AHRQ's findings regarding the value of real time continuous glucose monitoring (rt-CGM) and sensor-augmented insulin pump therapy (rt-CGM with continuous subcutaneous insulin infusion (CSII)) in improving the clinical outcomes and lives of people with type 1 diabetes. Per the findings in the draft review, for patients with type 1 diabetes, rt-CGM used alone or in conjunction with CSII significantly lowers A1C compared to the finger stick method of self-monitoring of blood glucose (SMBG). These findings will help educate providers, patients, and payers about the value of rt-CGM for patients with type 1 diabetes and ensure that patients with diabetes have appropriate access to this life-changing technology.	Thank you for your comments on this portion of the report.

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Medtronic/Francine Kaufman	General	However, we believe that the draft review's conclusions regarding the value of continuous subcutaneous infusion (CSII) for adult and pediatric patients does not appropriately capture the value of this technology for patients with diabetes. While we agree with the finding that CSII improves the quality of life for patients with diabetes, we believe that other clinical benefits of CSII compared with MDI were inadequately addressed in the draft review. Our comments in the remainder of this letter focus on the following two concerns: 1. Additional randomized controlled trials (RCTs) should have been included in the meta-analysis on the effectiveness of CSII vs. MDI. 2. Evidence from observational studies should be included for additional clinical and patient reported outcomes in the assessment to provide additional insight into the value of CSII in the real-world setting.	We recognized that RCTs may not have included important clinical outcomes and we decided a priori, based on the recommendation of our Technical Expert Panel, to include observational studies for clinical outcomes. This is described in our Methods. With our comprehensive search strategy, we did not identify observational studies meeting our inclusion criteria that addressed microvascular and macrovascular clinical outcomes. We did identify a sufficient number of RCTs that included the patient reported outcome of quality of life and did not need to include observational studies for this outcome.
Reviewer 4	Title/Scope	Title: Misleading; glucose monitoring devices are not compared, nor are all of the methods of insulin delivery; the title “Comparative Effectiveness of Intensive Insulin Delivery and the Use of Continuous Glucose Monitoring vs. Self Monitoring of Blood Glucose (SMBG) in Diabetes Mellitus” is more precise.	Our title was incorrectly posted and the correct title should include "methods" and not "devices" and read "Comparative Effectiveness and Safety of Intensive Insulin Delivery and Glucose Monitoring Methods in Diabetes Mellitus." We believe this title is an accurate description of what our report examines.
Abbott/Eileen Bockoff	Title/Scope	The draft title of the AHRQ review is “Comparative Effectiveness of Multiple Daily Injections or Insulin Pump Therapy with or without Continuous Glucose Monitoring for Diabetes.” We would note, however, that what AHRQ appears to contemplate is a review of several overlapping treatment and diagnostic tools used by individuals with diabetes. Specifically, in the draft Key Questions, AHRQ proposes a multifactorial examination of a variety of combinations of treatments and monitoring technologies for	Our goal was to evaluate the effectiveness of CSII vs MDI and rtCGM vs SMBG in multiple populations, when possible. For CGM, we found that the knowledge base was not sufficiently robust to divide into subpopulations, although we acknowledge that the effect may differ in certain subpopulations (eg older vs younger), mostly driven by the adherence to the device. We believe that one of the important functions of the systematic review is to identify gaps in the knowledge base that require further investigation. This would include investigating the comparative effectiveness of

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		patients using intensive insulin therapy, including comparisons of the use of (1) multiple daily injections (MDI) versus continuous subcutaneus insulin infusion (CSII), and (2) and continuous glucose monitoring (CGM) versus self-monitoring of blood glucose (SMBG). These results would be further differentiated by diabetes type, age, and pregnancy status. The broad nature of these questions appear to lend themselves to more than one review. We believe that AHRQ's comparative effectiveness analysis would benefit from a more careful focus on those patients most likely to use intensive insulin therapy (MDI and CSII), since existing clinical data is not robust enough to provide a meaningful analysis of all of the narrow subpopulations and therapy combinations identified by AHRQ. Given that there is more extensive evidence regarding CSII and CGM use in Type 1 adults, we recommend that this population be the focus of the AHRQ review. Approximately 8% of pregnant women develop gestational diabetes (GDM) annually representing a small pool of individuals. Current screening for GDM occurs most commonly at about 28 weeks and, if found to be positive, treatment involves use of intensive management for approximately 6-8 weeks, a relatively short duration of time. It is uncommon for women with gestational diabetes to use CSII or CGM; SMBG is the management tool of choice. These combined factors lead to the probability that data may be insufficient to examine separately this patient population. While early clinical evidence indicates the promise of CGM systems to provide more comprehensive data for health care management decisions and reduction in the occurrence of hypo- and	rtCGM in subpopulations

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		hyperglycemia, all of which may lead to improved outcomes, CGM is still an evolving technology. AHRQ may want to reconsider inclusion of CGM in its review and concentrate its analysis on insulin therapy. At this time, use of CGM comprises a relatively small population leading to insufficient sample sizes. Composition of existing clinical data may not be suitable to stratify by insulin administration method, age, pregnancy status, and diabetes type. Additional evidence on the clinical benefits of CGM is now emerging, and ongoing robust data is expected in the future. This is described more fully in the clinical literature referenced as an attachment. AHRQ may wish to defer examining this population until additional evidence is available. If AHRQ does decide to examine CGM as part of its insulin therapy review, we recommend that the review pay careful attention to issues of patient adherence and utilization of data as it relates to therapy management decisions. The ability to successfully improve metabolic control with use of CGM technology was clearly demonstrated in a 2009 study conducted by the Juvenile Diabetes Research Foundation (JDRF). Participants between the ages of 13-21 who did not adhere to device wear were found to have the poorest primary study outcome. We also note that outcomes data related to CGM may be impacted by the lack of specific treatment guidelines for this technology. The American Association of Clinical Endocrinologists (AACE) has issued consensus statements that are intended to guide treatment strategies. However, health care providers and patients continue to work on developing parameters for the best use of CGM technologies as they relate to individual	

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		populations. In addition, the American Diabetes Association's (ADA) 2010 Clinical Practice Recommendations highlight the usefulness of CGM in conjunction with intensive insulin regimens in selected adults (age 25 or more) with Type 1 diabetes. We recommend that AHRQ concentrate any review of CGM technology on this patient population	
Abbott/Eileen Bockoff	Title/scope	Considering the small population of individuals with Type 2 diabetes or GDM that use CSII, we recommend that this question be streamlined to concentrate on the impact of MDI versus CSII for individuals: (1) with Type 1 diabetes, (2) with Type 2 diabetes on insulin, and (3) pre-existing Type 1 diabetes in pregnancy.	see above
Reviewer 4	Abstract/Analysis	Abstract and Analysis: The paper reviewed CSII vs. MDI, rt-CGM vs. SMBG, and CSII with rt-CGM vs. MDI with rt-CGM, although the review of rt-CGM vs. SMBG on pages 53-64 includes studies that were done on subjects using CSII, MDI, and unspecified type of intensive therapy (Review Methods, page iv, lines 20-24); this made this section and the section on "Comparative Effects of rt-CGM and SMBG among Patients with Type 1 Diabetes" (pages 53-118) confusing, and difficult to interpret.	Based on the available literature, we have listed the comparisons that we were able to make: in the rt-CGM section, we compare studies using CSII/MDI + rt-CGM vs. CSII/MDI without rt-CGM; in the section about sensor augmented pump, we compared effect of CSII + rt-CGM vs. MDI + SMBG. This section includes these two sets of comparisons. While the comparisons may not be initially intuitive, we described the results in two separate sections in an attempt to provide more clarity.
Reviewer 4	Abstract	Page iv, line 32; to be more clear, the sentence should state that "In children and adults with type 1 diabetes, CSII use was associated with improved quality of life…" (consistent with page 72, line 26).	This statement in the abstract has been changed as suggested.

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Reviewer 4	Objectives	Objectives: page ES-4, page 6, pages 12-13, Figure 1, and throughout the document; KQ2: should this state rt-CGM vs. SMBG and rt-CGM with CSII vs. rt-CGM with MDI (i.e., KQ3) (see #4 above). Can the studies be divided in this manner? If not, why 2 different analyses?	We have added a summary of the forms of intensive insulin therapy used in the rt-CGM versus SMBG comparison. Five studies used CSII only and four studies used CSII or MDI. There were no studies that used MDI alone. Consequently, were could not perform a sub-analysis comparing rt-CGM versus SMBG stratified by intensive insulin delivery method (CSII or MDI). We point this out as a limitation in the discussion.
Reviewer 4	Introduction	Methods: page ES-2, lines 35-36 and page 3, line 29: pain is probably less of a barrier to SMBG than other barriers such as motivation, behavioral skills, cost, lifestyle, and skills training, to name a few; this statement is too simplistic.	We agree that there are other barrier and have altered this statement as follows in the Executive Summary and Introduction: "The challenges to use of SMBG are the associated pain, costs, behavioral and technical skills, required motivation, and intrusiveness that affects adherence to this technique and is a barrier to tight glycemic control."
Reviewer 4	Introduction	Page 2, line15; this statement is incorrect; in the DCCT, even though intensively treated subjects had a greater incidence of severe hypoglycemia, there was no difference between intensively and conventionally treated subjects in quality of life scores (see Reference 7)	We have deleted the phrase regarding quality of life to accurately reflect DCCT findings.
Reviewer 4	Introduction	Page 2, “Measurement of Glycemic Control;” this paragraph is not completely accurate; please see the Clinical Practice Recommendations by the American Diabetes Association in Diabetes Care, Volume 34, January, 2011, pp S17-S21. The frequency of blood glucose monitoring depends on the population (children, adults, adolescents, pregnant women, type 1 or type 2 diabetes), the treatment, and treatment goals.	We have altered the statements in this section to be more clear regarding current recommendations as follows: "Self-monitoring of blood glucose (SMBG) three or more times daily is recommended for patients using multiple insulin injections or insulin pump therapy and Fasting and 2-hour post-prandial blood glucose levels are also measured and their results can assist patients and their physicians in making short-term adjustments in insulin therapy; however, these measures are more variable.{#7037} The role of SMBG for patients using less-frequent insulin injections, noninsulin therapies, or medical nutrition therapy are less clear."
Reviewer 4	Introduction	Page 3, line 17; reference 10 does not seem to be an appropriate reference for this statement.	This was an error that has been corrected.

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Reviewer 4	Introduction	Page 4, line 49, 50; insert the applicable references to comparable glycemic control after word 3, line 49, and at the end of line 49 instead of inserting all of the references at the end of line 49.	This has been corrected as suggested.
Reviewer 5	Introduction	Introduction: Is clear with appropriate questions and references to state of the art	Thank you for your comment!
Reviewer 6	Introduction	Overall I think the introduction is good. HOwever I think the discussion on the lack of studies comparing CSII with MDI in type 2 diabetes in the Executive SUmmary (pg ES-3, lines 20-24) is not clearly stated enough. The next paragraph regarding pregnancy is much more clear and detailed. Excellent and clear discussion of the knowledge gaps.	We have expanded this section to emphasize the knowledge gap in this population that still exists.
Roche diagnostics	Introduction	The Food and Drug Administration (FDA) does not allow any rtCGM device to be used as a "stand alone" device. Decisions about insulin dosing cannot be made based on the rt-CGM result but need to be based on traditional SMBG.	We have clarified this point in the introduction.
Peer Reviewer 1	Introduction	balanced and adequate	Thank you for your comments!
Peer Reviewer 2	Introduction	Frames the study well. Tables A and B are quite helpful	Thank you for your comments!

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	Introduction	The Introduction appropriately differentiates the forms of diabetes and the consequences of poor glycemic control. It should include more information on the overall demographic characteristics of the disorders in order to better explain the deficiencies of the available literature. For example, type 1 diabetes is a disease predominantly affecting the Caucasian population, so criticizing the literature for lack of minority participation would be like marginalizing the sickle cell literature because it only reports on Blacks. Second, only a small minority of type 2 diabetic subjects are treated by intensified insulin therapy, and the results of the ACCORD, ADVANCE and VADT studies have significantly altered the goals of therapy in those over the age of 60 to render studies in this population difficult if not unethical.	We appreciate this additional distinction and have added these important points to the discussion on p. ES-49-50 and p. 106-107. A reason for looking at subgroups is because they may have higher rates of complications or adverse outcomes. Thus, knowing whether interventions have a differential impact on outcomes for these subgroups is of value (it could also widen or narrow a disparity).

Commentator & Affiliation	Section	Comment	Response
Dexcom/David Price	Introduction	Key question 2 is asking the wrong question. "In patients using intensive insulin therapy, does the type of glucose monitoring have a different effect on process measures, intermediate outcomes, and clinical outcomes in people with diabetes?" Glucose monitoring, whether self monitored blood glucose (SMBG) or continuous glucose monitoring (CGM), is not a therapy and does not directly affect process measures or clinical outcomes. Unlike medications, a subject does not just measure glucose and realize benefits or risks. For continuous glucose monitoring and self monitored blood glucose (SMBG) to have a benefit, patients or health care professionals must act on the results and modify therapy or lifestyle. Hence, when a patient uses either CGM, the clinical outcome is equally determined by factors independent of whether or not a patient was randomized to a treatment arm. Specifically, the success of the device to achieve an outcome depends upon how frequently the patient uses the device and whether and how they act on the results. This is turn is dependent in part on the patient's educational level, experience with the device, motivation level, and training, as well as the health care practitioner's level of competency for training, experience with the device and downloads, and visit frequency. As examples, if device training is complex, patients may be de-motivated and confused. Inadequate patient training could result in device burnout or inappropriate responses to the devise information.	We agree that appropriate use of the device is critical. To the extent that was possible, we compiled data regarding compliance and training.

Commentator & Affiliation	Section	Comment	Response
Dexcom/David Price	ES	Even though there are no RCT comparing MDI and CGM vs CSII and MDI, I think it is well known in the clinical arena that MDI vs. CSII does not result in any improved glucose control. However, by introducing real time CGM, one sees a significant impact in improving A1c, reducing hypoglycemia especially time spent in hypoglycemia. I strongly believe that until such time a real closed loop is available use of real time CGM is far more beneficial in patients using MDI or CSII plus at this time it will turn out to be cost effective. Please refer to our manuscript that I have attached from Diabetes Care and our other previous work published in Diabetes Care, Diabetes Technology & Therapeutics, and other leading indexed journal.	We agree that this technology potentially offers advantages, but our goal was to understand the knowledge base underlying the belief in its utility.
Roche diagnostics	ES	The executive summary needs to be adapted given any acceptance raised by the commenters. The profound differences in comparison to previous work by the Cochrane Collaboration (Misso et al.) and others (Cummins et al. and Pańkowska et al.) need to be explained. Based on those analyses the value of CSII vs. MDI in terms of HbA1c improvement is proven in patients with type 1 diabetes (children, adolescents and adults). In type 2 adult patients an inclusion of the study by Berthe et al. could still lead to significant HbA1c improvements. Advocating adjusting insulin therapy based on rt-CGM alone -like it is implied in the question SMBG vs. rt-CGM- would constitute an off-label use. With regards to sensor-augmented pumps the evidence is overall low to insufficient, except the outcome HbA1c, but here the AHRQ draft report state that the data is heterogeneous. That means that further research is needed.	Re: rtCGM alone, we will clarify that SMBG is required to be performed in addition to CGM. All the clinical trials identified using rtCGM included concomitant SMBG for calibration. We have reviewed the Cochrane Collaboration Meta-analysis by Misso et al. Unlike our review, their review included studies where regular insulin was utilized in the CSII arms. Our review only included studies that utilized insulin analogs in the CSII arms as this is the current clinical practice. The study by Berthe et al. was excluded because the non-CSII comparison arm used premixed lispro/NPH, which is not the current clinical practice for delivering intensive insulin therapy by MDI.

Commentator & Affiliation	Section	Comment	Response
Roche diagnostics	ES-7 error	It appears that on page ES 7 AHRQ meant Figure B within "see inclusion and exclusion criteria listed in Table B" instead of "Table B" because page ES 11 provides this label for Table B: "Table B. Quality of life assessment tools used in each category".	This has been fixed. Thanks!
Peer Reviewer 1	Methods	The inclusion and exclusion criteria are reasonable, the search strategies logical, and the outcome measures clearly defined. Nevertheless, the report does not include (possibly because RCT data to not exist) clinically important outcome measures including episodes of DKA, emergency room visits, and hospitalizations before, during and after the study periods, At the least these should be listed as limitations of the approach.	In selecting outcomes for our report, we did not choose those mentioned because we did not anticipate finding studies that systematically addressed these based on our knowledge of the literature. During our review, we found that studies did not consistently report on these outcomes and this is a limitation of the literature that affected our inclusion and exclusion criteria.
Peer Reviewer 2	Methods	Appropriate--though given the importance of quality of life in results and summary statement, and the fact that 17 studies used 15 instruments, better definition of "validation" would be helpful to end users.	We only included quality of life measures that included a reference to a study where they attempted to validate the results.
Peer Reviewer 3/TEP	Methods	Standard systematic review and meta-analytical techniques have been utilized. As a result, some of the deficiencies they find in the literature are true, but irrelevant. For example, the prevalence of type 1 diabetes in those over the age of 60 is quite limited and compromised by micro- and macrovascular complications rendering the application of the questions to this group impossible to study, if not irrelevant. Similarly, despite the epidemic of type 2 diabetes, the prevalence of type 2 diabetes in pregnancy is also quite low making the question clinically irrelevant.	We acknowledge that type 1 diabetes is uncommon in the elderly and that most pregnant women with pre-existing diabetes have type 1 diabetes. We have added statements to the introduction addressing these issues. "The prevalence of type 2 diabetes increases with age and approximately 26.9% of adults 65 years of age and older have diagnosed and undiagnosed diabetes , the majority of which is type 2 diabetes. " and "The majority of pregnant women with pre-existing diabetes have type 1 diabetes ."
Dexcom/David Price	Methods	There are several methodological challenges: The search ended almost 1 year ago in October 2010 and consequently missed 2 major studies pertinent to the question asked. Battelino et al published a	We agree that there are certain methodological challenges when grouping technologies that are evolving. We grouped technologies that appeared to be relatively homogeneous.

Commentator & Affiliation	Section	Comment	Response
		multicenter, randomized controlled study in Diabetes Care in February, 2011, that looked at the impact of CGM use on hypoglycemia in adults and and adolescents with type 1 diabetes. This study demonstrated an approximate 50% reduction in hypoglycemia with significant reduction in A1C. Ehrhardt published a randomized controlled study of the glycemic effect of CGM use in patients with type 2 diabetes not on meal-based insulin. Once again, significant A1C reduction was demonstrated in the subjects randomized to rt-CGM. This technology assessment excluded Glucowatch as Glucowatch is no longer used in clinical practice. This is appropriate as the poor usability and performance of Glucowatch not only prevented commercial success but also affected intermediate and clinical outcomes. However, the review did include 2 Dexcom devices that are no longer used in clinical practice, the day Dexcom Short Term Sensor (3-day) and the Dexcom SEVEN. Unlike pharmaceutical products, medical technology devices rapidly innovate(~ 18 months) and possess shorter lifecycles (~12-24 months). Therefore, relying on published RCT literature for comparative effectiveness evaluations can unfairly represent rapidly emerging technologies. Studies conducted on first generation devices do not generally represent current therapies. As technologies evolve, the performance and "usability" incrementally improve, likely effecting clinical outcomes. In addition to the generational improvements, there is significant heterogeneity of CGM devices. Devices from different manufacturers differ in performance and usability. For example, accuracy in the hypoglycemia range and overall vary significantly. Some devises are 3 days,	

Commentator & Affiliation	Section	Comment	Response
		Dexcom's device is for use up to 7 days. Needle and sensor sizes vary significantly. Some devises have complicated calibration schemes or require calibration at steady state,other devises do not. These differences likely impact the persistant use of the device and confidence in the information generated by the device. A device not worn or not believed will certainly diminish measured benefits. Endpoints were looked at in isolation. Looking at the effect of CGM or SMBG use on A1C or on hypoglycemia by themselves may be misleading. A1C reduction may occur at the expense of increased hypoglycemia and reduction in hypoglycemia could come at the expense of increased A1C. Combined endpoints are more important and should be considered-reduction in A1C without an increase in hypoglycemia or reduced hypoglycemia without an increase in A1C.	
Peer Reviewer 4	Methods	Methods: Observational studies and randomized clinical trials should be analyzed and reported separately.	They have been analyzed separately. The only section of the report that includes observational studies is the section on pregnancy. All other sections include RCTs.
Peer Reviewer 4	Methods	Inclusion/exclusion criteria, quality assessment, applicability, classified evidence bodies (pages 8-13): We are familiar with many of the studies reviewed in this document, and disagree with some of the authors' conclusions about the quality of some of the studies (good, fair, poor). This makes us wonder about the methods used to determine the quality of the studies. The tools used to determine quality should be more clearly described. For example, describe more clearly what is meant by adequate allocation sequence generation and adequate allocation concealment (page 11, lines 10-15).	We used Cochrane's Risk of Bias tool to assess the quality of randomized controlled trials. This is appropriately cited in the Methods chapter. Furthermore, it is described in Appendix B.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	Methods	methods are clear with one exception. It would help the reader to know the exact ctriteria for assigning an reviewed paper a good, fair or poor category. i happen to agree with all the evaluations having read those papers (and reviewed some pre publication) , but all readers of this may not understand the requisites of a good study and what makes one week	Please see the Quality Assessment section of the Methods chapter.
Peer Reviewer 6	Methods	I believe the inclusion and exclusion criteria are justifiable and the search strategies are explicitly stated. The logic made sense to me. The definitions and diagnostic criteria for the outcome measures are appropriate and consistent with standard practice. And the statistical methods used are standard and appropriate. I have no issues with this section of the report.	Thank you for your comments.
Peer Reviewer 1	Results, p. 57	The key messages are described explicitly. This reviewer would have liked to have seen the r value describing the correlation between sensor compliance and change in HbA1c (page 57)	Thank you; The r values are included in the revised report.
Peer Reviewer 2	Results	THe data is quite complete. For many but not all of the study, subscales are reported for QOL. (I did not see that for the JRF study- which cited improved QOL for glycemic control and socal scales)	We agree that many studies used QOL subscales.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3/TEP	Results	The results are laid out quite logically and are internally consistently. The presentation within each demographic of changes in A1c, hypoglycemia, hypoglycemia, nocturnal hypoglycemia, severe hypoglycemia, hyperglycemia, weight, and quality of life allows rapid comparison across demographic groups and facilitates reading and understanding. The tables and figures contribute to the understanding of the findings. The flow is logical and becomes particularly useful as the authors take the reader from CSII v MDI, through rt-CGM v SMBG, to the logical combination with the sensor-augmented pump combining the two. This was nicely done.	Thank you for your comments!
Medtronic/Francine Kaufman	Adult T1DM	The AHRQ draft report identified 9 controlled trials that evaluated the effectiveness and safety of CSII versus MDI among adults with type 1 diabetes. However only 4 (Bolli 2009, DeVries 2002, Thomas 2007 and Tsui 2001) out of the 9 studies were included in the meta-analysis for the A1C outcome. For the 5 studies that were not included (Bruttomesso 2008, Hanaire-Broutin 2000, Hirsch 2005, Hoogma 2006 and Lepore 2003), no information was reported in Table 4 of Appendix D for the A1C outcome; however, we verified that all 5 of these studies captured A1C as an endpoint. Therefore, it is not clear why the 5 latter studies were omitted from the meta-analysis as they appear to contain relevant information that could inform the analysis.	We have added to the results section for adults with type 1 diabetes the reasons that there articles were not included in the meta-analysis.

Commentator & Affiliation	Section	Comment	Response
Medtronic/Francine Kaufman	Adults T2DM	Medtronic has identified one randomized controlled trial (RCT) in the published literature (Berthe et al, 2007) conducted in the adult type 2 population that was excluded from the AHRQ draft report. The reason for exclusion was not clear, and we feel that this study is relevant for informing the evaluation of effectiveness of CSII vs. MDI in adult type 2 patients. We would encourage the authors of the draft AHRQ draft report to consider this additional study as part of the evidence base or provide a more clear justification for exclusion.	Please see our summary table of excluded studies. This study included premixed lispro/NPH insulin in the MDI arm instead of at least 3 daily injections of non-mixed insulins.
Medtronic/Francine Kaufman	Observational studies	While Medtronic recognizes the potential limitations and risk of bias in observational studies, a large number of non-randomized studies addressing other important clinical outcomes have been conducted to evaluate CSII and should be considered as part of this evidence review. The AHRQ draft report states that in addition to RCTs, observational evidence was included in the draft review, but only for select clinical outcomes (microvascular, macrovascular, maternal, or fetal outcomes). "Real-world" experience is critical to understanding the effectiveness of treatments for chronic illnesses. This is particularly important in the case of diabetes, where a very strong placebo effect has been documented in clinical trials. Because data from observational studies of individuals using CSII versus MDI can provide a more relevant perspective on the effectiveness of CSII, observational studies should be considered for the full range of clinical and patient reported measures included in the review. The role of observational research was highlighted in a health technology assessment in the UK that suggested RCTs conducted on CSII might underestimate health gains seen in routine care (NICE	While observational studies do provide some evidence regarding comparative effectiveness, it is our opinion that, if adequate RCT data are available, that this type of data is far superior as it is less subject to confounding by unmeasured variables and other biases. As stated above, there was adequate RCT evidence for several of our relevant intermediate and patient-reported outcomes.

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		technology appraisal guidance 151). In their review and appraisal of the evidence, the National Institutes for Health and ClinicalExcellence (NICE) noted that: "Although observational studies carried a greater risk of bias than the RCTs, they were much larger, of longer duration and more representative of the people likely to be considered for CSII therapy in routine clinical practice than the populations in RCTs available." The body of evidence from observational studies contributed the following information to the NICE review and appraisal process: "The Assessment Group reported 18 observational studies in the adult/mixed age group, all of which showed a statistically significant decrease in HbA1c levels after initiation of CSII therapy. In the children/adolescent age group, the Assessment Group identified 23 observational studies, 20 of which showed a decrease in HbA1c levels after starting CSII therapy with the difference reaching statistical significance in 13 studies. Furthermore, of the 3 studies showing an increase in HbA1c, 2 were not statistically significant and the third study did not report the level of statistical significance." Excluding observational studies for the key clinical endpoint of A1C reduction as well as patient reported outcomes greatly reduces the applicability of this assessment for key stakeholders, including patients and providers. Therefore, we strongly recommend that AHRQ include high quality observational studies in this assessment. To address concerns about bias, AHRQ should consider an approach similar to the NICE appraisal of CSII to select appropriate observational studies for inclusion in this assessment.	

Commentator & Affiliation	Section	Comment	Response
Lifescan/Animas	KQ1	The AHRQ draft cites several Cochrane sources but fails to cite a 2010 Cochrane meta-analysis that is pertinent to key question 1 regarding the comparative effectiveness of CSII versus MDI. This Cochrane report is a (generic inverse variance) meta-analysis that used a random-effects model and 20 studies (976 participants with type 1 diabetes randomized to either CSII or MDI). Study duration ranged from six days to four years. The meta-analysis showed a statistically significant mean difference of -0.3% A1c (95% confidence interval (CI) -0.4 to -0.1, P = 0.001) in favor of CSII. This Cochrane report concluded that there may be benefit in using CSII over MDI for improving glycemic control and improving health-related QoL for people with type 1 diabetes. The AHRQ draft also omits a study that showed that CSII provided better glycemic control for type 1 patients and improved QoL scores for patients with type 1 and type 2 diabetes compared with basal-bolus MDI. This study found that patients with type 2 diabetes had similar glycemic control with CSII compared to MDI, but that "patient satisfaction was significantly higher with CSII." Finally, at least one study has concluded that CSII appears to be a good alternative for patients with type 2 diabetes – especially when MDI therapy has failed. The AHRQ draft also omits recent evidence regarding insulin pumps with automated insulin suspension. In a recent study, the use of an insulin pump with low glucose suspend technology was associated with reduced nocturnal hypoglycemia and high patient acceptance. Additionally, the AHRQ draft did not cite a 4-year study of CSII that found it to be safe and effective over the long term for a pediatric population	We have added a discussion of the Cochrane review and reasons of divergent findings. Unlike our review, their review included studies where regular insulin was utilized in the CSII arms. Re: the automated insulin suspension technology, we agree that this represents a potentially beneficial innovation but it is beyond the scope of the review.

Commentator & Affiliation	Section	Comment	Response
		with no increase in severe hypoglycemia and a stable improvement in glycemic control.	
Lifescan/Animas	KQ1 recommendation	LifeScan and Animas recommend that the AHRQ summary conclusion for key question 1 be revised to state that there is good evidence for the clinical benefit of CSII over MDI for both adult and pediatric patients with type 1 diabetes. However, there is insufficient evidence for the clinical benefit of CSII for other subpopulations (e.g., type 2 diabetes, elderly, gestational diabetes) perhaps due to the paucity of research in these areas.	The grading of our strength of evidence is described in our methods section and in the Methods Guide which can be found on the Effective Health Care website. We believe that the conclusions regarding the effect and strength of evidence are well-supported. Further details can be found on page 13 of the full report.
Roche diagnostics	Adults T1DM	Could AHRQ please explain the "Other reason" why the paper by Berthe et al. was not included?: "In comparison with CIT, a significant reduction in HbA1c was observed in both intensified regimens, with a drop from 9.0 ± 1. 6 % to 8.6 ± 1.6 % at the end of the MDI period and to 7.7 ± 0.8 % at the end of the CSII period ($p < 0.03$)."	Please see our summary table of excluded studies. This study included premixed lispro/NPH insulin in the MDI arm instead of at least 3 daily injections of non-mixed insulins. In current practice, intensive insulin therapy as MDI is not delivered as pre-mixed insulin.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	CSII vs. MDI	Pages 18, 31, 43; studies that were evaluated in this review used many different MDI regimens; as stated, MDI regimens included NPH and regular, as well as insulin glargine, insulin aspart, and insulin lispro. NPH and Regular insulin are not insulin analogues and have very different pharmacologic activity from the insulin analogues glargine, aspart, and lispro; the results between CSII and different regimens of MDI could be significant, especially those using NPH and regular insulin compared with insulin glargine and insulin lispro/aspart; these studies were assessed as a whole without distinction of the MDI regimen used; this is also important as the authors made a point of excluding studies in which insulin pump therapy used regular insulin.	We decided to limit our studies to those where rapid-acting insulin analogs were used in the insulin pump (as opposed to regular insulin) as this is the current clinical practice. Regarding insulins used in the MDI arms, we agree that the composition of the MDI regimens (analog vs non-analog) could affect their efficacy and safety relative to CSII. We elected to include studies with MDI arms using long and rapid-acting analog and/or NPH and regular insulin because both regimens are still used in clinical practice. NPH and regular insulin-based MDI regimens may still be used to treat hyperglycemia in pregnancy and type 2 diabetes. In most cases, we did not have enough studies to evaluate MDI arm composition as a source of heterogeneity qualitatively or in our meta-analyses. When relevant, we have made a note of the possible modifying effect of insulin type. We do not feel that this issue affects our overall conclusions but have added this important caveat to the discussion section. In theory, this comparison should favor the rapid acting CSII, particularly in terms of HbA1c, hypoglycemia outcomes, and quality of life.
Peer Reviewer 4	Results	The authors drew conclusions about the importance and quality of studies reviewed, and the inclusion or lack of inclusion of results. Shouldn't studies of higher quality be given more weight when coming to conclusions about the relative benefit of an intervention on individual outcomes?	We agree, which is why we have also included evidence grading throughout the report and in the summary of our key findings.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Results	Lower fear of hypoglycemia with rt-CGM is an important finding (page 61) and should be emphasized, along with the finding that there was no increase in hypoglycemia with the use of rt-CGM vs. SMBG despite there being improved HbA1c associated with rt-CGM. These two results are important since the risk of hypoglycemia is a major limiting factor in improving glycemic control as the authors stated on page 2. This is especially important for people with Type 1 diabetes who have hypoglycemia unawareness. The use of rt-CGM has the potential for increasing the safety of subjects with Type 1 diabetes, preventing potentially devastating consequences of having an episode of severe hypoglycemia when using intensive insulin therapy to achieve near normal blood glucose control.	We agree and have added this point to the discussion.
Peer Reviewer 6	Results	The amount of detail presented in the results section seems excessive to the standard diabetes practitioner. However, it seems necessary to cover all of the information; I don't see that it can be shortened appreciably. The characteristics of the studies are clearly described and the key messages are explicit and applicable. I particularly appreciated the table outlining the various types of quality of life studies as this is a hard concept to understand when described in the body of a paper. The figures, tables and appendices are adequate, clear and descriptive. I am not aware of any studies that the investigators overlooked. The key points are well described and clear. I did not determine any discrepancies or unanswered questions.	Thank you for your comments!

Commentator & Affiliation	Section	Comment	Response
Abbott/Eileen Bockoff	KQ2, T1DM or T2DM status?	A number of randomized, controlled clinical trials have evaluated the effects of CGM in the treatment of Type 1 diabetes; however, the effects of CGM in the treatment of Type 2 diabetes has been less-frequently studied. Moreover, very small populations of individuals with Type 2 diabetes use both rt-CGM and CSII. As a result, we would expect limited clinical evidence regarding the effectiveness of rt-CGM versus SMBG in this population. We therefore recommend that Question 2 be limited at this time to a review of related evidence pertaining to individuals with Type 1 diabetes.	We searched broadly and identified this area as a gap in the knowledge base
Abbott/Eileen Bockoff	KQ2, age	Given that evidence associated with the benefits of CGM systems is just beginning to emerge, it may be premature to expect to find robust clinical data stratified by the age classifications AHRQ suggests. We therefore recommend that AHRQ limit this question to the adult population. The American Diabetes Association (ADA) 2010 Clinical Practice Recommendations state that continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens can be a useful tool to lower A1C in selected adults (age ≥25 years) with Type 1 diabetes. If AHRQ decides to include children in this review, we would note that according to the ADA, while there is less evidence regarding the A1C-lowering potential in teens and younger adults, CGM may be helpful in these groups. The JDRF study, which showed that children under the age of 13 also had a reduction in HbA1c, clearly demonstrated that CGM success correlates with adherence to ongoing use of the device. Likewise, the JDRF continues to study the role and importance of CGM as an emerging technology with significant potential benefit to certain subsets of diabetes patients. The	Thank you for your comment. While we realize that data may be limited for certain age populations, the key questions were relevant to those making decisions about health care. We believe that identifying areas where evidence may be lacking is of benefit.

Commentator & Affiliation	Section	Comment	Response
		JDRF has a dedicated commitment to this technology, as evidenced by its Juvenile Diabetes Research Foundation CGM Study Group's extensive publications on the use of this technology. Finally, while AHRQ states in its review of "Blood Glucose Monitoring Techniques" that success in lowering HbA1c depends on adherence to ongoing use of a CGM device, the issue of adherence is especially critical for the adolescent/young adult population. In designing its review, we recommend that AHRQ carefully consider whether the impact of adherence levels has been adequately considered in research to date, particularly for the pediatric and adolescent population.	
Abbott/Eileen Bockoff	KQ2, pregnancy status	Given the small population of individuals with GDM and Type 2 diabetes that use both rt-CGM and CSII, we recommend AHRQ focus its examination on pregnancy complicated by pre-existing Type 1 diabetes at this time.	Pregnant women with T1DM was the population of interest for the review. While we looked, we did not find studies in pregnant women with type 2 diabetes.
Lifescan/Animas	KQ2	The AHRQ draft cites the Star 3 trial results (reference 72), rated this evidence as 'good', and concluded that sensor-augmented pump use is associated with a greater reduction in A1c effect compared with SMBG in non-pregnant individuals with type 1 diabetes. LifeScan and Animas believe that the AHRQ concluding statement should be modified to better align with the conclusions of the Star3 trial report – namely, that senor-augmented pump use has been shown to provide clinical benefit for adults and children with type 1 diabetes. In addition, there is some evidence that rt-CGM provides significant improvement in QoL and reduces incidence of severe hypoglycemia in type 1 diabetes.The AHRQ draft states: "Studies have not compared these two glucose monitoring approaches (CGM and SMBG) in pregnant women with type 1 diabetes or	We cannot conclude that the A1c benefit related to sensor-augmented pumps will clearly provide a clinical benefit as this was not specifically examined in the available studies. Re: the advisability of including clinical outcomes, while we agree that the tool needs to be used correctly in order to see a benefit, the overall goal of this device is to improve clinical outcomes in persons who use it. We evaluated the studies in pregnant women included in the ACCE Continuous Glucose Monitoring Task Force Guidelines and these four studies used retrospective (professional CGM) and not rt-CGM, the latter of which was the focus of our report. This distinction has been clarified in the discussion.

Commentator & Affiliation	Section	Comment	Response
		individuals with type 2 diabetes." However, we found articles that support rt-CGM use in these and other populations: The American Association of Clinical Endocrinologists (AACE) Consensus Panel statement cited a number of studies where SMBG and CGM were compared. The Panel concluded, "… the literature has shown that CGM in pregnant women with DM can reveal high postprandial blood glucose levels unrecognized by intermittent blood glucose determinations, and provides a useful educational tool to help patients improve adherence to their management regimens." The AACE Consensus Panel also cites a randomized clinical trial of pregnant women with type 1 diabetes (n=46) or type 2 diabetes (n=25) allocated to antenatal care plus CGM (n=38) or to standard antenatal care (n=33). The conclusion was that "patients using CGM had lower mean hemoglobin A1c levels (5.8% vs. 6.4%); infants of CGM-using women had decreased median birth weight percentiles (69% vs. 93%) and a reduced risk of macrosomia (odds ratio 0.36; 95% CI, 0.13-0.98; P = .05"). In addition, at least one study has shown rt-CGM benefit in patients with type 2 diabetes. Garg S et al concluded that rt-CGM use for periods up to 72 h is accurate and safe in insulin-requiring subjects with type 1 and type 2 diabetes. This study concluded that rt-CGM can "significantly improve glycemic excursions by reducing exposure to hyperglycemia without increasing the risk of hypoglycemia, which may reduce long-term diabetes complications and their associated economic costs." Note: The entire premise of the question concerning the relative benefit of rt-CGM versus SMBG in relation to clinical outcomes may be suspect. While it is true	

Commentator & Affiliation	Section	Comment	Response
		that rt-CGM provides more data, including glycemic trends, both rt-CGM and SMBG are tests that simply provide data. Data per se cannot be expected to influence outcomes without associated and appropriate interventions. The expectation that the mere availability of test data should somehow influence outcomes has created controversy and confusion. The AHRQ draft would benefit from clarifying this confusion.	
Lifescan/Animas	KQ2 recommendation	LifeScan and Animas recommend that the AHRQ summary conclusion for key question 2 be revised to state that there is good evidence for the clinical benefit of senor-augmented pump use for adults and children with type 1 diabetes. With regard to clinical outcomes research in other subpopulations (e.g., type 2 diabetes, elderly), future trials of these technologies should focus on rt-CGM in conjunction with appropriate and associated interventions. In conclusion, although LifeScan and Animas agree with the AHRQ draft regarding gaps in the literature regarding CSII and rt-CGM safety, efficacy and QoL in specific subgroup populations, we feel that the AHRQ systematic review did not cite several pertinent studies, inclusion of which would change the concluding statements as recommended. We thank the AHRQ for the opportunity to comment on this important review.	The grading of our strength of evidence is described in our methods section and in the Methods Guide which can be found on the Effective Health Care website. We believe that the conclusions regarding the effect and strength of evidence are well-supported. Further details can be found on page 13 of the full report.

Commentator & Affiliation	Section	Comment	Response
Abbott/Eileen Bockoff	KQ3, T1 or T2DM	As previously noted, while the effects of CGM in the treatment of Type 1 diabetes has been studied in a number of trials, the effects of CGM in the treatment of Type 2 diabetes has been less-frequently studied. Moreover, very small populations of individuals with Type 2 diabetes use both rt-CGM and CSII. As a result, we would not expect adequate clinical evidence regarding the effectiveness of rt-CGM versus SMBG in this population. We therefore recommend that Question 2 be limited at this time to a review of related evidence pertaining to individuals with Type 1 diabetes	While we realized that data may be lacking for certain populations we believe that the question has relevance for those making decisions about the care for those with T2DM. The absence of evidence is cited as a research gap.
Abbott/Eileen Bockoff	KQ3, age	The AACE Continuous Glucose Monitoring Task Force "Consensus Statement" on Continuous Glucose Monitoring observes with regard to adults, "No data exist to suggest CSII is a better option than multiple daily injections in patients using personal CGM." AACE cites findings that in many of the randomized pediatric clinical trials of personal CGM, patient outcomes have been similar for both CSII-treated patients and multiple daily injection methods of insulin administration. This is another area where more evidence may need to be developed before a meaningful comparative effectiveness review can be conducted.	We agree that this is an area where evidence is lacking. We believe that identifying gaps in evidence such as these is still of benefit for those making decisions for pediatric patients with diabetes.
Abbott/Eileen Bockoff	KQ3, pregnancy	As previously noted, given the small population of pregnant women that use both rt-CGM and CSII, we recommend AHRQ focus its examination on pre-existing Type 1 diabetes in pregnancy at this time.	While we realized that data may be lacking for certain populations we believe that the question has relevance for those making decisions about the care for pregnant women with T2DM. The absence of evidence is cited as a research gap.

Commentator & Affiliation	Section	Comment	Response
Abbott/Eileen Bockoff	Additional references	We are attaching a list of references from the clinical literature discussing the newly-emerging evidence regarding CGM technology's usefulness for certain populations of patients with diabetes and its key contributions to several clinically-challenging situations in ongoing diabetes care for individuals who are insulin requiring. We recommend that these articles be included in AHRQ's review of available evidence regarding this technology.	Thank you for bringing to our attention these references. We have examined them and found that they did not meet the inclusion criteria as outlined in our methods section. Please see Appendix D for further details.
Roche diagnostics	SMBG vs rt-CGM	The consensus from all the clinical guidelines is that SMBG and the use of insulin are ultimately linked together for the safe and effective use of insulin therapy and that SMBG is key and necessary to safely treat patients, regardless of age, and to prevent both short and long term complications. Based upon the 2010 American Diabetes Association: Standards of Medical Care in Diabetes; SMBG is a prerequisite for CGM. "CGM through the measurement of interstitial glucose is available. These sensors require calibration with SMBG and the latter are still recommended for making acute treatment decisions."AHRQ may want to reconsider if SMBG vs. rt-CGM is an appropriate research question for this HTA draft report: "Accuracy, especially with the first rt-CGM devices, was also problematic to the point that the Food and Drug Administration (FDA) would not allow any device to be used as a "stand alone" device, i.e. decisions about insulin dosing could not be made based on the rt-CGM result but rather based on traditional SMBG. Although these devices are quickly improving in accuracy, to date there has been no change from the FDA in the labeling of these devices, which are intended for use with traditional home blood glucose	We will clarify that SMBG is required to be performed in addition to CGM. All the clinical trials identified using rtCGM included concomitant SMBG for calibration.

Commentator & Affiliation	Section	Comment	Response
		monitoring. Furthermore, some of the perceived accuracy concerns may be partly due to lag time." Therefore, SMBG enables diabetes patients to effectively control and adjust their therapy. Accuracy of blood glucose measurement would be a potential outcome one would need to consider in the comparison SMBG vs. rt-CGM. Blood glucose monitoring systems need to meet the standard DIN EN ISO 15197:2003: >=95% of the BG results shall fall within +-15mg/dL of the reference method at BG concentrations <75mg=dL and within +-20% at BG concentrations >= 75mg=dL. A further tightening of this standard is currently under discussion within ISO TC 212.	
Roche diagnostics	SAP	With regards to sensor-augmented pumps the evidence is overall low to insufficient, except the outcome HbA1c, but here the AHRQ draft report state that the data is heterogeneous. That means that further research is needed. The meta-regression performed by AHRQ is conducted post-hoc and is not level of evidence like pre-planned outcome assessment in a trial protocol. Furthermore, beneficial effects of sensor-augmented pump therapy over MDI are mostly attributed not only to the use of glucose sensors but equally to the use of insulin pumps.	We agree with the post-hoc nature of the meta-regression and have labeled it as such.
Roche diagnostics	Figure 11	With regards to figure 11, we would appreciate further clarification if the axis "Mean between group difference in HbA1c (%)" is meant as absolute or relative change. The figure could be interpreted as if a sensor compliance of about 80% would lead to an approximately 5% absolute HbA1c reduction in comparison to using SMBG.	It is a 0.5%, not 5%, additional reduction in HbA1c in the rt-CGM group. The figures on the Y axis contain decimal points in the tenths place.

Commentator & Affiliation	Section	Comment	Response
Roche diagnostics	Figure 10	Figure 10: With regards to sensor-augmented pumps the evidence is overall low to insufficient, except the outcome HbA1c, but here the AHRQ draft report state that the data is heterogeneous. That means that further research is needed. The meta-regression performed by AHRQ is conducted post-hoc and is not level of evidence like pre-planned outcome assessment in a trial protocol. Furthermore, beneficial effects of sensor-augmented pump therapy over MDI are mostly attributed not only to the use of glucose sensors but equally to the use of insulin pumps. With regards to figure 11, we would appreciate further clarification if the axis “Mean between group difference in HbA1c (%)” is meant as absolute or relative change. The figure could be interpreted as if a sensor compliance of about 80% would lead to an approximately 5% absolute HbA1c reduction in comparison to using SMBG	We agree that the meta-regression was post-hoc and have added this to the limitations on p. ES-48 and p. 105. The issue that the beneficial effect of the sensor-augmented pump could be do the rt-CGM or the insulin pump is addressed in the future research section of the discussion in the following statement: "Current studies examining the comparative effectiveness of rt-CGM versus SMBG on outcomes have included mixed populations receiving intensive insulin therapy as CSII and/or MDI; however, they have not determined the effect of these two glucose monitoring strategies in individuals treated with only CSII or only MDI. Such a study would help to elucidate whether the observed benefit of sensor-augmented pump compared with MDI/SMBG on glycemic control is secondary to the rt-CGM technology, the mode of intensive insulin delivery, or both."
Peer Reviewer 4	SAP	Page 65; 4th and 6th bullets and Strength of Evidence on page 69: The statements within each bullet seem contradictory. Explain why the evidence was low despite reporting studies that had positive results associated with hyperglycemia and quality of life when using sensor-augmented pumps.	Please see the Methods chapter and the Methods Guide for Effectiveness and Comparative Effectiveness Reviews for a description of how strength of evidence is determined. Strength of evidence is our confidence that the result is a reflection of the truth.
Peer Reviewer 4	SAP	Page 71: the authors should state if the results are applicable.	Applicability is discussed at the end of each results section and in the discussion.
Peer Reviewer 5	Results	There is a lot of repetition between the text and the tables which I found distracting. I think a discussion of the tables would suffice as they seem to have all the details.	We have attempted to summarize the text as succinctly as we can with references to the tables and figures.
Peer Reviewer 4	Limitation	Meta-analyses are in themselves subject to bias and risk. These were performed on several outcomes. The limitations of these analyses should be clearly stated.	These limitations have been added to the discussion.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Quality of life	Page 14, Table 3: It is confusing to evaluate each measure of quality of life separately. The results can be reported on each assessment tool, however, a broad analysis of quality of life that includes results obtained on quality of life in general, incorporating all of the different tools, would be useful. In a broader view, all of the tools measure some aspect of quality of life.	While agreeing that the separate measures do all measure some aspect of quality of life, they each measure different domains and have been verified in different settings. In addition, considering the studies in our review, the qualitative heterogeneity was so great as to make it impossible to pool the different measures through statistical techniques.
Peer Reviewer 5	Discussion	results are clearly stated except that the importance of age on the effectiveness of the glucose sensor was not sufficiently stressed	We have added information about the effect of age on outcomes and adherence to the discussion.
Peer Reviewer 6	Discussion	The implications of the major findings are clearly stated and the limitations of the review/studies are described adequately. This section is particularly well organized for all of the difficult adn varied information that had to be covered. The investigators did not omit any important literature that I am aware of. The future research section is clear and easily translated into new research, although I think a stronger emphasis on the need for more work in Type 2 diabetes should be explicitly stated, given the rising prevalence of that form of diabetes and the relative paucity of information on these specific topics.	Thank you for your comments. We have added the following statement regarding future studies of type 2 diabetes: "Future studies should focus on individuals with type 2 diabetes requiring insulin to determine the most effective manner in which to delivery intensive insulin therapy and monitor blood glucose. Given the rise in prevalence of type 2 diabetes in the general population, the number of those individuals requiring insulin therapy will likely rise. "
Roche diagnostics	Discussion	In this section a comparison and a discussion of why the draft report significantly differs from other relevant systematic reviews besides Jeitler et al.(21), Pickup and Sutton (22) (Misso et al. (5), Cummins et al. (4), Pankowska et al.(6) would be of value. With regard to rt-CGM versus SMBG, AHRQ may want to acknowledge that according to FDA decisions about insulin dosing could not be made based on the rt-CGM result but rather based on traditional SMBG	We have updated the discussion to summarize how our systematic review and meta-analysis compares to prior studies, including proposed reasons for observed differences. We have also clarified through the document, in the introduction and discussion, that rt-CGM is to be used as an adjunct to SMBG.

Commentator & Affiliation	Section	Comment	Response
Roche diagnostics	Discussion	Beyond that, the discussion could provide reasoning about appropriateness of a post-hoc meta- regression about the dependence of HbA1c reduction on sensor compliance and what it means for further evidence needs. It could also take into account that coverage with evidence development decisions were recently taken in Washington State and in France.	The issue of compliance and benefit was also investigated by Pickup and in JDRF and has strong rationale. We have added the following statement to the "Future Research" needs sections regarding that issue: "Studies should also incorporate measures of adherence to treatment as adherence is important for the effectiveness of any intensive insulin therapy or glucose monitoring system. Our data and others show that rt-CGM is most effective in those compliant with wearing the sensor at least 60% of the time. Thus, sensor compliance may be a marker for overall treatment adherence and explain the HbA1c fall, independent of the sensor."
Dexcom/David Price	Discussion	In the discussion section, there is mention of the lack of demonstrated reduction in severe hypoglycemia with CGM as well as reference to a meta-analysis by Pickup et al (published after October, 2010) that came to the same conclusion. However, it was not mentioned is that no study was designed to demonstrate reductions in severe hypoglycemia. Beck et al presented a sample size analysis in the Journal of Diabetes Science and Technology in 2011 for a trial to demonstrate reduction of severe hypoglycemia. He found that the sample size and study duration required to demonstrate a reduction in severe hypoglycemia would be prohibitive unless patients with very high risk reduction of hypoglycemia were selected, the patients were followed for a prolonged period of time, or the observed reduction in severe hypoglycemia was huge. The limitations section of the discussion is inadequate. As discussed in the above comments, the analysis combined all CGM systems, even though different generations and different manufacturer's system are heterogeneous in terms of usability and performance. As devices are not therapies, the way patients and HCPs use the data is crucial to whether	The Battelino paper was identified in our updated search, and included.

Commentator & Affiliation	Section	Comment	Response
		or not they achieve glycemic benefit. The implications section of the discussion of the discussion does conclude that rt-CGM is superior to SMBG patients with type 1 diabetes in those that are compliant with wearing the monitoring. We concur and the data would be even stronger if the Battelino paper was included. It also calls out that the available literature does not allow looking at CGM versus SMBG in patients using MDI or CSII as the major outcomes studies combined both approaches. However, there are a number of published studies that have performed the comparison of CGM benefit in CSII and MDI patients. Studies by Rodbard published in Diabetes Technology and therapeutics in 2009, and Garg, published in Diabetes Care in 2011, suggest a near equivalent benefit (in particular related to reduction of hypoglycemia) of CGM whether intensive insulin uses CSII or MDI. This was confirmed in a planned subset analysis in the Batellino study.	

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Discussion/conclusion	The discussion is balanced; the authors cite appropriately the limitations of the review, including very importantly the lack of a sufficient number RCTs of insulin pump therapy in infants and toddlers. Many clinicians think that relative to MDI, pump therapy is most effective in that age group (see for example Litton et al. J Pediatr. 2002 Oct;141(4):490-5, which for some reason is not listed in the excluded papers - it was a case study but the first to show benefits of pump therapy in very young children). With respect to real time CGM, it should be noted that the strong correlation between sensor compliance and efficacy might indicate (a) that rtCGM is clearly effective and should be encouraged for children with T1D; and/or (b) that sensor compliance is a marker for overall compliance and motivation (e.g. with dietary and exercise goals as well as insulin administration) and might not explain directly the fall in HbA1c. This question should be addressed in future studies.	We agree with the adherence issues and have added the following statements to the "Future Research" section: "Studies should also incorporate measures of adherence to treatment as adherence is important for the effectiveness of any intensive insulin therapy or glucose monitoring system. Our data and others show that rt-CGM is most effective in those compliant with wearing the sensor at least 60% of the time. Thus, sensor compliance may be a marker for overall treatment adherence and explain the HbA1c fall, independent of the sensor."
Peer Reviewer 2	Discussion/conclusion	I think that the discussion could be improved by providing more detail on the QOL issues and compliance issues, and what factors might predict severe hypoglyemia and compliance	We have added additional information to the discussion.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3/TEP	Discussion	As mentioned above, the reliance on pure systematic review methodology leads to deficiencies that are spurious. Studies in minority subjects with type 1 diabetes, those over the age of 60 and pregnant type 2 subjects are neither feasible nor relevant; therefore they are not a weakness in the literature, just in the analysis. The impact of the interventions on hard endpoints of microvascular and macrovascular events would be ideal, but again is not feasible. I personally believe these points need to be emphasized, rather than leaving the reader to simply think that they are knowledge gaps. I completely agree with the authors on the need for more homogeneous definitions of outcome measures relative to hyperglycemia, hypoglycemia, and quality of life. A firm recommendation to use the ADA definitions of hypoglycemia (DIABETES CARE, VOLUME 28, 1245, 2005) in all future trial is absolutely warranted.	We agree with these excellent points. We have added the following clarifications to the limitations section of the discussion highlighting that it may not be feasible to study certain populations: Since few studies focused on or included children 12 years of age or younger or 65 years of age or older, or pregnant women with pre-existing type 2 diabetes, we were unable to draw conclusions about the effectiveness of insulin delivery and glucose monitoring methods devices in these populations. However, this likely reflects that fact that type 1 diabetes is much rarer in minority and elderly individuals and few pregnant women have pre-existing type 2 diabetes, making it less feasible and relevant to perform studies in these sub-populations." Regarding microvascular and macrovascular outcomes, we have added the following statement: "While data on these outcomes would be ideal, it would require a very large RCT of several years duration, which may not be feasible to perform, particularly because individuals may switch therapies over time." We have added the suggested hypoglycemia reference to the "Future Studies" section.
Peer Reviewer 1	Clarity and usability	yes to all, but with all of the limitations of the review clearly specified	Thank you for your comments!
Peer Reviewer 2	Clarity and usability	This is well structured and organized. I found the major points I was most interested in clearly presented, but the report is likely to be dense for most readers	Thank you for your comments and we agree that the report is dense but conforms to evidence reporting guidelines. The Executive Summary is intended to provide a comprehensive but more succinct overview.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Clarity and usability	In the abstract, the conclusion notes that "insulin therapy can be individualized to maximize their quality of life." That is a true statement--and from personal perspective based upon an evaluation of the patient goals (e.g. active lifestyle) as well as medical evaluation (achieving tight control with a goal of minimizing hypoglycemia). However, from a policy perspective, it is equally important to note the factors that identify patients who might opitmally benefit (especially about compliance issues)	The abstract has word limitations but we discuss these issues, particularly adherence, in the discussion.
Peer Reviewer 3/TEP	Clarity and usability	This is a nicely organized and well written report that identifies the data base, describes the study characteristics and findings, combines the studies into understandable combinations, and reaches conservative and defensible conclusions	Thank you for your comments!
Peer Reviewer 5	Clarity and usability	As discussed above---a lot of repetition. However points are clear	Thank you for your comment.
Peer Reviewer 6	Clarity and usability	The report is VERY well organized and structured. The authors are to be commended for a structure that makes a very complex topic understandable. The main points are clearly presented, although again I think there should be more emphasis on the need for more work in type 2 diabetes. Yes, the conclusions are useful for both policy as well as practice. I particularly appreciated the call for inclusion of ethnic and minority patients in future studies for greater variety, particularly given the fact that these populations are disproportionately affected by the disease.	Thank you for your comments!
Peer Reviewer 4	Organization	The organization of this review is confusing. Key Points and Evidence Grades are listed first under a major subheading, and then the Study Design and Results are reported. We think the reverse order would be better; present the evidence and then the conclusions.	While we appreciate the suggestion, we have structured this report consistent with the format for AHRQ evidence reports.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Report organization	The document is long, tedious, and confusing in its current form; perhaps dividing the document into two documents would be better (one document comparing CSII vs. MDI in various populations, and one document comparing rt-CGM vs. SMBG).	We appreciate that the report is dense with details and have tried to emphasize the key points in an organized fashion in the Executive Summary. Per AHRQ guidelines, we are unable to divide the report into two documents. We also believe it is useful to present the comparative effectiveness of the intensive insulin therapy and glucose monitoring methods together in one document.
Peer Reviewer 4	Appendix C	Appendix C, Exclusion Report-explain what the "other reason" is for exclusion of the paper.	Other reasons for exclusion are usually particular to the study. For instance, the device was not being used appropriately.
Peer Reviewer 4	Appendix D	The division of the Tables at the end of the document are difficult to follow as they are divided by "Design, Interventions, Outcomes, and Study Quality"; it would be easier if all of this information were listed together for each study.	Thank you for this suggestion.
Peer Reviewer 4	Appendix D	The Tables at the end of the report list lispro and regular as short-acting insulins, and NPH as a long-acting insulin. This is incorrect; insulin lispro and insulin aspart are rapid-acting insulins, regular is a short-acting insulin, and NPH is an intermediate-acting insulin; NPH insulin is quite different from the long-acting insulin glargine (see #15 above).	We have clarified out footnotes to indicate what we really intended--glargine and NPH are basal insulins and aspart, lispro, and regular insulin are prandial insulins.

Commentator & Affiliation	Section	Comment	Response
Roche diagnostics	Appendix A	While AHRQ explicitly searched for "hyperglycemia", AHRQ did not search for hypoglycemia. This is in contrast to the objectives of the systematic review:"Objectives: To systematically review whether the mode of intensive insulin therapy using rapid- acting insulin analogs (multiple daily injections [MDI] versus continuous subcutaneous insulin infusion [CSII]) and/or the mode of blood glucose monitoring (self-monitoring of blood glucose [SMBG] versus real time-continuous glucose monitoring [rt-CGM]) 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." It may be assumed that both aspects will be covered by most studies, but there can be cases where the study is restricted to only hypoglycemia: In search conducted on September 6th 201199 PubMed and 62 Embase hits we found by adding "Hypoglyc(a)em*" to the search terms. AHRQ excluded in the Embase search publications about certain drugs which do not have much relation to diabetes: „OR 'budesonide'/exp OR 'budesonide' OR 'methylprednisolone'/exp OR methylprednisolone' OR 'prednisolone'/exp OR 'prednisolone' OR 'prednisone'/exp OR 'prednisone' OR '6- methylprednisolone':ab,ti OR budesonide:ab,ti OR corticosteroid*:ab,ti OR glucocorticosteroid*:ab,ti OR prednisolone:ab,ti OR	We have reviewed the additional citations brought into the search by including the term "hypoglycem*". None of these citations were relevant.

Commentator & Affiliation	Section	Comment	Response
		prednisone:ab,ti)“ The reason for exclusion of these drug terms appears not to be clear. AHRQ may want to revisit this topic and may want to decide to run an updated search. The purpose of the double use of the term “NOT ([animals]/lim NOT [humans]/lim)” was not clear to us.	The inclusion of these additional terms was a typo in the appendix, and has been corrected.
Peer Reviewer 4	Terminology	Use blood glucose and not blood sugar throughout the document	This has been fixed. Thanks!
Roche diagnostics	update	Overall, AHRQ may want to consider revisiting the search strategy, the relevance of the report for comparative effectiveness and the dependency of the results in comparison to other systematic reviews in the field. Guiding questions may be: Is patient experience sufficiently captured? Is medical evidence including observational evidence sufficiently represented in the review? How the value of rt-CGM can appropriately be assessed given that decisions about insulin dosing still need traditional SMBG?	We have reviewed the additional citations brought into the search by including the term "hypoglycem*". None of these citations were relevant.
Roche diagnostics	References	The references would need to be updated accordingly in case of acceptance of additional documents.	We are have updated our references accordingly.