Effective Health Care Program

Future Research Needs Paper
Number 32

Insulin Delivery and Glucose Monitoring Methods: Future Research Needs

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Insulin Delivery and Glucose Monitoring Methods: Future Research Needs

Identification of Future Research Needs From Comparative Effectiveness Review No. 57

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Agency for Healthcare Research and Quality
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Addendum to Future Research Needs for Insulin Delivery and Glucose Monitoring Methods

This report was posted for public comment on the AHRQ Effective Health Care Web site from March 1, 2013, to March 28, 2013. In response to the comments received, the authors added the following discussion points:

1. We acknowledge the importance of studying minority subgroups who may experience disproportionately higher rates of complications related to diabetes. The original systematic review by Golden et al. found most previous studies did not report the racial and ethnic composition of the study samples. For those studies that did, most participants were white. This is probably because type 1 diabetes mellitus is more prevalent in whites than in minority populations. This was cited as an evidence gap in the original report, and we agree that recruitment of minority patients in research studies is important.
2. While our report identified real-time-continuous glucose monitoring (rt-CGM) as "superior" to self-monitoring of blood glucose (SMBG) in lowering HbA1c, it is important to note, consistent with the original systematic review, that all of the rt-CGM devices add to, but don't replace, regular blood sugar checks with a glucometer.
3. While data on long-term microvascular or macrovascular complications would be informative, it would require a large RCT several years in duration. Also this type of RCT may not be feasible, particularly because persons may switch therapies over time. Additional patient sources, such as a registry or clinical network (e.g. T1D Exchange) may be required to identify potential participants. Moreover, we acknowledge that future studies should better study quality of life as an outcome. We did not include other outcomes, such as glucose variability and hypoglycemia awareness, as specific research needs because they were not within the scope of the original review by Golden et al., and thus cannot ascertain what research may have already addressed these questions, although we acknowledge their importance.
4. We recognize additional research may be required to better study the potential interactions between adiposity, physical activity and clinical outcomes such as HbA1c, QOL, functional and fitness measurements, and microvascular or macrovascular disease progression. We did not include this as specific research need because it was not within the scope of the original review by Golden et al., and thus cannot ascertain what research may have already addressed this question, although we acknowledge its importance.
5. We acknowledge that our stakeholder group may not be representative of all those who have a stake in research on insulin delivery and glucose monitoring. A different type of study (e.g., a survey) might be needed to further explore the views of stakeholders about the research priorities we identified. However, the value of the Delphi method is to obtain agreement in a small group without having any one person dominate the process. The method is efficient without geographic constraints, and allows all group members to have an equal voice. Although the optimal number of stakeholders in a Delphi study never reaches a consensus in the literature, a small number may be sufficient when the stakeholders have a similar level of familiarity with the topic. Following the constraints of our project timeline, we aimed to recruit a small panel of 5–9 stakeholders. We invited 14 experts in the field of insulin delivery

and glucose management to serve as expert stakeholders until we had at least 5 stakeholders who were able to participate in the process. The final five-member stakeholder panel included one academic physician in the field of pediatric endocrinology, three physicians in the field of adult endocrinology, and one patient with type 1 diabetes mellitus for more than 50 years. All endocrinologist stakeholders are experienced clinicians, who handled complicated diabetic patients and had experience in managing patients with all modalities included in the report.

This report is based on research conducted by the Johns Hopkins University Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10061-I). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

An important part of evidence reports is to not only synthesize the evidence, but also to identify the gaps in evidence that limited the ability to answer the systematic review questions. AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that is needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

We welcome comments on this Future Research Needs document. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Background

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

Type 1 diabetes, which accounts for 5 to 10 percent of all diabetes cases, is characterized by insulin deficiency and a need for daily insulin administration to sustain life, maintain normoglycemia, and maintain normal body weight and promote normal growth and development in children.[1] Type 2 diabetes, which accounts for 90 to 95 percent of diabetes in the U.S., is the result of a combination of insulin resistance and impaired insulin secretion by the beta cells of the endocrine pancreas.[1] Although the relative contribution of each of these factors to the course of type 2 diabetes varies by patient, eventually beta cell failure can lead to insulin deficiency, necessitating insulin therapy.

In current practice, tight glycemic control is achieved through the use of physiological basal and meal-time (prandial) insulin that, when used together, mimic normal pancreatic function (e.g., peakless basal insulin secretion, rapid release of insulin in response to meals, and rapid resolution of the prandial insulin peak). Patients take these medications either as three or more daily injections [multiple daily injections (MDI)], or by external continuous subcutaneous insulin infusion (CSII) via a pump, which provides a more physiological means to deliver insulin.

Following publication of the Diabetes Control and Complications Trial, self-monitoring of blood glucose (SMBG) by fingerstick replaced the assessment of glucose by urine dipstick to allow more specific and timely feedback on the degree of hyperglycemia.[5] The challenges to use of SMBG are the associated pain, costs, behavioral and technical skills, required motivation, and intrusiveness. These challenges directly affect adherence to this technique and are barriers to tight glycemic control. In response to these issues, the health care industry has developed continuous glucose monitoring (CGM) systems that record blood glucose levels throughout the day and night with a significantly decreased need for fingerstick measurements.

A CGM system, in conjunction with intensive insulin treatment, can be a useful tool to lower blood glucose values in adults who are at least 25 years of age and have type 1 diabetes. Success in lowering blood glucose levels depends on adherence to ongoing use of the device.[6]

The United States Food and Drug Administration first approved real-time continuous glucose monitoring (rt-CGM) in 2005. rt-CGM differs from conventional (retrospective) CGM in that it provides blood glucose feedback data to the patient while he or she is wearing the device and does not need to be downloaded and evaluated after data collection. This advantage of rt-CGM has resulted in it being the preferred method of CGM in the clinical setting.

CSII is currently recommended for patients with type 1 diabetes who are not achieving glycemic goals despite adherence to a maximum MDI regimen. This is especially true when

patients also have wide and erratic glycemic excursions, frequent severe hypoglycemia and/or hypoglycemia unawareness, marked dawn phenomenon (pre-breakfast rise in blood glucose seen when bedtime basal insulin effect diminishes),[5,7] or are pregnant or planning to become pregnant. Experts may also recommend CSII for patients with type 1 diabetes who feel that pump therapy may be more suitable to their lifestyle, regardless of the level of glycemic control.[5] Experts currently recommend rt-CGM for patients with type 1 diabetes who have hypoglycemia unawareness or frequent hypoglycemia (where hemoglobin A1c [HbA1c] is over the recommended target), have excess glycemic excursions, or are pregnant or plan to be pregnant.[8]

Given new technologies in insulin delivery and glucose monitoring, clinicians are now faced with determining which patient populations benefit most from the use of CSII and rt-CGM in terms of improved glycemic, clinical, and patient-reported outcomes. Because both technologies are expensive and require extensive training and oversight by health care professionals, it is critical to determine how to select patients for their use. It is also important to point out that the most adherent and engaged patients will likely achieve beneficial outcomes as both forms of intensive insulin therapy (MDI and CSII) and both forms of glucose monitoring (rt-CGM and SMBG) require the patient to partner with his/her health care provider.

Our recent systematic review examined specific questions about the comparative effectiveness of insulin delivery and glucose monitoring methods (see Table A).[9] The review found that intensive insulin therapy delivered either by CSII and MDI is equally effective in lowering glycated hemoglobin (HbA1c) levels in adolescents and adults with type 1 diabetes. Intensive insulin therapy delivered by both methods resulted in similar rates of severe hypoglycemia for adolescents and adults with type 1 diabetes. The review also found evidence that rt-CGM is superior to SMBG in lowering HbA1c, without altering the risk balance of severe hypoglycemia, particularly among those who are compliant with wearing the monitoring device. Even though CSII and MDI without rt-CGM have similar effects on HbA1c, the addition of rt-CGM to CSII is superior to MDI/SMBG in lowering HbA1c. Thus, the addition of this monitoring method to SMBG and intensive insulin therapy can assist in achieving glycemic targets in individuals with type 1 diabetes. However, the review also identified several important gaps in the evidence, as shown in Figure A.[9] The objective of this report is to prioritize the needs for research addressing those gaps in the existing literature on management of insulin-requiring diabetes by engaging expert stakeholders using a modified Delphi method.

Methods

Stakeholder Identification

Expert stakeholders for this project were representative of clinicians, researchers, private and federal agencies, and patients. Fourteen experts in the field of insulin delivery and glucose management were identified and invited to serve as expert stakeholders. The stakeholders included one academic physician in the field of pediatric endocrinology, three physicians in the field of adult endocrinology and one patient with diabetes mellitus.

Stakeholder Engagement

We used a modified Delphi method to identify and prioritize existing gaps in the scope of the systematic review[9] as it pertains to insulin delivery and glucose monitoring methods in seven steps across four phases (Figure B). The Delphi method involves iterative rounds of responses by

group members, providing aggregated feedback about other members' responses until consensus is reached. For each round, we used a Web-based assessment tool (SurveyMonkey™, Palo Alto, CA), with the list of the research gaps. Consensus among stakeholders was pre-defined as agreement in responses of 50 percent or higher in three or more options for each category of Future Research Needs. Categories that did not achieve 50% or greater consensus among the stakeholders on three or more options in phase 2 were returned for the stakeholders, with their compiled feedback from phase 2, to reprioritize.

Phase 1

We developed an analytic framework (Figure A) to identify potential populations, delivery and monitoring methods, and outcomes gaps from the 2012 evidence report. As indicated in the analytic framework, we focused on the population of patients having type 1 or type 2 diabetes, with subpopulations defined by age categories. We did not include pregnant women as a separate category in this report because we thought it would require a separate process to adequately assess the needs for future research in pregnant women having type 1 diabetes, type 2 diabetes, or gestational diabetes. In the analytic framework for this study, we included the types of interventions that are currently being evaluated for delivering insulin continuously or for monitoring glucose continuously, even though we did not have any studies about the artificial pancreas or the reactive low glucose suspend pump in the original evidence report.

We then searched the results and discussion sections of the evidence report, using the analytic framework, to identify potential research gaps. A Web-based assessment tool was populated with the identified research gaps. For each research gap category, an optional, free-text field was provided for stakeholders to identify gaps not listed in the assessment tool. Novel stakeholder and/or investigator identified research gaps, including insulin delivery methods, glucose monitoring methods, and outcomes were included for prioritization during phases 2 and 3 and were eligible for inclusion in the final research question development in phase 4.

Phase 2

The Stakeholders were provided with a copy of the Executive Summary of the 2012 evidence report,[9] were asked to read the full Executive Summary for familiarization of the findings, and were asked to independently identify the highest priority gaps for future research among individuals with type 1 diabetes and with type 2 diabetes within each of the following categories: populations, insulin delivery methods, glucose monitoring methods and outcomes. First, we asked the stakeholders to rate the three highest priority age-based populations with type 1 diabetes and with type 2 diabetes. Second, we asked stakeholders to rate the highest priority insulin delivery method and the highest priority blood glucose monitoring method for each age stratum of each diabetes type. Finally, we asked the stakeholders to rate the three highest priority outcomes for each age stratum for each diabetes type. Stakeholders were given the opportunity to add insulin delivery methods, glucose monitoring methods, and outcomes not on the list as an 'other' free-text option.

Phase 3

Feedback from phase 2 was compiled and analyzed for agreement. Compiled stakeholder feedback for prioritized research gaps that did not achieve consensus were sent back to the stakeholders to re-rate the priorities in an attempt to build consensus.

Phase 4

Research questions were developed based on feedback from stakeholders that achieved consensus during the second and third rounds. The stakeholders were presented with their compiled feedback from the second and third phases along with the research questions developed. They were asked to provide feedback on the clarity, utility, study design feasibility and priority of the research questions.

Results

We identified evidence gaps among populations, insulin delivery and glucose monitoring methods, and outcomes. The gaps varied by diabetes type. Results from the stakeholder prioritization are presented by diabetes type.

Type 1 Diabetes

Phase 1

During phase 1 of this study, the stakeholders were presented with gaps identified by the research team (see Tables B, C, D, and E). The stakeholders indicated that additional research was needed for children (age less than 13 years), adolescents (age 13 to 19 years), and adults (age 20-64 years) with type 1 diabetes (see Table B). Potential research needs for insulin delivery methods were related to CSII (i.e. insulin pump), reactive low glucose suspend pumps (i.e. pump that automatically suspends insulin delivery when glucose reaches low threshold), artificial pancreas (i.e. overnight closed loop, senses upper and lower glucose thresholds), and sensor-augmented insulin pumps (see Table C). Potential topics for future research on blood glucose monitoring methods were SMBG, retrospective continuous glucose monitoring, and rt-CGM (see Table D). Outcomes identified for future research were HbA1c, adherence, non-severe hypoglycemia, severe hypoglycemia, and hyperglycemia (see Table E).

Phase 2

During phase 2, three expert stakeholders ranked adolescents as the highest priority group for future research in patients with type 1 diabetes. (see Table B) One stakeholder ranked children and one ranked adults as the highest priority group for future research in patients with type 1 diabetes. Among children with type 1 diabetes, three stakeholders ranked the artificial pancreas as the highest research need for insulin delivery while one stakeholder identified the reactive glucose suspend pump and one rated the sensor-augmented insulin pump as the highest priorities for this population. Among adolescents with type 1 diabetes, three stakeholders also ranked the artificial pancreas as the highest priority for future research while two prioritized the sensor-augmented insulin pump. For adults with type 1 diabetes, two stakeholders identified the artificial pancreas and two identified the sensor-augmented insulin pump as the highest priority for future research. One stakeholder identified the reactive low glucose suspend pump as the highest priority for future research. Four stakeholders ranked the reactive low glucose suspend pump as the highest priority for future research among the elderly with type 1 diabetes and one stakeholder ranked the artificial pancreas as the highest priority in the elderly (see Table C).

For glucose monitoring methods in patients with type 1 diabetes, all Stakeholders agreed that the highest priority was research on rt-CGM (see Table D).

Three Stakeholders ranked adherence as the highest priority outcome for future research in children with type 1 diabetes. For adolescents, two stakeholders rated adherence as highest

priority outcome while the other two ranked severe hypoglycemia as highest priority outcome. Among adults, three Stakeholders ranked severe hypoglycemia as the highest priority outcome; and in the elderly, all Stakeholders rated severe hypoglycemia as a high priority outcome in future research (see Table E).

Phase 3

Consensus was achieved during phase 2, negating the need to build consensus in phase 3.

Phase 4

When presented with the research questions developed from feedback in earlier rounds, Stakeholders prioritized glucose monitoring as a higher research need above insulin delivery methods.

Type 2 Diabetes

Phase 1

When the stakeholders focused on insulin-requiring type 2 diabetes in phase 1 of this study, they indicated that additional research was needed in adolescents (age 13 to 19 years), adults (age 20–64 years) and the elderly (age greater than 64) (Table F). For patients with type 2 diabetes, potential research needs for insulin delivery methods identified and/or rated by the stakeholders were related to CSII (i.e., insulin pump), reactive low glucose suspend pumps (i.e., pump that automatically suspends insulin delivery when glucose reaches low threshold), artificial pancreas (i.e., overnight closed loop, senses upper and lower glucose thresholds), and sensor-augmented insulin pumps (see Table G). In this population, potential priorities for research on blood glucose monitoring methods identified and/or rated by the stakeholders were SMBG, retrospective continuous glucose monitoring, and rt-CGM (see Table H). Outcomes rated as priorities for future research in this population were HbA1c, adherence, nonsevere hypoglycemia, severe hypoglycemia, hyperglycemia, and weight (see Table I).

Phase 2

During phase 2, three stakeholders ranked adults as the highest priority group for future research among insulin-requiring type 2 diabetes patients. One stakeholder ranked adolescents and one ranked elderly as the highest priority group for future research in patients with type 2 diabetes (see Table F). Among the patients with insulin-requiring type 2 diabetes, three stakeholders ranked the sensor-augmented insulin pump as the highest research need related to insulin delivery while one stakeholder ranked CSII and one identified the artificial pancreas as the highest priorities for future research on insulin delivery in patients with type 2 diabetes (see Table G).

For future research on glucose monitoring methods in patients with insulin-requiring type 2 diabetes, three stakeholders prioritized rt-CGM and two prioritized SMBG. (see Table H)

Two stakeholders prioritized HbA1c, one prioritized severe hypoglycemia and one ranked weight as the highest priority outcome for future research in adolescents with insulin-requiring type 2 diabetes. Three stakeholders prioritized HbA1c, one prioritized adherence and one ranked hyperglycemia as the highest priority outcome for future research among adults with insulin-requiring type 2 diabetes. Three stakeholders prioritized HbA1c, one prioritized severe

hypoglycemia and one ranked hyperglycemia as the highest priority outcome for future research among the elderly with insulin-requiring type 2 diabetes (see Table I).

Phase 3

Consensus was also achieved during phase 2 for the research priorities on insulin-requiring type 2 diabetes.

Phase 4

When presented with the research questions developed from feedback in earlier rounds, Stakeholders prioritized glucose monitoring as a higher research need above insulin delivery methods.

Research Questions

Based on stakeholder feedback from phase 2 regarding populations, interventions, comparisons, and outcomes, the following four research questions were identified by our stakeholders as high priorities for future research:

1. For adolescents with type 1 diabetes, what is the comparative effectiveness of an artificial pancreas versus other methods of insulin delivery for the outcomes of adherence and severe hypoglycemia?
2. For adolescents with type 1 diabetes, what is the comparative effectiveness of rt-CGM versus other methods of glucose monitoring for the outcomes of adherence and severe hypoglycemia?
3. For adults with insulin-requiring type 2 diabetes, what is the comparative effectiveness of a sensor-augmented insulin pump versus other methods of insulin delivery for the outcome HbA1c?
4. For adults with insulin-requiring type 2 diabetes, what is the comparative effectiveness of rt-CGM versus other methods of glucose monitoring for the outcome HbA1c?

This report reinforces the needs for future research that we outlined in the original evidence report,[9] and points to specific types of studies that should have a high priority. In the original report, we identified a need for well-conducted randomized controlled trials (RCTs) of intensive insulin therapy delivered via CSII versus MDI in young children with type 1 diabetes and elderly patients with both type 1 and type 2 diabetes. Based on the input from our stakeholders, higher priority should be given to RCTs of intensive insulin therapy options, including the artificial pancreas, in adolescents with type 1 diabetes. Such studies should be accompanied by efforts to assess the comparative effectiveness of rt-CGM versus other methods of glucose monitoring. At a minimum, the protocols of RCTs of intensive insulin therapy options in adolescents will need to specify the type of glucose monitoring method to be used, so that the effects of differences in insulin therapy can be distinguished from differences in the glucose monitoring methods.

In our original evidence report, we highlighted the need for studies in the elderly. However, for this report on Future Research Needs, the stakeholders made it clear that the entire adult population with type 2 diabetes remains a high priority for future research. For this important population, RCTs are the strongest and most appropriate study design for determining the comparative effectiveness of the sensor augmented pump compared with other insulin delivery methods. As indicated above, such trials should be accompanied by efforts to assess the

comparative effectiveness of rt-CGM versus other methods of glucose monitoring, with protocols that clearly specify the type of glucose monitoring method to be used.

Since the cost of long-term RCTs may be prohibitive for addressing all of the outcomes of interest for all of the comparisons of interest, prospective observational studies will continue to have a role. Observational studies will be particularly important in determining the comparative effectiveness of CSII versus MDI and rt-CGM versus SMBG in terms of clinically relevant long-term microvascular and macrovascular outcomes.

Discussion

The majority of stakeholders prioritized adolescents with type 1 diabetes and adults with insulin-requiring type 2 diabetes as the populations in greatest need for future research. For each population, rt-CGM was identified as the highest priority for future research on glucose monitoring methods, while the research priorities on insulin delivery methods and outcomes of interest varied by population. When asked to prioritize the final research question within each category, glucose monitoring methods were universally prioritized above insulin delivery methods.

While the stakeholders rated adolescents with type 1 diabetes as the highest priority, the original investigators commented that future studies should focus on populations in which diabetes is growing (i.e., elderly individuals with type 1 and type 2 diabetes, insulin-treated type 2 diabetes, minority populations). This difference may be because the stakeholders took a clinical perspective that focused on treatment while the investigators took a research perspective that focused on the gaps in data. On the other hand, adherence as an outcome was rated high by both stakeholders and the original investigators. It is important to note that stakeholders identified and rated the artificial pancreas as the highest priority for future research, despite the fact that the technology of artificial pancreas is at the developmental stage, not widely used in practice, and was not included in the original Comparative Effectiveness Review for lack of eligible studies. Nonetheless, this consensus reflected the urge to develop a better and more convenient system for diabetes treatment.

Long-term clinical outcomes were not specifically included for prioritization by the stakeholders. While prevention of long-term macrovascular and microvascular complications is the ultimate goal of interventions for type 1 and type 2 diabetes, such trials would need an extremely long time for followup. Comparative effectiveness studies would require very large numbers of patients to be followed for many years to show significant macrovascular and microvascular effects, especially if only small HbA1c differences are seen, something much too costly to do. Supported by strong ratings from the stakeholders, we feel HbA1c is a reasonable surrogate endpoint, and should be used when looking at the comparative effectiveness of rt-CGM and the sensor-augmented insulin pump, versus other interventions.

Our study had several strengths. First, we used an established approach for consensus building. Second, we invited experts from multiple disciplines as stakeholders including practicing endocrinologists, clinical researchers, and a patient, which increased the generalizability. Third, the stakeholders reached consensus with only one round of survey, which reflected high level of consistency.

Nonetheless, this study has some limitations. First, our study was limited to the scope of the original evidence report. The original investigators determined the research gaps based on their own findings. Stakeholders did not independently identify research gaps on the basis of populations, interventions, and outcomes, but rather by the limited options that we provided

according to our analytic framework. This limitation is offset by the benefit of keeping the study focused on the populations and interventions that were included in our analytic framework. This study did not specifically address the needs for future research in pregnant women because we thought it would require a separate study to adequately determine the research needs for pregnant women having type 1 diabetes, type 2 diabetes, or gestational diabetes. Another limitation is that the complexity of the concepts in this topic may be a barrier for patient stakeholders to contribute. The decision making process associated with prioritizing clinical interventions could potentially be a daunting task for non-clinicians and non-researchers in the field. Clinicians have a level of standardized education and training in the field. The average patient may or may not have the requisite breadth of knowledge and experience to prioritize interventions for the entire field of insulin delivery and glucose monitoring research. Still, in our study, this was minimized by a patient Stakeholder with a longstanding history of diabetes and who has taken an active role in his care throughout his life. Finally, due to the abundance of outcomes gaps in the literature, it was prohibitive to present all potential outcomes to the stakeholders for prioritization. This limitation was minimized by allowing the stakeholders the option to identify research gaps using a free-text field after reading the Executive Summary of the full Comparative Effectiveness Review.

We feel that the research questions developed by comprehensive feedback from our panel of expert stakeholders represent the highest research priorities in the field of insulin delivery and glucose monitoring methods. We recognize that there are many additional gaps, including insulin delivery and glucose monitoring research for elderly patients with type 1 diabetes; however, the inductive approach to building consensus for research question development resulted in four high priority research needs.

Conclusion

For type 1 diabetes, three expert stakeholders ranked adolescents as the highest priority age group for future research, and three stakeholders ranked the artificial pancreas as the highest priority for future research. For future research on glucose monitoring methods in patients with type 1 diabetes, all Stakeholders identified rt-CGM as the highest priority. For younger populations (children and adolescents) of patients with type 1 diabetes, adherence was ranked as the highest priority outcome for inclusion in future research. For adults and elderly patients with type 1 diabetes, most stakeholders ranked severe hypoglycemia as the highest priority outcome for inclusion in future research. Among insulin-requiring type 2 patients with diabetes, three stakeholders ranked adults as the highest priority age group for future research. For all patients with insulin-requiring type 2 diabetes, three Stakeholders ranked the sensor-augmented insulin pump as the highest priority for research on insulin delivery methods. Likewise, for future research on glucose monitoring methods in patients with insulin-requiring type 2 diabetes, three stakeholders identified rt-CGM as the highest priority. Most stakeholders ranked HbA1c as the highest priority outcome to include in future research on insulin-requiring type 2 diabetes.

Tables

Table A. Key Questions from Comparative Effectiveness Review

KQ 1	In patients receiving intensive insulin therapy, does mode of delivery (MDI vs. CSII) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus?
KQ 2	In patients using intensive insulin therapy (MDI or CSII), does the type of glucose monitoring (rt-CGM vs. SMBG) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus (i.e., what is the incremental benefit of rt-CGM in patients already using intensive insulin therapy)?

Abbreviations: KQ = Key Question; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; rt-CGM = Real-time continuous glucose monitoring; SMBG = Self-monitoring of blood glucose

Table B. Stakeholder identification and prioritization of populations of greatest importance for future research for insulin delivery and blood glucose monitoring methods among patients with type 1 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Populations			
Children (<13 years)	1	*	
Adolescent (13-19 years)	3	*	‡
Adult (20-64 years)	1	*	
Elderly (>=65 years)	0	*	

*Indicates consensus achieved in the previous round; reprioritization not required.
‡Indicates an identified research need.

Table C. Stakeholder identification and prioritization of insulin delivery methods of greatest importance for future research among patients with type 1 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Children			
Continuous subcutaneous insulin infusion (insulin pump)	0	*	
Reactive low glucose suspend pump (automatically suspends insulin delivery when glucose reaches low threshold)	1	*	
Artificial pancreas (overnight closed loop, sense upper and lower thresholds)	3	*	
Sensor-augmented insulin pump	1	*	
Adolescents			
Continuous subcutaneous insulin infusion (insulin pump)	0	*	
Reactive low glucose suspend pump (automatically suspends insulin delivery when glucose reaches low threshold)	0	*	
Artificial pancreas (overnight closed loop, sense upper and lower thresholds)	3	*	‡
Sensor-augmented insulin pump	2	*	
Adults			
Continuous subcutaneous insulin infusion (insulin pump)	0	*	
Reactive low glucose suspend pump (automatically suspends insulin delivery when glucose reaches low threshold)	1	*	
Artificial pancreas (overnight closed loop, sense upper and lower thresholds)	2	*	
Sensor-augmented insulin pump	2	*	
Elderly			
Continuous subcutaneous insulin infusion (insulin pump)	0	*	
Reactive low glucose suspend pump (automatically suspends insulin delivery when glucose reaches low threshold)	4	*	
Artificial pancreas (overnight closed loop, sense upper and lower thresholds)	1	*	
Sensor-augmented insulin pump	0	*	

*Indicates consensus achieved in the previous round; reprioritization not required.
‡Indicates an identified research need.

Table D. Stakeholder identification and prioritization of blood glucose monitoring methods of greatest importance for future research among patients with type 1 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Children			
Self-monitored blood glucose	0	*	
Retrospective continuous glucose monitoring	0	*	
Real-time continuous glucose monitoring	5	*	
Adolescents			
Self-monitored blood glucose	0	*	
Retrospective continuous glucose monitoring	0	*	
Real-time continuous glucose monitoring	5	*	‡
Adults			
Self-monitored blood glucose	0	*	
Retrospective continuous glucose monitoring	0	*	
Real-time continuous glucose monitoring	5	*	
Elderly			
Self-monitored blood glucose	0	*	
Retrospective continuous glucose monitoring	0	*	
Real-time continuous glucose monitoring	5	*	

*Indicates consensus achieved in the previous round; reprioritization not required.
‡Indicates an identified research need.

Table E. Stakeholder identification and prioritization of clinical outcomes of greatest importance for future research of insulin delivery and glucose monitoring methods among patients with type 1 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Children			
HbA1c	0	*	
Adherence	3	*	
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	1	*	
Hyperglycemia	1	*	
Adolescents†			
HbA1c	0	*	
Adherence	2	*	‡
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	2	*	‡
Hyperglycemia	0	*	
Adults			
HbA1c	1	*	
Adherence	1	*	
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	3	*	
Hyperglycemia	0	*	
Elderly			
HbA1c	0	*	
Adherence	0	*	
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	5	*	
Hyperglycemia	0	*	

Abbreviation: HbA1c = hemoglobin A1c

*Indicates consensus achieved in the previous round; reprioritization not required.

‡Indicates an identified research need.

†One Stakeholder abstained.

Table F. Stakeholder identification and prioritization of populations of greatest importance for future research among insulin-requiring patients with type 2 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Adolescent (13-19 years)	1	*	
Adult (20-64 years)	3	*	‡
Elderly (>=65 years)	1	*	

*Indicates consensus achieved in the previous round; reprioritization not required.
‡Indicates an identified research need.

Table G. Stakeholder identification and prioritization of insulin delivery methods of greatest importance for future research among insulin-requiring patients with type 2 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Continuous subcutaneous insulin infusion (insulin pump)	1	*	
Reactive low glucose suspend pump (automatically suspends insulin delivery when glucose reaches low threshold)	0	*	
Artificial pancreas (overnight closed loop, sense upper and lower thresholds)	1	*	
Sensor-augmented insulin pump	3	*	‡

*Indicates consensus achieved in the previous round; reprioritization not required.
‡Indicates an identified research need.

Table H. Stakeholder identification and prioritization of blood glucose monitoring methods of greatest importance for future research among insulin-requiring patients with type 2 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Self-monitored blood glucose	2	*	
Retrospective continuous glucose monitoring	0	*	
Real-time continuous glucose monitoring	3	*	‡

*Indicates consensus achieved in the previous round; reprioritization not required.
‡Indicates an identified research need.

Table I. Stakeholder identification and prioritization of clinical outcomes of greatest importance for future research of insulin delivery and glucose monitoring methods among patients with type 2 diabetes by population

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Adolescents			
HbA1c	2	*	
Adherence	1	*	
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	1	*	
Hyperglycemia	0	*	
Weight	1	*	
Adults			
HbA1c	3	*	‡
Adherence	1	*	
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	0	*	
Hyperglycemia	1	*	
Weight	0	*	
Elderly			
HbA1c	3	*	
Adherence	0	*	
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	1	*	
Hyperglycemia	1	*	
Weight	0	*	

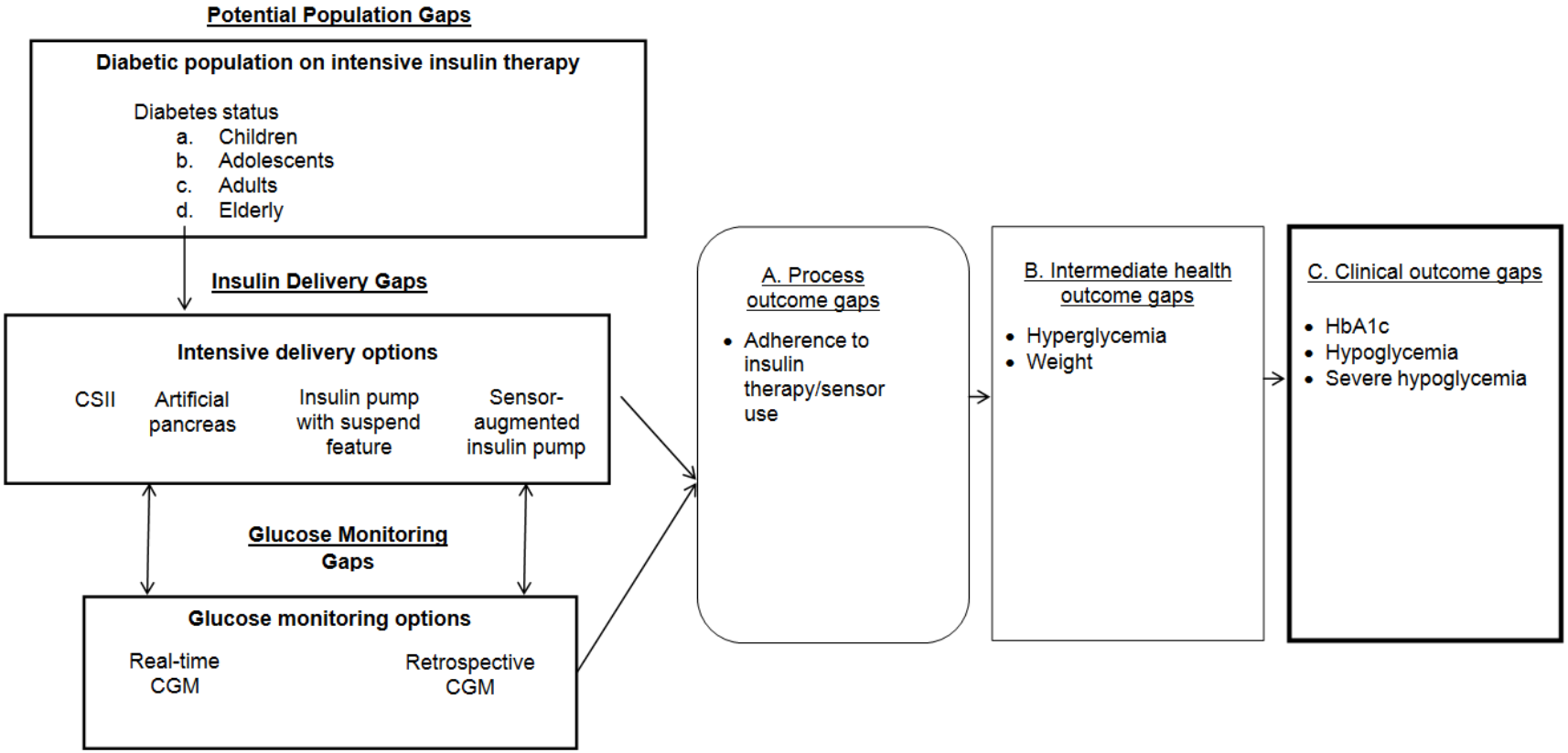
Abbreviation: HbA1c = hemoglobin A1c

*Indicates consensus achieved in the previous round; reprioritization not required.

‡Indicates an identified research need.

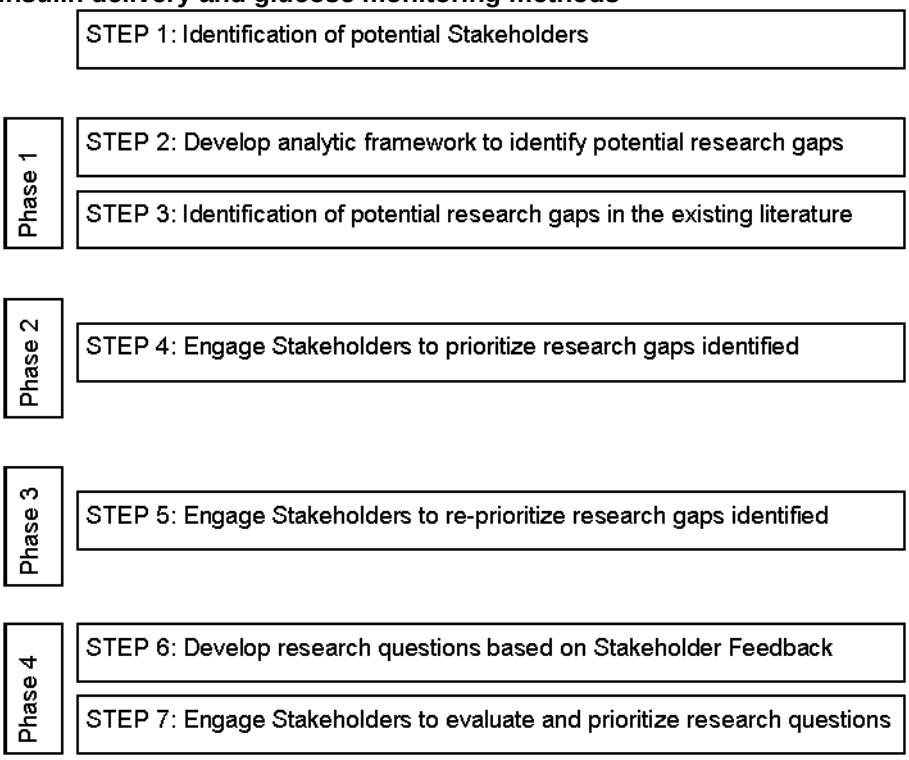
Figures

Figure A. Analytic framework for identification of potential research gaps in phase 1



Abbreviations: CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; HbA1c = hemoglobin A1c

Figure B. Outline of key steps for identification and prioritization of Future Research Needs for insulin delivery and glucose monitoring methods



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Background

Context

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

Type 1 diabetes, which accounts for 5 to 10 percent of all diabetes cases, is characterized by insulin deficiency and a need for daily insulin administration to sustain life, maintain normoglycemia, and maintain normal body weight and promote normal growth and development in children.[1] Type 2 diabetes, which accounts for 90 to 95 percent of diabetes in the U.S., is the result of a combination of insulin resistance and impaired insulin secretion by the beta cells of the endocrine pancreas.[1] Although the relative contribution of each of these factors to the course of type 2 diabetes varies by patient, eventually, beta cell failure can lead to insulin deficiency, necessitating insulin therapy.

In current practice, tight glycemic control is achieved through the use of physiological basal and meal-time (prandial) insulin that, when used together, mimic normal pancreatic function (e.g. peakless basal insulin secretion, rapid release of insulin in response to meals, and rapid resolution of the prandial insulin peak). Patients take these medications either as three or more daily injections [multiple daily injections (MDI)], or by external continuous subcutaneous insulin infusion (CSII) via a pump, which provides a more physiological means to deliver insulin.

Following publication of the Diabetes Control and Complications Trial, self-monitoring of blood glucose (SMBG) by finger stick replaced the assessment of glucose by urine dipstick to allow more specific and timely feedback on the degree of hyperglycemia.[5] The challenges to use of SMBG are the associated pain, costs, behavioral and technical skills, required motivation, and intrusiveness. These challenges directly affect adherence to this technique and are barriers to tight glycemic control. In response to these issues, the health care industry has developed continuous glucose monitoring (CGM) systems that record blood glucose levels throughout the day and night with a significantly decreased need for fingerstick measurements.

A CGM system, in conjunction with intensive insulin treatment, can be a useful tool to lower blood glucose values in adults who are at least 25 years of age and have type 1 diabetes. Success in lowering blood glucose levels depends on adherence to ongoing use of the device.[6]

The United States Food and Drug Administration first approved real-time continuous glucose monitoring (rt-CGM) in 2005. rt-CGM differs from conventional (retrospective) CGM in that it provides blood glucose feedback data to the patient while he or she is wearing the device and does not need to be downloaded and evaluated after data collection. This advantage of rt-CGM has resulted in it being the preferred method of CGM in the clinical setting.

CSII is currently recommended for patients with type 1 diabetes who are not achieving glycemic goals despite adherence to a maximum MDI regimen. This is especially true when

patients also have wide and erratic glycemic excursions, frequent severe hypoglycemia and/or hypoglycemia unawareness, marked dawn phenomenon (pre-breakfast rise in blood glucose seen when bedtime basal insulin effect diminishes),[5,7] or are pregnant or planning to become pregnant. Experts may also recommend CSII for patients with type 1 diabetes who feel that pump therapy may be more suitable to their lifestyle, regardless of the level of glycemic control.[5] Experts currently recommend rt-CGM for patients with type 1 diabetes who have hypoglycemia unawareness or frequent hypoglycemia (where hemoglobin A1c [HbA1c] is over the recommended target), have excess glycemic excursions, or are pregnant or plan to be pregnant.[8]

Given new technologies in insulin delivery and glucose monitoring, clinicians are now faced with determining which patient populations benefit most from the use of CSII and rt-CGM in terms of improved glycemic, clinical, and patient-reported outcomes. Because both technologies are expensive and require extensive training and oversight by health care professionals, it is critical to determine how to select patients for their use. It is also important to point out that the most adherent and engaged patients will likely achieve beneficial outcomes as both forms of intensive insulin therapy (MDI and CSII) and both forms of glucose monitoring (rt-CGM and SMBG) require the patient to partner with his/her health care provider.

Our recent systematic review examined specific questions about the comparative effectiveness of insulin delivery and glucose monitoring methods (see Table 1).[9] The review found that intensive insulin therapy delivered either by CSII and MDI is equally effective in lowering glycated hemoglobin (HbA1c) levels in adolescents and adults with type 1 diabetes. Intensive insulin therapy delivered by both methods resulted in similar rates of severe hypoglycemia for adolescents and adults with type 1 diabetes. The review also found evidence that rt-CGM is superior to SMBG in lowering HbA1c , without altering the risk balance of severe hypoglycemia, particularly among those who are compliant with wearing the monitoring device. Even though CSII and MDI without rt-CGM have similar effects on HbA1c , the addition of rt-CGM to CSII is superior to MDI/SMBG in lowering HbA1c . Thus, the addition of this monitoring method to SMBG and intensive insulin therapy can assist in achieving glycemic targets in individuals with type 1 diabetes. However, the review also identified several important gaps in the evidence, as shown in Figure 1.[9] The objective of this report is to prioritize the needs for research addressing those gaps in the existing literature on management of insulin-requiring diabetes by engaging expert stakeholders using a modified Delphi method.

Identification of Evidence Gaps

Populations

There is a need for well-conducted randomized controlled trials (RCTs) of intensive insulin therapy delivered via CSII versus MDI in children with type 1 diabetes and in elderly patients with both type 1 and type 2 diabetes. Studies in the elderly are important as diabetes prevalence increases with age.[2] Only a small number of studies in non-adolescent children have compared CSII with MDI on glycemic and non-glycemic outcomes and studies comparing rt-CGM with SMBG have included a mixture of children and adults without stratifications focused exclusively on children.

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. Finally, studies of type 2 diabetes

should include ethnically diverse populations because type 2 diabetes is more common in blacks than in whites.[10]

Interventions

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.

Study Design

Our report highlights the need for several areas of future research examining the effect of insulin delivery and glucose monitoring devices in the management of diabetes mellitus. To allow cross-comparisons, future RCTs should use a uniform definition of hypoglycemia, preferably that recommended by the American Diabetes Association.[11] 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 feasible to undertake RCTs examining these outcomes. Future studies should also seek to identify and use an agreed-upon set of general and diabetes-specific and treatment-related quality of life measures to allow comparisons across studies, including reporting of standard errors and confidence intervals to allow quantitative, pooled assessments. Studies should 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 other data show that rt-CGM is most effective in those compliant with wearing the sensor at least 60 percent of the time.[12,13] Thus, sensor compliance may be a marker for overall treatment adherence and explain the HbA1c reduction, independent of the sensor.

Methods

Research Gap Identification

We developed an analytic framework (Figure 1) to identify potential populations, insulin delivery and glucose monitoring methods, and outcomes gaps from the 2012 evidence report. As indicated in the analytic framework, we focused on the population of patients having type 1 or type 2 diabetes, with subpopulations defined by age categories. We did not include pregnant women as a separate category in this report because we thought it would require a separate process (and a different group of stakeholders) to adequately assess the needs for future research in pregnant women having type 1 diabetes, type 2 diabetes, or gestational diabetes (the evidence report did not include gestational diabetes and did not find any studies on pregnant women with type 2 diabetes). In the analytic framework for this study, we included the types of interventions that are currently being evaluated for delivering insulin continuously or for monitoring glucose continuously, even though we did not have any studies about the artificial pancreas or the reactive low glucose suspend pump in the original evidence report. In the original evidence report, we excluded studies of interventions that were no longer used in clinical practice, but we did not specifically exclude these new interventions.

We then searched the results and discussion sections of the evidence report, using the analytic framework, to identify potential research gaps. A Web-based assessment tool was populated with the identified research gaps specific to the induction of remission and the maintenance of remission. For each research gap category, an optional, free-text field was provided for stakeholders to identify gaps not listed in the assessment tool.

Criteria for Prioritization

The stakeholders were provided with a copy of the Executive Summary of the 2012 evidence report, were asked to read the full Executive Summary for familiarization of the findings, and were asked to independently identify the highest priority gaps for future research among individuals with type 1 diabetes and with type 2 diabetes within each of the following categories: populations, insulin delivery methods, glucose monitoring methods and outcomes. First, we asked the stakeholders to rate the three highest priority age-based populations with type 1 diabetes and with type 2 diabetes. Second, we asked stakeholders to rate the highest priority insulin delivery method and the highest priority blood glucose monitoring method for each age stratum of each diabetes type. Finally, we asked the stakeholders to rate the three highest priority outcomes for each age stratum for each diabetes type. Stakeholders were given the opportunity to add insulin delivery methods, glucose monitoring methods, and outcomes not on the list as an ‘other’ free-text option.

Engagement of Stakeholders, Researchers, and Funders

Stakeholder Identification

Expert Stakeholders for this project were representative of clinicians, researchers, private and federal agencies and patients. Fourteen experts in the field of insulin delivery and glucose management were identified and invited to serve as expert Stakeholders. One academic

physician in the field of pediatric endocrinology, three physicians in the field of adult endocrinology and one patient agreed to serve as Stakeholders for this project.

Stakeholder Engagement

We used a modified Delphi method to identify and prioritize existing gaps in the published literature as it pertains to insulin delivery and glucose monitoring methods in seven steps across four phases (Figure 2). The Delphi method involves iterative rounds of responses by group members, providing aggregated feedback about other members' responses until consensus is reached. For each round, we used a Web-based assessment tool (SurveyMonkey™, Palo Alto, CA), with the list of the research gaps. Consensus among stakeholders was pre-defined as agreement in responses of 50% or higher in three or more options for each category of Future Research Needs. Categories that did not achieve 50% or greater consensus among the stakeholders on three or more options in phase 2 were returned for the stakeholders, with their compiled feedback from phase 2, to reprioritize.

We developed an analytic framework (Figure 1) to identify potential populations, insulin delivery methods, glucose monitoring methods, and outcomes gaps from the 2012 evidence report. We then searched the results and discussion sections of the evidence report, using the analytic framework, to identify potential research gaps. A Web-based assessment tool was populated with the identified research gaps specific to the induction of remission and the maintenance of remission. For each research gap category, an optional, free-text field was provided for stakeholders to identify gaps not listed in the assessment tool.

Research questions were developed based on feedback from stakeholders that achieved consensus during the second and third rounds. The stakeholders were presented with their compiled feedback from the second and third phases along with the research questions developed. They were asked to provide feedback on the clarity, utility, study design feasibility and priority of the research questions.

Research Question Development and Research Design Considerations

Research questions were developed based on feedback from stakeholders that achieved consensus during the second and third rounds. The stakeholders were presented with their compiled feedback from the second and third phases along with the research questions developed. They were asked to provide feedback on the clarity, utility, study design feasibility and priority of the research questions.

Identification of Ongoing Research

Clinical research repositories and research-related sites including ClinicalTrials.gov, NIH Reporter, the Canadian Institutes of Health Research, the World Health Organization Clinical Trials Registry, and the European Union Clinical Trials Register were searched to identify ongoing or recently completed studies related to insulin pump therapy and blood glucose monitoring for insulin-requiring patients with diabetes. Appendix A details the search strategies used for each repository.

Results

Research Needs

Type 1 Diabetes

Phase 1

During phase 1 of this study, population research gaps identified included children (age less than 13 years), adolescents (age 13 to 19 years), adults (age 20-64 years), and the elderly (age ≥ 65 years) with type 1 diabetes (see Table 2). Potential research needs for insulin delivery methods were CSII (i.e. insulin pump), reactive low glucose suspend pumps (i.e. pump that automatically suspends insulin delivery when glucose reaches low threshold), artificial pancreas (i.e. overnight closed loop, senses upper and lower glucose thresholds), and sensor-augmented insulin pumps (see Table 3). Potential blood glucose monitoring methods for future research identified were SMBG, retrospective continuous glucose monitoring, and real-time continuous glucose monitoring (see Table 4). Outcomes identified for future research were HbA1c , adherence, non-severe hypoglycemia, severe hypoglycemia, and hyperglycemia (see Table 5).

Phase 2

During phase 2, three expert stakeholders ranked adolescents as the highest priority among type 1 patients with diabetes for future research. (see Table 2). One stakeholder ranked children and one ranked adults as the highest priority for future research. Among children with type 1 diabetes, three Stakeholders ranked artificial pancreas as the highest research need for insulin delivery while one Stakeholder ranked reactive glucose suspend pump and one ranked sensor-augmented insulin pump as the highest priorities for this population. Among adolescents with type 1 diabetes, three Stakeholders also ranked artificial pancreas as the highest priority for future research while two prioritized sensor-augmented insulin pump. For adults with type 1 diabetes, two Stakeholders prioritized artificial pancreas and two prioritized sensor-augments insulin pump for future research. One Stakeholder prioritized reactive low glucose suspend pump as the highest priority for future research. Four stakeholders ranked reactive low glucose suspend pump as the highest priority for future research among the elderly with type 1 diabetes and one Stakeholder ranked artificial pancreas as the highest priority (see Table 3).

For glucose monitoring methods, all stakeholders prioritized rt-CGM for anyone with type 1 diabetes (see Table 4).

Three stakeholders ranked adherence as the highest priority among children with type 1 diabetes. For adolescents, two stakeholders rated adherence as highest priority while the other two ranked severe hypoglycemia as highest priority. Among adults, three stakeholders ranked severe hypoglycemia as high priority; and in elderly, all stakeholders rated severe hypoglycemia as a high priority (see Table 5).

Phase 3

Consensus was achieved during phase 2, negating the need to build consensus in phase 3.

Phase 4

When presented with the research questions developed from feedback in earlier rounds, Stakeholders prioritized glucose monitoring as a higher research need above insulin delivery methods.

Type 2 Diabetes

Phase 1

During phase 1 of this study adolescents (age 13 to 19 years), adults (age 20-64 years) and elderly (age greater than 64) with type 2 diabetes were identified as research gaps (see Table 6). Research gaps for insulin delivery methods were CSII (i.e. insulin pump), reactive low glucose suspend pumps (i.e. pump that automatically suspends insulin delivery when glucose reaches low threshold), artificial pancreas (i.e. overnight closed loop, senses upper and lower glucose thresholds), and sensor-augmented insulin pumps (see Table 7). Potential blood glucose monitoring methods for future research identified were SMBG, retrospective continuous glucose monitoring, and rt-CGM (see Table 8). Outcomes identified for future research were HbA1c , adherence, non-severe hypoglycemia, severe hypoglycemia, hyperglycemia, and weight (see Table 9).

Phase 2

During phase 2, three Stakeholders ranked adults as the highest priority among insulin-requiring patients with type 2 diabetes for future research. One stakeholder ranked adolescents and one ranked elderly as the highest priority for future research (see Table 6). Among the patients with insulin-requiring type 2 diabetes, three Stakeholders ranked sensor-augmented insulin pump as the highest research need for insulin delivery while one stakeholder ranked CSII and one prioritized artificial pancreas as the highest priorities for this future research (see Table 7). For glucose monitoring methods, three Stakeholders prioritized rt-CGM and two prioritized SMBG for patients with insulin-requiring type 2 diabetes (see Table 8).

Two Stakeholders prioritized HbA1c , one prioritized severe hypoglycemia and one ranked weight as the highest priority among adolescents with insulin-requiring type 2 diabetes. Three Stakeholders prioritized HbA1c , one prioritized adherence and one ranked hyperglycemia as the highest priority among adults with insulin-requiring type 2 diabetes. Three Stakeholders prioritized HbA1c , one prioritized severe hypoglycemia and one ranked hyperglycemia as the highest priority among the elderly with insulin-requiring type 2 diabetes (Table 9).

Phase 3

Consensus was also achieved for insulin-requiring type 2 diabetes during phase 2.

Phase 4

When presented with the research questions developed from feedback in earlier rounds, Stakeholders prioritized glucose monitoring as a higher research need above insulin delivery methods.

Research Questions

Based on stakeholder feedback from phase 2 regarding populations, intervention comparisons, and outcomes, the following four research questions developed for future research were prioritized by our stakeholders:

1. For adolescents with type 1 diabetes, what is the comparative effectiveness of an artificial pancreas versus other methods of insulin delivery for the outcomes of adherence and severe hypoglycemia?
2. For adolescents with type 1 diabetes, what is the comparative effectiveness of rt-CGM versus other methods of glucose monitoring for the outcomes of adherence and severe hypoglycemia?
3. For adults with insulin-requiring type 2 diabetes, what is the comparative effectiveness of a sensor-augmented insulin pump versus other methods of insulin delivery for the outcome HbA1c ?
4. For adults with insulin-requiring type 2 diabetes, what is the comparative effectiveness of rt-CGM versus other methods of glucose monitoring for the outcome HbA1c ?

This report reinforces the needs for future research that we outlined in the original evidence report,[9] and points to specific types of studies that should have a high priority. In the original report, we identified a need for well-conducted RCTs of intensive insulin therapy delivered via CSII versus MDI in young children with type 1 diabetes and elderly patients with both type 1 and type 2 diabetes. Based on the input from our stakeholders, higher priority should be given to RCTs of intensive insulin therapy options, including the artificial pancreas, in adolescents with type 1 diabetes. Such studies should be accompanied by efforts to assess the comparative effectiveness of rt-CGM versus other methods of glucose monitoring. At a minimum, the protocols of RCTs of intensive insulin therapy options in adolescents will need to specify the type of glucose monitoring method to be used, so that the effects of differences in insulin therapy can be distinguished from differences in the glucose monitoring methods.

In our original evidence report, we highlighted the need for studies in the elderly. However, for this report on Future Research Needs, the stakeholders made it clear that the entire adult population with type 2 diabetes remains a high priority for future research. For this important population, RCTs are the strongest and most appropriate study design for determining the comparative effectiveness of the sensor augmented pump compared with other insulin delivery methods. As indicated above, such trials should be accompanied by efforts to assess the comparative effectiveness of rt-CGM versus other methods of glucose monitoring, with protocols that clearly specify the type of glucose monitoring method to be used.

Since the cost of long-term RCTs may be prohibitive for addressing all of the outcomes of interest for all of the comparisons of interest, prospective observational studies will continue to have a role. Observational studies will be particularly important in determining the comparative effectiveness of CSII versus MDI and rt-CGM versus SMBG in terms of clinically relevant long-term microvascular and macrovascular outcomes.

Identification of Ongoing Research

We searched clinical research repositories and research-related sites including ClinicalTrials.gov, NIH Reporter, the Canadian Institutes of Health Research, the World Health

Organization Clinical Trials Registry, and the European Union Clinical Trials Register to identify ongoing/recently completed studies related to insulin pump therapy and blood glucose monitoring for insulin-requiring patients with diabetes. Appendix B includes a summary of findings from these searches. Thirteen potentially relevant studies were identified.

Discussion

The majority of stakeholders prioritized adolescents with type 1 diabetes and adults with insulin-requiring Type 2 Diabetes as the populations in greatest need for future research. For each population, rt-CGM was prioritized as the highest method of glucose monitoring for future research, while the method of insulin delivery and outcomes of interest varied by population. When asked to prioritize the final research question within each category, glucose monitoring methods were universally prioritized above insulin delivery methods.

While the stakeholders rated adolescents with type 1 diabetes the highest priority, the original Comparative Effectiveness Review (CER) investigators commented future studies should focus on populations in which diabetes is growing (i.e. elderly individuals with type 1 and type 2 diabetes, insulin-treated type 2 diabetes, minority populations). This difference may be because the stakeholders took a clinical perspective that focused on treatment while the CER investigators took a research perspective that focused on the gaps in data. On the other hand, adherence as outcome was rated high by both stakeholders and the original CER investigators. It is important to note that stakeholders rated the artificial pancreas as the highest priority for the future research, despite the fact that the technology of artificial pancreas is at the developmental stage, is not widely used in practice, and was not included in the original Comparative Effectiveness Review for lack of eligible studies. Nonetheless, this consensus reflected the urge to develop a better and more convenient system for diabetes treatment.

Long-term clinical outcomes were not specifically included for prioritization by the stakeholders; however, stakeholders were given the opportunity to independently identify long-term outcomes for future research. While we feel that long-term clinical outcomes, such as mortality, macrovascular complications, and microvascular complications, are the ultimate goal of interventions for both type 1 and type 2 diabetes populations, such trials would need an extensively long time for followup. The Diabetes Control and Complications Trial showed a significant reduction in microvascular complications after only 6.5 years, and macrovascular complications after 15 years; however, these significant differences were achieved only with a very wide difference in HbA1c of approximately 2% between intervention and placebo groups.[5] In the United Kingdom Prospective Diabetes Study, it took 10 years for an HbA1c difference of 0.9% to show a reduction in microvascular complications and 20 years to show a reduction in macrovascular complications.[14] Comparative effectiveness studies would require very large number of patients to be followed for many years to show significant micro and macrovascular effects, especially if only small A1c differences are seen, something much too costly to do. Supported by strong rating from the stakeholders, we feel HbA1c is a reasonable surrogate endpoint, and should be used as such when looking at the comparative effectiveness of rt-CGM and sensor-augmented insulin pump, versus other interventions.

Our study had several strengths. First, we used an established approach for consensus building. Second, we invited experts from multiple disciplines as stakeholders including practicing endocrinologists, clinical researchers, and a patient, which increased the generalizability. Third, the stakeholders reached consensus with only one round of survey, which reflected high level of consistency.

Nonetheless, this study has some limitations. First, our study was limited to the scope of the original CER. The original investigators determined the research gaps based on their own findings. Stakeholders did not independently identify research gaps on the basis of populations, interventions, and outcomes, but rather by the limited options that we provided according to our analytic framework. This limitation is offset by the benefit of keeping the study focused on the

populations and interventions that were included in our analytic framework. This study did not specifically address the needs for future research in pregnant women because we thought it would require a separate study (with a different group of stakeholders) to adequately determine the research needs for pregnant women having type 1 diabetes, type 2 diabetes, or gestational diabetes. Another limitation is that the complexity of the concepts in this topic may be a barrier for patient stakeholders to contribute. The decision making process associated with prioritizing clinical interventions could potentially be a daunting task for non-clinicians and non-researchers in the field. Clinicians have a level of standardized education and training in the field. The average patient may or may not have the requisite breadth of knowledge and experience to prioritize interventions for the entire field of insulin delivery and glucose monitoring research. Still, in our study, this was minimized by a patient Stakeholder with a longstanding history of diabetes and who has taken an active role in his care throughout his life.

Conclusion

For type 1 diabetes, three expert Stakeholders ranked adolescents as the highest priority among patients with type 1 diabetes for future research, and three Stakeholders ranked artificial pancreas as the highest priority for future research. For glucose monitoring methods, all stakeholders prioritized rt-CGM for anyone with type 1 diabetes. For younger populations (children and adolescents) adherence was ranked highest by many Stakeholders. For adults and elderly, the majority ranked severe hypoglycemia as high priority. Among insulin-requiring patients with type 2 diabetes, three stakeholders ranked adults as the highest priority. For all patients with insulin-requiring type 2 diabetes, three stakeholders ranked sensor-augmented insulin pump as the highest research need for insulin delivery. Likewise, for glucose monitoring methods, three stakeholders prioritized rt-CGM for patients with insulin-requiring type 2 diabetes. For outcomes, majority of the stakeholders ranked HbA1c as the highest priority.

Tables

Table 1. Key Questions from Comparative Effectiveness Review

KQ 1	In patients receiving intensive insulin therapy, does mode of delivery (MDI vs. CSII) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus?
KQ 2	In patients using intensive insulin therapy (MDI or CSII), does the type of glucose monitoring (rt-CGM vs. SMBG) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus (i.e., what is the incremental benefit of rt-CGM in patients already using intensive insulin therapy)?

Abbreviations: KQ = Key Question; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; rt-CGM = Real-time continuous glucose monitoring; SMBG = Self-monitoring of blood glucose

Table 2. Stakeholder identification and prioritization of populations of greatest importance for future research for insulin delivery and blood glucose monitoring methods among patients with type 1 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Populations			
Children (<13 years)	1	*	
Adolescent (13-19 years)	3	*	‡
Adult (20-64 years)	1	*	
Elderly (>=65 years)	0	*	

*Indicates consensus achieved in the previous round; reprioritization not required.
‡Indicates an identified research need.

Table 3. Stakeholder identification and prioritization of insulin delivery methods of greatest importance for future research among patients with type 1 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Children			
Continuous subcutaneous insulin infusion (insulin pump)	0	*	
Reactive low glucose suspend pump (automatically suspends insulin delivery when glucose reaches low threshold)	1	*	
Artificial pancreas (overnight closed loop, sense upper and lower thresholds)	3	*	
Sensor-augmented insulin pump	1	*	
Adolescents			
Continuous subcutaneous insulin infusion (insulin pump)	0	*	
Reactive low glucose suspend pump (automatically suspends insulin delivery when glucose reaches low threshold)	0	*	
Artificial pancreas (overnight closed loop, sense upper and lower thresholds)	3	*	‡
Sensor-augmented insulin pump	2	*	
Adults			
Continuous subcutaneous insulin infusion (insulin pump)	0	*	
Reactive low glucose suspend pump (automatically suspends insulin delivery when glucose reaches low threshold)	1	*	
Artificial pancreas (overnight closed loop, sense upper and lower thresholds)	2	*	
Sensor-augmented insulin pump	2	*	
Elderly			
Continuous subcutaneous insulin infusion (insulin pump)	0	*	
Reactive low glucose suspend pump (automatically suspends insulin delivery when glucose reaches low threshold)	4	*	
Artificial pancreas (overnight closed loop, sense upper and lower thresholds)	1	*	
Sensor-augmented insulin pump	0	*	

*Indicates consensus achieved in the previous round; reprioritization not required.
‡Indicates an identified research need.

Table 4. Stakeholder identification and prioritization of blood glucose monitoring methods of greatest importance for future research among patients with type 1 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Children			
Self-monitored blood glucose	0	*	
Retrospective continuous glucose monitoring	0	*	
Real-time continuous glucose monitoring	5	*	
Adolescents			
Self-monitored blood glucose	0	*	
Retrospective continuous glucose monitoring	0	*	
Real-time continuous glucose monitoring	5	*	‡
Adults			
Self-monitored blood glucose	0	*	
Retrospective continuous glucose monitoring	0	*	
Real-time continuous glucose monitoring	5	*	
Elderly			
Self-monitored blood glucose	0	*	
Retrospective continuous glucose monitoring	0	*	
Real-time continuous glucose monitoring	5	*	

*Indicates consensus achieved in the previous round; reprioritization not required.
‡Indicates an identified research need.

Table 5. Stakeholder identification and prioritization of clinical outcomes of greatest importance for future research of insulin delivery and glucose monitoring methods among patients with type 1 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Children			
HbA1c	0	*	
Adherence	3	*	
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	1	*	
Hyperglycemia	1	*	
Adolescents†			
HbA1c	0	*	
Adherence	2	*	‡
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	2	*	‡
Hyperglycemia	0	*	
Adults			
HbA1c	1	*	
Adherence	1	*	
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	3	*	
Hyperglycemia	0	*	
Elderly			
HbA1c	0	*	
Adherence	0	*	
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	5	*	
Hyperglycemia	0	*	

Abbreviation: HbA1c = glycated hemoglobin

*Indicates consensus achieved in the previous round; reprioritization not required.

‡Indicates an identified research need.

†One Stakeholder abstained.

Table 6. Results of each phase for the identification and prioritization of future research for insulin delivery and blood glucose monitoring methods among insulin-requiring patients with type 2 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Adolescent (13-19 years)	1	*	
Adult (20-64 years)	3	*	‡
Elderly (>=65 years)	1	*	

*Indicates consensus achieved in the previous round; reprioritization not required.
‡Indicates an identified research need.

Table 7. Stakeholder identification and prioritization of insulin delivery methods of greatest importance for future research among insulin-requiring patients with type 2 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Continuous subcutaneous insulin infusion (insulin pump)	1	*	
Reactive low glucose suspend pump (automatically suspends insulin delivery when glucose reaches low threshold)	0	*	
Artificial pancreas (overnight closed loop, sense upper and lower thresholds)	1	*	
Sensor-augmented insulin pump	3	*	‡

*Indicates consensus achieved in the previous round; reprioritization not required.
‡Indicates an identified research need.

Table 8. Stakeholder identification and prioritization of blood glucose monitoring methods of greatest importance for future research among insulin-requiring patients with type 2 diabetes

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Self-monitored blood glucose	2	*	
Retrospective continuous glucose monitoring	0	*	
Real-time continuous glucose monitoring	3	*	‡

*Indicates consensus achieved in the previous round; reprioritization not required.
‡Indicates an identified research need.

Table 9. Stakeholder identification and prioritization of clinical outcomes of greatest importance for future research of insulin delivery and glucose monitoring methods among patients with type 2 diabetes by population

Phase 1: Identification	Phase 2: Number of Stakeholders Rating Research Gap as Highest Priority (n=5)	Phase 3: Number of Stakeholders Re-rating Gap as Highest Priority (n=5)	Phase 4: High Priority Gap(s) Included as Part of the Final Research Question in Final Research Questions
Adolescents			
HbA1c	2	*	
Adherence	1	*	
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	1	*	
Hyperglycemia	0	*	
Weight	1	*	
Adults			
HbA1c	3	*	‡
Adherence	1	*	
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	0	*	
Hyperglycemia	1	*	
Weight	0	*	
Elderly			
HbA1c	3	*	
Adherence	0	*	
Non-severe hypoglycemia	0	*	
Severe hypoglycemia	1	*	
Hyperglycemia	1	*	
Weight	0	*	

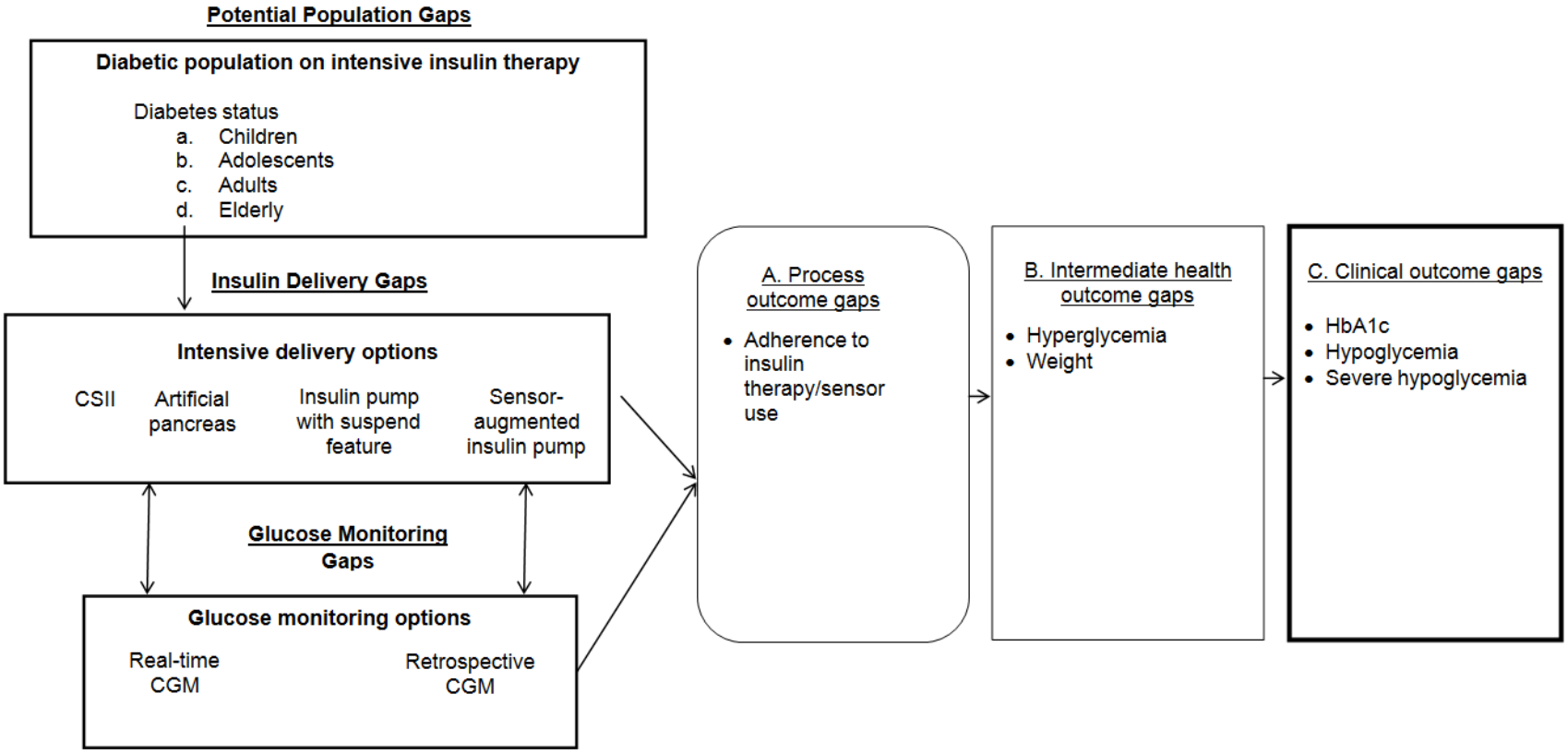
HbA1c = hemoglobin A1c

*Indicates consensus achieved in the previous round; reprioritization not required.

‡Indicates an identified research need.

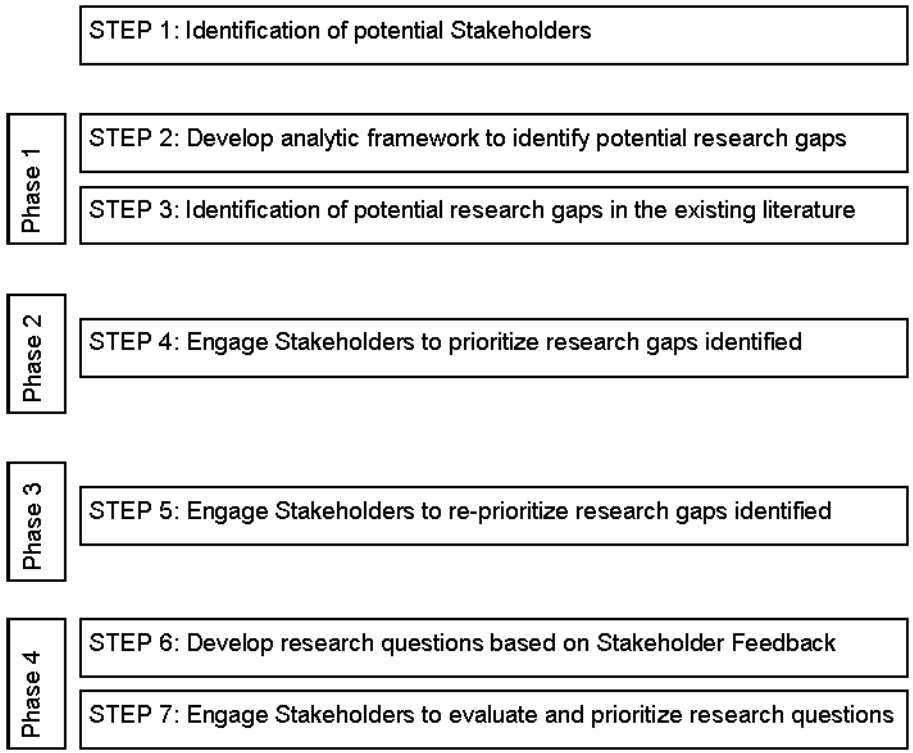
Figures

Figure 1. Analytic framework for identification of potential research gaps in phase 1



CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; HbA1c = hemoglobin A1c

Figure 2. Outline of key steps for identification and prioritization of Future Research Needs for insulin delivery and glucose monitoring methods



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Acronyms and Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CER	Comparative Effectiveness Review
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
EPC	Evidence-based Practice Center
HbA1c	Hemoglobin A1c
KQ	Key Question
MDI	Multiple daily injections
RCT	Randomized controlled trial
rt-CGM	Real-time continuous glucose monitoring
SMBG	Self-monitoring of blood glucose
U.S.	United States

Appendix A. Search Strategies for Ongoing Studies

Resource URL	Search Parameters	Search Terms/Strategy
ClinicalTrials.gov clinicaltrials.gov/	Advanced search, Conditions field used	Insulin pump OR continuous subcutaneous insulin infusion therapy OR CSII
EU Clinical Trials Register www.clinicaltrialsregister.eu/	Not applicable	Insulin pump OR continuous subcutaneous insulin infusion therapy OR CSII
NIH Reporter projectreporter.nih.gov/reporter.cfm	Projects field searched	Insulin pump OR continuous subcutaneous insulin infusion therapy OR CSII
Canadian Institutes of Health Research www.cihr-irsc.gc.ca/	Funding Decisions Data field searched	Insulin pump OR continuous subcutaneous insulin infusion therapy OR CSII
World Health Organization International Clinical Trials Registry Platform Search Portal apps.who.int/trialsearch/	Searched Condition field, Recruitment status = ALL	Insulin pump OR continuous subcutaneous insulin infusion therapy OR CSII

Abbreviation: CSII = continuous subcutaneous insulin infusion.

Appendix B. Potentially Relevant Ongoing/Recently Completed Studies

Title/ Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Effect of CSII and CGM on Progression of Late Diabetic Complications **Identifier(s):** NCT01454700	**Start date:** December 2011 **Estimated study completion date:** December 2014 **Estimated primary completion date:** December 2014 (Final data collection date for primary outcome measure)	**Purpose:** To investigate whether the combination of insulin pump therapy and continued glucose monitoring (CGM) is superior to multiple daily insulin injections to prevent progression of albuminuria in patients with type 1 diabetes **Study design:** Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Type 1 Diabetes Mellitus **Intervention(s):** Device: Insulin pump therapy (CSII) plus continuous glucose monitoring (CGM) Other: Multiple daily insulin injections (MDI) **Estimated enrollment:** 80	Steen Andersen Medtronic	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT01454700

Title/ Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Continuous Glucose Monitoring and Insulin Pump Therapy in Diabetic Gastroparesis (GLUMIT-DG) **Identifier(s):** NCT01030341	**Start date:** May 2011 **Estimated study completion date:** December 2013 **Estimated primary completion date:** July 2013 (Final data collection date for primary outcome measure)	**Purpose:** To assess the safety, feasibility, and potential (uncontrolled) efficacy of continuous glucose monitoring (CGMS) in conjunction with an insulin pump to improve glycemic control for treatment of type 1 and type 2 diabetic patients with gastroparesis **Study design:** Endpoint Classification: Safety/Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Diabetic Gastroparesis **Intervention(s):** Device: CGMS and insulin pump **Estimated enrollment:** 40	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT01030341

Title/ Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Sensor-Augmented Insulin-Pump Therapy in New-onset Diabetes After Transplantation (SAPT-NODAT) **Identifier(s):** NCT01680185	**Start date:** August 2012 **Estimated study completion date:** August 2015 **Estimated primary completion date:** December 2013 (Final data collection date for primary outcome measure)	**Purpose:** To test the hypotheses that intensive subcutaneous insulin treatment with short acting insulin, applied continuously through an insulin pump improves glycemic control. **Study design:** Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Prevention **Condition(s):** Hyperglycemia **Intervention(s):** Drug: Insulin lispro, Humalog (Eli Lilly) in insulin pump Drug: Human insulin isophane, Humulin N (Eli Lilly) Other: Standard of care **Estimated enrollment:**	Medical University of Vienna	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT01680185

Title/ Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: The REPOSE (Relative Effectiveness of Pumps Over MDI and Structured Education) Trial **Identifier(s):** NCT01616784	**Start date:** November 2011 **Estimated study completion date:** May 2015 **Estimated primary completion date:** May 2015 (Final data collection date for primary outcome measure)	**Purpose:** To establish the added benefit of CSII therapy over multiple injections on glycaemic control and hypoglycaemia in individuals with Type 1 diabetes receiving similar high quality structured training (Dose Adjustment For Normal Eating:DAFNE) in insulin therapy. **Study design:** Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Type 1 Diabetes **Intervention(s):** Other: CSII (Insulin Pump) plus DAFNE Other: MDI (levermir® & quick acting insulin) plus DAFNE **Estimated enrollment:** 280	Sheffield Teaching Hospitals NHS Foundation Trust Cambridge University Hospitals NHS Foundation Trust Dumfries & Galloway NHS NHS Lothian NHS Greater Glasgow and Clyde Harrogate & District NHS Foundation Trust King's College Hospital NHS Trust	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT01616784

Title/ Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Insulin Pump Therapy in Adolescents With Newly Diagnosed Type 1 Diabetes (T1D) **Identifier(s):** NCT00357890	**Start date:** December 2005 **Estimated study completion date:** October 2013 **Estimated primary completion date:** September 2013 (Final data collection date for primary outcome measure)	**Purpose:** To evaluate the Effect of Continuous Subcutaneous Insulin Infusion in Adolescents With Newly-diagnosed Type 1 Diabetes on Insulin Resistance, Beta-cell Function and the Honeymoon Period. **Study design:** Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Diabetes Mellitus, Insulin-Dependent **Intervention(s):** Device: Pump therapy (CSII) Drug: Multiple daily injections (MDI) using insulin glargine + rapid acting analog **Estimated enrollment:** 12	Nemours Children's Clinic	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT00357890

Title/ Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: OpT2mise Glucose Control in Type 2 Diabetes Mellitus (DM) With Insulin Pump Therapy **Identifier(s):** NCT01182493	**Start date:** December 2010 **Estimated study completion date:** June 2013 **Estimated primary completion date:** December 2012 (Final data collection date for primary outcome measure)	**Purpose:** To evaluate the comparative effectiveness of insulin pump therapy versus multiple daily injections in insulin-taking type 2 Diabetes Mellitus who are sub optimally controlled with multiple daily injections (MDI). **Study design:** Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Diabetes Mellitus, Type 2 **Intervention(s):** Device: Insulin Pump (Medtronic Minimed Paradigm® VEO) **Estimated enrollment:** 400	Medtronic	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT01182493
Title: Closing the Loop Between Glucose Sensor and Insulin Pump-developing an Algorithm **Identifier(s):** NCT00541515	**Start date:** October 2007 **Estimated study completion date:** October 2012 **Estimated primary completion date:** October 2012 (Final data collection date for primary outcome measure)	**Purpose:** An open interventional data collection study in order to build a database to close the loop between glucose sensor and insulin pump **Study design:** Endpoint Classification: Safety/Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Diabetes, Type I **Intervention(s):** Device: 2 continuous glucose sensors, temperature sensor and insulin pump **Estimated enrollment:** 80	Rabin Medical Center	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT00541515

Title/ Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Performance Study of the SOLO 2.0 Insulin Pump **Identifier(s):** NCT01500928	**Start date:** July 2011 **Estimated study completion date:** Not reported **Estimated primary completion date:** July 2012 (Final data collection date for primary outcome measure)	**Purpose:** To evaluate the performance of the SOLO (version 2.0) micropump insulin delivery system, in Type 1 diabetic patients who use insulin pumps for their treatment. **Study design:** Endpoint Classification: Safety Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Type 1 Diabetes **Intervention(s):** Device: SOLO insulin pump **Estimated enrollment:** 40	Medingo Ltd.	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT01500928

Title/ Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Continuous Subcutaneous Insulin Infusion strAtegy Versus Multiple Daily Insulin Injections strAtegy (CAMACS) **Identifier(s):** NCT01574508	**Start date:** December 2011 **Estimated study completion date:** December 2014 **Estimated primary completion date:** December 2013 (Final data collection date for primary outcome measure)	**Purpose:** To compare the different efficacy of two transient intensive insulin treatment strategies: Continuous subcutaneous insulin infusion (CSII) and multiple daily insulin injections (MDI) in patients who are not well controlled with oral hypoglycaemic agents. **Study design:** Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Type 2 Diabetes **Intervention(s):** Drug: Transient Continuous Subcutaneous Insulin Infusion Drug: Transient Multiple Daily Insulin Injections **Estimated enrollment:** 120	Shanghai Jiao Tong University School of Medicine	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT01574508

Title/ Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Efficacy of Continuous Subcutaneous Insulin Infusion Versus Basal-bolus Multiple Daily Injections Regimen in Type 2 Diabetes **Identifier(s):** NCT00942318	**Start date:** March 2009 **Estimated study completion date:** November 2012 **Estimated primary completion date:** February 2012 (Final data collection date for primary outcome measure)	**Purpose:** To compare, over a one-year period, the efficacy of CSII (with aspart insulin) and basal-bolus multiple daily injections (MDI) treatment (with detemir x 2/d and aspart before meals) in type 2 diabetic patients, already treated by basal-bolus regimen for at least 6 months, who didn't reach adequate target for glycemic at baseline (HbA1c>7 -10%). **Study design:** Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Type 2 Diabetes Mellitus **Intervention(s):** Drug: Detemir insulin, Aspart insulin, Metformin **Estimated enrollment:** 52	University Hospital, Toulouse	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT00942318

Title/ Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Closing the Loop in Adults With Type 1 Diabetes in the Home Setting **Identifier(s):** NCT01440140	**Start date:** March 2012 **Estimated study completion date:** April 2013 **Estimated primary completion date:** March 2013 (Final data collection date for primary outcome measure)	**Purpose:** To compare real-time continuous subcutaneous glucose monitoring (CGM) combined with overnight automated closed-loop glucose control, and real-time CGM alone in the home setting. **Study design:** Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Crossover Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Type 1 Diabetes Mellitus **Intervention(s):** Other: Closed-loop Other: Conventional insulin pump delivery **Estimated enrollment:** 30	University of Cambridge Diabetes UK	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT01440140
Title: Outpatient Pump Shutoff Pilot Feasibility and Efficacy Study **Identifier(s):** NCT01591681	**Start date:** July 2012 **Estimated study completion date:** July 2013 **Estimated primary completion date:** July 2013 (Final data collection date for primary outcome measure)	**Purpose:** To see whether low blood sugar at night can be reduced by using a system that turns off the insulin pump automatically. **Study design:** Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Prevention **Condition(s):** Type 1 Diabetes **Intervention(s):** Device: Pump suspension **Estimated enrollment:** 60	In Home Closed Loop Study Group National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT01591681

Title/ Identifier(s)	Study Dates	Description	Sponsor OR Principal Investigator Collaborator(s)	Source
Title: Study of PaQ™ (a Simple Patch on Insulin Delivery Device) in Patients With Type 2 Diabetes Mellitus **Identifier(s):** NCT01535612	**Start date:** March 2012 **Estimated study completion date:** October 2012 **Estimated primary completion date:** October 2012 (Final data collection date for primary outcome measure)	**Purpose:** To evaluate the ability of a patient, who has type 2 diabetes (T2DM) who is currently treated with basal/bolus insulin therapy, to use PaQ™ (a simple patch on insulin delivery device) to control his/her blood glucose. **Study design:** Endpoint Classification: Safety/Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Type 2 Diabetes Mellitus **Intervention(s):** Device: PaQ™ continuous subcutaneous insulin infusion (CSII) device **Estimated enrollment:** 20	CeQur Corporation International Diabetes Center at Park Nicollet	ClinicalTrials.gov clinicaltrials.gov/ct2/show/NCT01535612