Future Research Prioritization: Comparative Effectiveness of Second- and Third-Line Therapies for Treatment of Type 2 Diabetes

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ABSTRACT

Type 2 diabetes generates a significant societal burden, mostly resulting from its devastating complications. Effective treatment of type 2 diabetes can reduce complication rates. While metformin is the consensus first-line treatment for type 2 diabetes, there is less certainty about the comparative effectiveness of the many second- and third-line treatment options. At the request of the Patient-Centered Outcomes Research Institute (PCORI), we developed a prioritized, stakeholder-informed research agenda designed to enhance treatment for type 2 diabetes and inform patient-centered selection of second- and third-line medical treatments. We solicited participation of 60 stakeholders, 30 of whom (50%) provided input related to diabetes treatment through teleconference participation, email feedback, and/or participation in the prioritization survey. Stakeholders ranked evidence gaps by importance from their perspectives using a forced-ranking prioritization method. Our diverse group of relevant stakeholders prioritized research exploring the comparative effectiveness of: 1) approaches for enhancing diabetes treatment adherence and persistence in real-world settings; 2) second- and third-line diabetes treatments for different patient populations; 3) different strategies for determining diabetes treatment success; and 4) different shared decision making approaches for choosing second- and third-line diabetes treatments in real-world settings.

INTRODUCTION

Type 2 diabetes affects over 29 million Americans and continues to increase in prevalence, with 1.7 million new cases in 2012.[1] As the seventh leading cause of death in the United States, diabetes may decrease life expectancy by as much as 10 to 15 years.[1,2] Beyond its impact on mortality, diabetes is a significant societal burden, with over $245 billion in annual costs.[3] Much of this expense results from the devastating complications of diabetes, which include vision loss, kidney injury, lower extremity amputation, heart attacks, and strokes. Along with these complications, people with poorly controlled type 2 diabetes commonly experience decreased sense of well-being, impaired quality of life, cognitive impairment, depression, periodontal disease, and other effects.

Treatment of type 2 diabetes typically begins with lifestyle modification and metformin, a medication that lowers blood sugar by reducing glucose production in the liver and enhancing muscle glucose uptake.[4] When lifestyle modification and metformin are insufficient to control blood sugar, additional medications are prescribed. The Surveillance Prevention and Management of Diabetes Mellitus (SUPREME-DM) study found that among 41,233 patients recently diagnosed with type 2 diabetes, 34% and 45% required additional of oral antihyperglycemic agents within 6 and 12 months, respectively.[5] Using metformin as initial diabetes therapy appears to be associated with a reduced need for subsequent treatment intensification.[6]

There are several options for second- and third-line therapies for type 2 diabetes, including sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and

insulin. While metformin is the consensus first-line pharmacologic treatment for type 2 diabetes,[7,8] clinical guidelines provide less clarity regarding optimal second- and third-line therapies.[7-10] The American Diabetes Association (ADA) Standards of Medical Care in Diabetes indicate that second- and third-line glucose-lowering agents should be chosen from available options based on patient preferences as well as various patient, disease, and drug characteristics.[11]

Ongoing comparative effectiveness studies may help inform the choice of second- and third-line pharmacologic agents for type 2 diabetes. Chief among these studies is the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) Study.[12] GRADE is a multicenter pragmatic trial designed to compare 4 medications commonly added to metformin: 1) glimepride (a sulfonylurea); 2) sitagliptin (DDP-4 inhibitor); 3) liraglutide (GLP-1 receptor agonist); and 4) glargine (long-acting insulin). Of note, GRADE does not evaluate SGLT2 inhibitors, a newer and increasingly used diabetes class. The GRADE study's primary outcome is time to treatment failure, which is defined as hemoglobin A1c ≥7% during the anticipated 5-year observation period. Secondary outcomes include microvascular complications, adverse effects, tolerability, quality of life, and cost-effectiveness. Estimated enrollment is 5000 subjects, and study follow-up is expected to conclude in 2020.

Given that: 1) the prevalence, morbidity, and costs of type 2 diabetes are increasing; 2) the comparative effectiveness of available second- and third-line medication for type 2 diabetes remains uncertain; and 3) GRADE will likely not conclude before 2020 and will not include all potentially relevant medication classes, further research comparing the effectiveness of second- and third-line therapies for type 2 diabetes is needed. Accordingly, the Patient-Centered

Outcomes Research Institute (PCORI) tasked the Duke Evidence Synthesis Group (ESG) with creating a prioritized agenda for research in this area that would: 1) incorporate the perspectives of relevant stakeholders; and 2) have a high likelihood of impacting practice within the next 3 to 5 years.

METHODS

Overview of Prioritization Approach

Our approach to prioritizing future research and developing recommendations for targeted future funding by PCORI broadly follows the steps utilized in the Agency for Healthcare Research and Quality (AHRQ)'s Evidence-based Practice Center (EPC) Program approach to identifying and prioritizing future research needs.[13] This approach involves appraisal of recent systematic reviews to identify important evidence gaps, transformation of evidence gaps into potential research questions, engagement of stakeholders to identify additional gaps and prioritize research questions, and scans of recently published and ongoing studies relevant to the list of stakeholder-prioritized research questions.

Selection and Engagement of Stakeholders

We engaged a diverse group of stakeholders, including clinical experts in diabetes treatment, researchers, representatives from federal and nongovernmental funding agencies, representatives from relevant professional societies, health care decision makers and policy makers, and representatives from related consumer and patient advocacy groups (Table 1). Within each of these categories, we sought to identify a person who was either familiar with the clinical area and its current uncertainties or brought a specific methodological expertise to the stakeholder panel.

We solicited stakeholder input during this project through teleconference-based group discussions, email communications, and web-based prioritization surveys.

Table 1. Stakeholder organizations and perspectives

Organization	Stakeholder Perspective	Purpose
American Academy of Family Physicians (AAFP)	Professional societies/researchers	AAFP and its chapters represent 120,900 family physician, resident, and medical student members. The AAFP is committed to helping family physicians improve the health of Americans by advancing the specialty of family medicine.
American Association of Clinical Endocrinologists (AACE)	Professional societies/researchers	AACE is a professional community of physicians specializing in endocrinology, diabetes, and metabolism committed to enhancing the ability of its members to provide the highest quality of patient care.
American College of Clinical Pharmacy (ACCP)	Professional societies/researchers	ACCP is a professional and scientific society that provides leadership, education, advocacy, and resources enabling clinical pharmacists to achieve excellence in practice and research. ACCP's membership is composed of practitioners, scientists, educators, administrators, students, residents, fellows, and others committed to excellence in clinical pharmacy and patient pharmacotherapy.
American Diabetes Association	Professional societies/researchers	Large professional society organization of almost 16,500 health care professionals and over 440,000 people with diabetes, with mission to prevent and cure diabetes and to improve the lives of all people affected by diabetes.
American Medical Association (AMA; Improving Health Outcomes)	Policy makers	Professional organization with goal of promoting the art and science of medicine and the betterment of public health. In 2013, AMA launched a strategic focus on cardiovascular disease and diabetes. A key part of this initiative is diabetes prevention by bridging the gap between primary care and community resources. AMA assists clinical practices in implementing new processes for identifying patients with prediabetes and referring them to the YMCA's Diabetes Prevention Program.
Centers for Disease Control and Prevention (Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion)	Policy makers	The Division of Diabetes Translation is a part of the National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services. The division does not support the direct provision of services, but facilitates the efficient, fair, and effective availability of these services to all Americans affected by diabetes. One goal of this division is to implement the National Diabetes Education Program (NDEP), a joint initiative

Organization	Stakeholder Perspective	Purpose
		sponsored by the CDC and the National Institutes of Health. The NDEP is based on a partnership of public and private organizations that are concerned about the health status of their constituents. The NDEP is designed to improve treatment and outcomes for people with diabetes, to promote early diagnosis, and to prevent the onset of diabetes. Program activities are directed to these audiences: the general public; people with diabetes and their families; health care providers; and payers and purchasers of health care and policymakers.
GlaxoSmithKline (GSK)	Product makers	GSK is a British multinational pharmaceutical company. It was the world's sixth-largest pharmaceutical and was established in 2000 by a merger of Glaxo Wellcome and SmithKline Beecham. GSK has a portfolio of products for major disease areas such as asthma, cancer, infections, mental health, diabetes, and digestive conditions.
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	Policy makers	The mission of NIDDK is to conduct and support medical research and research training and to disseminate science-based information on diabetes and other endocrine and metabolic diseases; digestive diseases, nutritional disorders, and obesity; and kidney, urologic, and hematologic diseases, to improve people's health and quality of life.
Patient Advocate	Patient advocacy	To represent research priorities and issues from the patient's perspective.
Society for General Internal Medicine (SGIM)	Professional societies/researchers	SGIM is a national medical society of 3,000 physicians who are the primary internal medicine faculty of every medical school and major teaching hospital in the United States. SGIM's mission is to lead excellence, change, and innovation in clinical care, education, and research in general internal medicine to achieve health care delivery that is comprehensive, technologically-advanced, and individualized; instills trust within a culture of respect; is efficient in the use of time, people, and resources; is organized and financed to achieve optimal health outcomes; maximizes equity; and continually learns and adapts.
UnitedHealth Group	Payers	UnitedHealth Group is a diversified health care company in the United States and a leader worldwide in helping people live healthier lives and helping to make the health system work better for everyone. UnitedHealth Group is an active participant in the Diabetes Prevention Program.
Young Men's Christian Association (YMCA) Diabetes Prevention Program	Policy makers; Patient advocacy	As a leading nonprofit for strengthening community through youth development, healthy living, and social responsibility, the YMCA believes that all people should be able to live life to its fullest, healthiest potential. In the YMCA's Diabetes Prevention

Organization	Stakeholder Perspective	Purpose
		Program a trained lifestyle coach will introduce topics in a supportive, small group environment and encourage participants as they explore how healthy eating, physical activity, and behavior changes can benefit their health.

Identification of Evidence Gaps

We used an iterative process to identify evidence gaps pertaining to second- and third-line treatments for type 2 diabetes. First, we identified and appraised recent published systematic reviews, clinical practice guidelines, and future research needs documents (including a topic brief developed for PCORI by the Johns Hopkins EPC in March 2015) to develop an initial list of evidence gaps. This list was neither exhaustive nor prioritized. Next, we organized these gaps according to broad themes and transformed them into a preliminary set of research questions. We distributed these questions to our stakeholders and asked them to review, modify, and add to the list. Stakeholders participated in a teleconference discussion of the questions and provided additional feedback via email. Our team reviewed this stakeholder input and produced a revised list of questions reflecting gaps in the evidence supporting second- and third-line treatments for type 2 diabetes. We circulated this revised list to the stakeholder team for review to ensure that our edits reflected their proposed additions.

Prioritization of Future Research

After we used stakeholder feedback to refine the proposed list of research questions, stakeholders were invited to help prioritize the list. Our online survey used a forced-ranking prioritization method described by the AHRQ EPC program, whereby participants were given 3 votes to allocate to any of the 5 identified research priorities, with a maximum of 3 votes per

item.[13] The stakeholders were not given specific prioritization criteria, but rather were told to decide, based on their perspective, which were the most important unanswered research questions pertaining to second- and third-line treatments for type 2 diabetes. We also asked stakeholders to self-report their perspective, recognizing that an individual stakeholder could represent more than one perspective. Possible perspectives included: patients and the public, providers, purchasers, payers, policy makers, product makers, and principal investigators. The stakeholder-prioritized research questions were then included in our horizon scan.

Horizon Scan of Studies Potentially Relevant to Prioritized Research Questions

We performed 2 database searches to identify recently published and ongoing studies relevant to the stakeholder-prioritized research questions. We searched PubMed to identify recent relevant studies published during the past 2 years and ClinicalTrials.gov for ongoing and recently completed studies. For the search of ClinicalTrials.gov, we used the keywords diabetes treatment OR "treatment of diabetes" OR "treatment of type" OR "treating diabetes" OR "treating type" and focused on ongoing Phase 3 or 4 studies. Appendix A provides the exact search strategy used for PubMed.

Members of our team reviewed the identified titles and abstracts. Articles were included if they met all of the following criteria: presented original data or secondary analysis of data from a randomized controlled trial (RCT), prospective or retrospective observational study, or relevant modeling study; included data related to type 2 diabetes treatment; and had a stated objective that could be categorized according to our identified list of research priorities.

For the ClinicalTrials.gov search, a member of the ESG team reviewed all study abstracts identified by the search and coded them as potentially relevant to one or more of the identified

research priorities. We then abstracted study type (such as observational or RCT), recruitment status, and sample size.

Survey of Patient Views of Research Needs

Based on a recommendation from one of our stakeholders, we contacted dQ&A (http://www.d-qa.com/about/) during our topic refinement process. dQ&A is a self-described "patient-centric diabetes market research company" that works with large panels of diabetes patients to answer diabetes-related questions. Although we could not directly contact the dQ&A patient panel given our timeline and resources, dQ&A did share findings from a recent (November 2014) survey performed to support the DiaTribe Foundation's (http://diatribe.org/foundation) involvement in FDA discussions related to diabetes. The survey queried people with diabetes about their thoughts regarding the most urgent needs associated with the disease, the daily impact of diabetes on their life, and barriers to their diabetes management. We considered responses from the 1247 type 2 patients included in this survey, and how these patients' concerns might relate to the proposed key questions. More information about the survey can be found at http://diatribe.org/foundation-anniversary-press-release.

RESULTS

Expansion of Evidence Gaps Through Stakeholder Engagement

We solicited participation of 60 stakeholders, and 30 (50%) individuals provided input related to diabetes treatment through participation on the teleconference, email feedback, and/or participation in the prioritization survey (Appendix B). These stakeholders represented the perspectives described in Table 1. Central themes from the stakeholders included the following:

- Definitively answering questions relating to how second- and third-line agents impact diabetes complications and other long-term outcomes would require large, long-term studies (similar in design and duration to GRADE). Stakeholders expressed concern that short-term studies (<5 years follow-up) may not provide optimal answers regarding long-term diabetes outcomes. Important shorter term outcomes like treatment choices, treatment adherence/persistence, diabetes control, other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains may be more feasible given PCORI's timeframe.
- Because there is no formal model for individualizing diabetes therapy, it could be of value to better understand what matters most to patients in choosing second- and third-line diabetes treatments, so that patient-centered factors can be integrated into therapeutic choices.
- In order to assure that chosen second- and third-line agents and goals of therapy reflect patients' values, there is a need to compare shared decision making approaches in real-world settings. Because patient choice has not always improved outcomes,[14] some stakeholders felt it would be important to formally compare shared decision making approaches versus provider-driven selection. Stakeholders also pointed out that the choice of second- and third-line diabetes treatment agents is often inherently limited by medication costs or insurance formularies, and that these external factors are critical to consider as part of shared decision making.
- The comparative effectiveness of different diabetes therapies in specific patient populations (e.g., based on demographics, socioeconomic factors, psychosocial factors, or other factors) is poorly understood, and understanding the advantages and disadvantages of different

treatments within specific populations would inform rational selection of second- and third-line treatments.

- Some stakeholders felt that strict reliance on hemoglobin A1c is an overly simplistic way of determining the success of diabetes treatment, and that using hemoglobin A1c as part of a framework that formally considered additional factors (e.g., patient values, overall diabetes complication risk, preservation of the body's ability to produce insulin, avoidance of overtreatment, and/or new technologies like continuous glucose monitoring) may help determine when second- and third-line agents should be initiated. Other stakeholders expressed that straying from hemoglobin A1c goal-directed decision making could lead to poorer diabetes control and higher complication rates.
- Because non-adherence to diabetes treatment remains a major contributor to poor outcomes,[15] comparing the effectiveness of strategies to support adherence in real-world settings would be valuable. Stakeholders cited diabetes self-management education, diabetes self-management support, adherence support interventions from research studies, and approaches utilized in clinical trials as potentially effective options to evaluate under real-world conditions.

Following the stakeholder teleconference and email discussion we finalized the research questions for prioritization:

1. Beyond the ability to lower hemoglobin A1c, what matters most to patients in choosing second-and third-line diabetes treatments? How does considering such patient-centered factors affect treatment choices, treatment adherence/persistence, diabetes control, other

patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains?

2. What is the comparative effectiveness of different shared decision making approaches for choosing second- and third-line diabetes treatments in real-world settings (including versus provider-driven selection)? How do different approaches to decision making affect treatment choices, treatment adherence/persistence, diabetes control, other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains? Are there certain aspects of diabetes treatment (e.g., medication choices, insulin use, dietary and lifestyle approaches, etc.) for which shared decision making should or should not be used?
3. What is the comparative effectiveness of second- and third-line diabetes treatments for different patient populations, including those defined by demographics (e.g., age, sex, race), socioeconomic factors (e.g., insurance status, financial stress, social support), psychosocial factors (e.g., self-efficacy, comorbid mental illness), and other factors (e.g., literacy, numeracy) in terms of treatment adherence/persistence, diabetes control, other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains? How can the choice between second-and third-line diabetes treatment options be better tailored for different populations in real-world settings?
4. What is the comparative effectiveness of different strategies for determining diabetes treatment success (for both metformin and second-/third-line treatments)? Specifically, how do treatment choices, treatment adherence/persistence, diabetes control, other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains differ with hemoglobin A1c goal-driven decision making versus approaches

that formally consider additional factors (e.g., patient values, overall diabetes complication risk, preservation of the body's ability to produce insulin, avoidance of overtreatment, and/or new technologies like continuous glucose monitoring)?

5. What is the comparative effectiveness of approaches for enhancing diabetes treatment adherence and persistence in real-world settings (for both metformin and second-/third-line treatments)? How can efficacious approaches to fostering adherence (e.g., diabetes self-management education, diabetes self-management support, treatment of comorbid mental illness, care delivery strategies that utilize communications technology to facilitate frequent contact, and approaches used in the setting of clinical trials) be feasibly implemented under real-world conditions?

Stakeholder Ranking of Research Questions

Table 2 shows the 5 potential research questions, along with the number of stakeholders who voted for each question and the perspectives represented by these votes. Twenty stakeholders completed the prioritization exercise, 6 of whom self-identified as patients, 13 as providers, 1 as payer, and 11 as principal investigators. No stakeholders self-identified as purchasers, policy makers, or product makers.

Stakeholders assigned highest priority to question 5 (comparative effectiveness of approaches for enhancing diabetes treatment adherence/persistence in real-world settings), followed by question 3 (comparative effectiveness of second- and third-line diabetes treatments for different patient populations), question 4 (comparative effectiveness of different strategies for determining diabetes treatment 'success'), and question 2 (comparative effectiveness of different shared decision making approaches for choosing second- and third-line diabetes treatments). Question 1

(what matters most to patients in choosing second-and third-line diabetes treatments) received the fewest votes, so was excluded from subsequent steps of the process.

Table 2. Final ranking of future research needs for second- and third-line therapies for treatment of type 2 diabetes

	Question	Score	Stakeholders, *n*	Perspectives[a]
1.	Beyond the ability to lower hemoglobin A1c, what matters most to patients in choosing second-and third-line diabetes treatments? How does considering such patient-centered factors affect treatment choices, treatment adherence/persistence, diabetes control, other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains?	7	6	3 patients, 3 providers, 3 PIs
2.	What is the comparative effectiveness of different shared decision making approaches for choosing second- and third-line diabetes treatments in real-world settings (including versus provider-driven selection)? How do different approaches to decision making affect treatment choices, treatment adherence/persistence, diabetes control, other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains? Are there certain aspects of diabetes treatment (e.g., medication choices, insulin use, dietary and lifestyle approaches, etc.) for which shared decision making should or should not be used?	9	9	3 patients, 4 providers, 3 PIs
3.	What is the comparative effectiveness of second- and third-line diabetes treatments for different patient populations, including those defined by demographics (e.g., age, sex, race), socioeconomic factors (e.g., insurance status, financial stress, social support), psychosocial factors (e.g., self-efficacy, comorbid mental illness), and other factors (e.g., literacy, numeracy) in terms of treatment adherence/persistence, diabetes control, other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains? How can the choice between second-and third-line diabetes treatment options be better tailored for different populations in real-world settings?	13	9	2 patients, 8 providers, 1 payer, 6 PIs

	Question	Score	Stakeholders, *n*	Perspectives[a]
4.	What is the comparative effectiveness of different strategies for determining diabetes treatment success (for both metformin and second-/third-line treatments)? Specifically, how do treatment choices, treatment adherence/persistence, diabetes control, other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains differ with hemoglobin A1c goal-driven decision making versus approaches that formally consider additional factors (e.g., patient values, overall diabetes complication risk, preservation of the body's ability to produce insulin, avoidance of overtreatment, and/or new technologies like continuous glucose monitoring)?	10	7	2 patients, 5 providers, 4 PIs
5.	What is the comparative effectiveness of approaches for enhancing diabetes treatment adherence and persistence in real-world settings (for both metformin and second-/third-line treatments)? How can efficacious approaches to fostering adherence (e.g., diabetes self-management education, diabetes self-management support, treatment of comorbid mental illness, care delivery strategies that utilize communications technology to facilitate frequent contact, and approaches used in the setting of clinical trials) be feasibly implemented under real-world conditions?	21	13	2 patients, 9 providers, 8 PIs

[a] Stakeholders could self-identify as representing more than one perspective.

Horizon Scan of Studies Potentially Relevant to Prioritized Research Questions

Our PubMed search identified 2270 articles. Of these, 62 met our inclusion criteria and included 1 systematic review, 37 RCTs, 15 cohort studies, 0 case–control study, and 9 other studies. Sample sizes ranged from 24 to 56,536. Fifty-two studies were active comparator studies, and 10 studies had no comparator. Because our questions addressed comparative effectiveness, we did not include placebo-controlled studies in our analysis. Two studies were potentially applicable to question 2; 53 to question 3; 3 to question 4; and 5 to question 5.

Our search of ClinicalTrials.gov yielded 140 studies. We identified 29 protocols as potentially relevant to the prioritized research questions. Projected sample sizes ranged from 24 to 5000 patients. Two were applicable to question 2; 21 were applicable to question 3; 2 were applicable to question 4; and 6 were applicable to question 5.

The Tables in Appendix C detail key characteristics of the included PubMed and ClinicalTrials.gov articles separately for each of the prioritized research questions.

Patient Survey on Unmet Needs

In order to gather additional patient perspectives on diabetes treatment, we reviewed responses (n=1247) to a dQ&A survey describing how diabetes impacts patients' lives. Factors identified as having a major lifestyle impact included the difficulty of diabetes self-management, the time burden of self-management, and the need to follow diet and exercise recommendations. Perceived barriers to diabetes management included adherence to diet and exercise recommendations, the cost of medications/care, side effects from treatment, and diabetes-related stress. We also reviewed 952 free-text comments regarding unmet needs in diabetes research from the 1247 type 2 patients surveyed. In general, these comments reflected a desire to reduce

the complexity of day-to-day diabetes self-management through: development of simple, effective, and safe treatments; improved strategies for weight management; and strategies to minimize symptoms from diabetes treatments and complications.

DISCUSSION

Because type 2 diabetes generates substantial morbidity and costs, effective treatment is central to improving patient-centered outcomes. Although metformin is the consensus first-line pharmacologic treatment for type 2 diabetes, ongoing uncertainty regarding optimal choices for second- and third-line pharmacologic treatments makes this a high-yield area for PCORI involvement. We engaged a diverse group of relevant stakeholders to refine and prioritize possible research questions for targeted PCORI funding initiatives.

A central theme of our stakeholder discussions was that, in order to definitively answer comparative effectiveness questions relating to long-term outcomes like diabetes complications, studies with longer follow-up periods (>5 years) would be required. This issue particularly applies to questions addressing the comparative effectiveness of pharmacologic diabetes therapies; for example, mean follow-up in GRADE is expected to be approximately 5 years. Because PCORI expressed the desire to fund research that would be likely to impact health care practice in the next 3 to 5 years, we used our stakeholders' input to formulate important research questions that would be answerable within this period. Rather than directly examining incidence of diabetes complications or other long-term outcomes, our prioritized questions address important shorter-term outcomes like treatment choices, treatment adherence/persistence,

diabetes control, other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains.

Prioritized Research Questions

Approaches for Enhancing Diabetes Treatment Adherence/Persistence in Real-World Settings

Non-adherence to diabetes therapies remains widespread, and is a major contributor to poor control. Only about half of patients take their medications as prescribed in the United States.[15] Since poor medication adherence is a complex issue with many contributing causes, there is no universal solution. Numerous approaches have been utilized to improve adherence, including diabetes self-management education and support, case management, tailored behavioral interventions, and short messaging service reminders; interventions have been delivered using a variety of platforms (e.g., in-person meetings, telephone, web-based platforms) and by a variety of staff (nurses, diabetes educators, pharmacists, physicians, peers, community health workers).[16] The effectiveness of existing approaches varies widely.[17,18]

Given the high priority assigned to question 5 (comparative effectiveness of approaches for enhancing diabetes treatment adherence/persistence in real-world settings) in our prioritization exercise, our stakeholders clearly feel that diabetes treatment non-adherence (across medication classes) is a major contributor to poor diabetes control and ensuing complications. Although there has been ample research in this area, measurably reducing the impact of treatment non-adherence nationwide will depend on translating effective approaches into real-world practice. Further, in order to meaningfully impact non-adherence, emphasis must be placed on approaches that are scalable, or amenable to feasible implementation in standard practice without loss of effectiveness.[15] Pragmatic research designed to compare the effectiveness of proven, scalable

approaches to enhancing diabetes treatment adherence (including metformin and second-/third-line therapies) in real-world settings would be likely to impact health care practice in the next 3 to 5 years.

Effectiveness of Second-/Third-Line Diabetes Treatments for Different Patient Populations

Certain populations, such as American Indians, Alaska Natives, and non-Hispanic blacks have higher rates of diabetes than other demographic groups,[1] and rates of diabetes treatment intensification appear to differ based on age, sex, and race.[5] Many patient factors are known to affect diabetes control, access to therapy, and treatment adherence, including demographics, insurance status, financial comorbid mental illness, and literacy/numeracy.[19-24] In light of this heterogeneity, our stakeholders felt that improving our understanding of which treatment approaches work best for different patient populations would greatly enhance diabetes prevention efforts, and should be a priority. We found a large number of prior and ongoing studies comparing different treatments that could be retrospectively analyzed with population differences in mind. It is also possible that these data may warrant systematic review or meta-analysis. Alternatively, prospective research could examine treatment adherence/persistence, diabetes control, other patient-centered outcomes, and maintenance of clinical gains with different diabetes treatment strategies in different populations.

Effectiveness of Different Strategies for Determining Diabetes Treatment 'Success'

Successful treatment of type 2 diabetes mellitus has traditionally been defined by hemoglobin A1c, which is logical, given that complications and costs rise exponentially as hemoglobin A1c increases.[25] While the ADA already recommends tailoring hemoglobin A1c targets based on patient characteristics and preferences,[11] a more comprehensive definition of success in treatment

of diabetes might extend beyond blood sugar control to formally consider overall cardiovascular risk, preservation of the body's ability to produce insulin, and possible concerns about overtreatment,[26] all in a manner informed by patients' values.[27] Some stakeholders expressed particular enthusiasm for the possibility of using continuous glucose monitoring as a novel means for assessing patient response to diabetes treatments, while others remained concerned about potential cost-benefit issues with such an approach.[11]

We found relatively little evidence for prior or ongoing research in this domain. It is possible that carefully designed studies examining how alternative approaches for determining diabetes treatment success affect treatment choices, treatment adherence/persistence, diabetes control, other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains could impact health care practice within 3 to 5 years. However, longer term outcomes of potential interest, such as development of complications and mortality, would be difficult to assess without longer-term follow-up.

Shared Decision Making for Choosing Second-/Third-Line Diabetes Treatments

Our stakeholders felt that research addressing the role of shared decision making in selecting second- and third-line diabetes treatment strategies should be a priority. Shared decision making is a process of communication, deliberation, and decision making in which: 1) the clinician shares information about relevant options with the patient, including the severity and probability of potential harms and benefits; 2) the patient explores and shares his or her preferences with the clinicians regarding these harms, benefits, and potential outcomes; and 3) the clinician and patient reach a mutual decision about the treatment plan through an interactive process of

reflection and discussion.[28] Decision aids or other tools may be utilized to facilitate the process of shared decision making.[29]

We found 4 relevant published decision aids that are available for public use,[30-33] and 2 ongoing trials that may inform this question. Given the uncertain real-world effectiveness of these decision aids, the relative paucity of ongoing research, the potential value of shared decision making in enhancing the patient-centeredness of choosing diabetes treatments, and PCORI's prior interest in promoting the use of shared decision making and decision aids,[34] this would appear to be a logical area for PCORI to fund additional research. By prospectively examining the comparative effectiveness of available strategies for shared decision making in real-world settings (including versus provider-driven selection) using outcomes like treatment choices, treatment adherence/persistence, diabetes control and other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains, such research could impact care in the next 3 to 5 years.

As above, stakeholders pointed out that choosing second- and third-line diabetes treatment agents is often inherently limited by medication costs or insurance formularies, and that such external factors are critical to consider as part of evaluating any shared decision making process is real-world settings.

Additional Research Questions

Because question 1 (what matters most to patients in choosing second-and third-line diabetes treatments) received the fewest stakeholder votes, we omitted this question from our final prioritized list. However, it is worth noting that an ongoing PCORI-funded study, "Advancing Stated-Preference Methods for Measuring the Preferences of Patients with Type 2 Diabetes"

(http://www.pcori.org/research-results/2013/advancing-stated-preference-methods-measuring-preferences-patients-type-2), is currently comparing innovative methods for examining patient preferences with regard to diabetes medications. Question 1 remains a potentially important research topic, and if it is of interest to PCORI, this ongoing study's findings would be highly relevant to the developing funding announcements in this domain.

Patient Survey Input

Our review of the dQ&A patient survey data indicated that the difficulty and time-intensiveness of diabetes self-management adherence has a major impact on patients' lives, while perceived barriers to diabetes control included diet and exercise adherence, the cost of medications, side effects, and diabetes-related stress. These survey findings may highlight cross-cutting themes to consider in developing funding initiatives targeting the prioritized research questions. Patients' concerns about adherence to self-management practices may support the patient-centeredness of our stakeholders' highest-ranked research topic, question 5 (comparative effectiveness of approaches for enhancing diabetes treatment adherence and persistence). If timing and resources allow, the dQ&A group may be a helpful resource to PCORI for targeted patient surveys on diabetes research needs.

Limitations

While we worked with our stakeholders to identify the most pertinent evidence gaps and research questions pertaining to selection of second- and third-line treatments for type 2 diabetes, the prioritized list may not reflect the full range of possible future research needs relating to this topic. Although our stakeholder group comprised renowned researchers, experienced clinicians, policy experts, and representatives of key professional organizations, payer organizations, and

patient groups, it is also possible that a different group of stakeholders might prioritize future research differently. Finally, because a comprehensive systematic review has not been performed for many of the identified evidence gaps, we cannot determine with certainty the degree to which prioritized future research needs have already been addressed.

CONCLUSIONS

Based on input from our stakeholder group, key research priorities pertaining to selection of second- and third-line treatments for diabetes include the comparative effectiveness of: 1) approaches for enhancing diabetes treatment adherence and persistence in real-world settings; 2) second- and third-line diabetes treatments for different patient populations; 3) different strategies for determining diabetes treatment 'success'; and 4) different shared decision making approaches for choosing second- and third-line diabetes treatments in real-world settings.

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Appendix A. Pub Med Search Strategy

Search date: June 24, 2015

Set #	Search Terms	Results
#1	"Diabetes Mellitus, Type 2/therapy"[Mesh]	36,077
#3	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR Clinical trial[pt] OR “clinical trial”[tiab] OR “clinical trials ”[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) OR ("evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR “evaluation studies”[tiab] OR "intervention studies"[MeSH Terms] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH Terms] OR "case-control"[tiab] OR "cohort studies"[MeSH Terms] OR cohort[tiab] OR "longitudinal studies"[MeSH Terms] OR "longitudinal”[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])	4,216,401
#4	#1 AND #2	17,568
#5	Limits: English, Date: 2013/06/24 – present	2270

Appendix B. Participating Stakeholders

Ronald Ackermann, MD, MPH
Director, Center for Community Health - Institute for Public Health and Medicine
Northwestern University
Perspective: Provider/Principal Investigator

Christel Aprigliano
Chief Executive Officer
The Diabetes Collective, Inc.
Perspective: Patient

Brooks Benson
Perspective: Patient

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Endocrinologist and Executive Director of the International Diabetes Center at Park Nicollet
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Professor of Medicine, School of Medicine
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Lair Janson
Perspective: Patient

Mary L. Johnson, BS, RN, CDE
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Appendix C. Supplementary Tables

Appendix Table C-1. Published and ongoing studies potentially relevant to Research Question 2 *[What is the comparative effectiveness of different shared decision making approaches for choosing second- and third-line diabetes treatments in real-world settings (including versus provider-driven selection)? How do different approaches to decision making affect treatment choices, treatment adherence/persistence, diabetes control, other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains? Are there certain aspects of diabetes treatment (e.g., medication choices, insulin use, dietary and lifestyle approaches, etc.) for which shared decision making should or should not be used?]*

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
Denig, 2014[1]	344 patients	To assess the effects of a patient oriented decision aid for prioritising treatment goals in diabetes compared with usual care on patient empowerment and treatment decisions
Branda, 2013[2]	103 patients	We cluster-randomized 10 practices in a concealed fashion to implement either a decision aid (DA) about starting statins or one about choosing antihyperglycemic agents.
Cohort Studies		
None	–	–
Case-Control Studies		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
Shared Decision Making Between Patients and GPs in the Treatment of Type 2 Diabetes in Primary Care. (NCT02285881)	156 patients	Ongoing (Estimated completion August 2015). The ADDITION-Europe study demonstrated two (almost) equally effective treatments but with slightly different intensities, it may be a good starting point to discuss with the patients their diabetes treatment, taking into account both the intensity of treatment, clinical factors and patients' preferences. The aim of the study was to evaluate whether such an approach increases the proportion of treatment goals that type 2 diabetes patients achieve.
Shared Decision Making With Pharmaceutical Care (NCT02373059)	75 patients	Ongoing (Estimated completion June 2015). A research study to enhance clinical discussion between patients and pharmacists using a shared decision making tool for type 2 diabetes or usual care.

Abbreviations not defined above: GP=general practitioner; N=number of studies/patients; RCTs=randomized controlled trials

Appendix Table C-2. Published and ongoing studies potentially relevant to Research Question 3 *[What is the comparative effectiveness of second- and third-line diabetes treatments for different patient populations, including those defined by demographics (e.g., age, sex, race), socioeconomic factors (e.g., insurance status, financial stress, social support), psychosocial factors (e.g., self-efficacy, comorbid mental illness), and other factors (e.g., literacy, numeracy) in terms of treatment adherence/persistence, diabetes control, other patient-centered outcomes*

(e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains? How can the choice between second-and third-line diabetes treatment options be better tailored for different populations in real-world settings?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
Blonde, 2015[3]	884 patients	To compare the efficacy and safety of long-acting glucagon-like peptide-1 receptor agonist dulaglutide with that of insulin glargine, both combined with prandial insulin lispro, in patients with type 2 diabetes.
Arakaki, 2014[4]	339 patients	To compare efficacy and safety of two, once-daily basal insulin formulations [insulin lispro protamine suspension (ILPS) vs. insulin glargine (glargine)] added to oral antihyperglycaemic medications (OAMs) and exenatide BID in suboptimally controlled type 2 diabetes (T2D) patients.
Brady, 2014[5]	99 patients	To compare a sulphonylurea with the glucagon like peptide-1 (GLP-1) receptor agonist liraglutide in combination with metformin in patients on mono/dual oral therapy with established type 2 diabetes fasting during Ramadan.
Buse, 2014[6]	413 patients	This trial investigated the contribution of the liraglutide component of IDegLira versus IDeg alone on efficacy and safety in patients with type 2 diabetes.
Diamant, 2014[7]	627 patients	Compared the efficacy and safety of exenatide twice daily or mealtime insulin lispro in patients inadequately controlled by insulin glargine and metformin despite up-titration
Diamant, 2014[8]	456 patients	In DURATION-3, exenatide once weekly was compared with insulin glargine (henceforth, glargine) as first injectable therapy. Here, we report the results of the final 3-year follow-up.
Dungan, 2014[9]	599 patients	Compared the safety and efficacy of once-weekly dulaglutide with that of once-daily liraglutide in metformin-treated patients with uncontrolled type 2 diabetes.
Forst, 2014[10]	342 patients	The efficacy and safety of canagliflozin, a sodium glucose co-transporter 2 inhibitor, was evaluated in patients with type 2 diabetes mellitus (T2DM) inadequately controlled with metformin and pioglitazone.
Forst, 2014[11]	39 patients	To investigate the effects of linagliptin compared with glimepiride on alpha and beta cell function and several vascular biomarkers after a standardized test meal
Jovanovic, 2014[12]	NR	To compare durability of glycemic control of twice-daily insulin lispro mix 75/25 (LM75/25; 75 % insulin lispro protamine suspension, 25 % insulin lispro) and once-daily insulin glargine (GL) added to oral antihyperglycemic medications in older patients (>/=65 years of age)
Leiter, 2014[13]	NR	To evaluate weekly subcutaneous albiglutide versus daily sitagliptin in renally impaired patients with type 2 diabetes and inadequately controlled glycemia on a regimen of diet and exercise and/or oral antihyperglycemic medications.

Study	N	Objective
Li, 2014[14]	178 patients	To compare the efficacy and safety of adding liraglutide, saxagliptin and vildagliptin to current therapy in Chinese type 2 diabetes subjects with poor glycemic control.
Mathieu, 2014[15]	236 patients	Two treatment strategies were compared in patients with type 2 diabetes (T2DM) on basal insulin requiring intensification: addition of once-daily (OD) liraglutide (Lira) or OD insulin aspart (IAsp) with largest meal
Pratley, 2014[16]	841 patients	We assessed two glucagon-like peptide-1 receptor agonists, once-weekly albiglutide and once-daily liraglutide, in patients with type 2 diabetes inadequately controlled on oral antidiabetic drugs
Ridderstrale, 2014[17]	1549 patients	Compared the efficacy and safety of the sodium glucose cotransporter 2 inhibitor empagliflozin and the sulfonylurea glimepiride as add-on to metformin in patients with type 2 diabetes.
Riddle, 2014[18]	588 patients	Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections
Rodbard, 2014[19]	401 patients	We compared stepwise addition of bolus insulin with a full basal-bolus regimen in patients with type 2 diabetes inadequately controlled on basal insulin plus oral antidiabetic drugs.
Tinahones, 2014[20]	476 patients	To compare the efficacy and safety of two insulin intensification strategies in patients with type 2 diabetes inadequately controlled on basal insulin glargine with metformin and/or pioglitazone
Cefalu, 2013[21]	1452 patients	We compared the efficacy and safety of canagliflozin, an SGLT2 inhibitor, with glimepiride in patients with type 2 diabetes inadequately controlled with metformin
Charbonnel, 2013[22]	653 patients	To compare treatment intensification strategies based on orally administered vs injectable incretin-based antihyperglycaemic agents in patients with type 2 diabetes mellitus on metformin monotherapy
Derosa, 2013[23]	NR	To evaluate which triple oral therapy between metformin + pioglitazone + sitagliptin and metformin + pioglitazone + glibenclamide can be more useful in improving glycaemic control and should be preferred in clinical practice
Ferrannini, 2013[24]	659 patients	To investigate the long-term safety and efficacy of empagliflozin, a sodium glucose cotransporter 2 inhibitor; sitagliptin; and metformin in patients with type 2 diabetes.
Kapitza, 2013[25]	145 patients	Assess the pharmacodynamics of lixisenatide once daily (QD) versus liraglutide QD in type 2 diabetes insufficiently controlled on metformin
Kim, 2013[26]	33 patients	To compare the effects of sitagliptin on glycemic change and 24-h blood glucose variability with those of the sulfonylurea glimepiride
Lavalle-Gonzalez, 2013[27]	1284 patients	To evaluate the efficacy and safety of canagliflozin vs placebo and sitagliptin in patients with type 2 diabetes who were being treated with background metformin

Study	N	Objective
Liu, 2013[28]	119 patients	To evaluate the efficacy and safety of add-on pioglitazone versus sitagliptin in patients with type 2 diabetes inadequately controlled on metformin and a sulfonylurea (SU)
Meneghini, 2013[29]	457 patients	Assessed the efficacy and safety of once-daily insulin initiation using insulin detemir (detemir) or insulin glargine (glargine) added to existing metformin in type 2 diabetes (T2D)
Nathan, 2013[30]	5000 patients	To compare commonly used diabetes medications, when combined with metformin, on glycemia-lowering effectiveness and patient-centered outcomes
Philis-Tsimikas, 2013[31]	458 patients	The efficacy and safety of insulin degludec (IDeg), a new basal insulin with an ultra-long duration of action, was compared to sitagliptin (Sita)
Rodbard, 2013[32]	725 patients	To compare long-term safety and efficacy of the basal insulin analogue degludec with glargine in insulin-naive subjects with Type 2 diabetes.
Rosenstock, 2013[33]	634 patients	To compare efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled with metformin
Schernthaner, 2013[34]	755 patients	To evaluate the efficacy and safety of canagliflozin, a sodium glucose cotransporter 2 inhibitor, compared with sitagliptin in subjects with type 2 diabetes inadequately controlled with metformin plus sulfonylurea
Yang, 2013[35]	521 patients	To investigate whether once daily biphasic insulin aspart 30 (BIAsp 30) is noninferior to once daily insulin glargine (IGlar) among Chinese and Japanese insulin-naive subjects with type 2 diabetes mellitus (T2DM)
Cohort Studies		
Saremi, 2015[36]	724 patients	To examine the effect of intensive glycemic control on cardiovascular disease events (CVD) among the major race/ethnic groups in a post-hoc analysis of the VADT.
Flory, 2014[37]	NR	To provide evidence on the comparative effectiveness of oral diabetes drug combinations.
Goke, 2014[38]	35,868 patients	This report presents results from a post-hoc analysis of patients in Germany who received vildagliptin or a sulfonylurea (SU) in combination with metformin.
Haraguchi, 2014[39]	106 patients	To retrospectively analyze the clinical parameters that contribute to the therapeutic outcome of GLP-1 analogues
Hoste, 2014[40]	1793 patients	To assess the efficacy and safety of vildagliptin versus other oral glucose-lowering drugs added to antidiabetic monotherapy in Belgian patients with type 2 diabetes mellitus, in comparison to the global EDGE study results.
Khunti, 2014[41]	761 patients	To compare and contrast the results of the UK cohort with the previously published global population results.
Klen, 2014[42]	176 patients	We investigated the influence of CYP2C9, KCNJ11 and ABCC8 polymorphisms on the response to SU currently used in everyday clinical practice.
Mahar, 2014[43]	244 patients	To assess the effect of vildagliptin in comparison to sulphonylurea (SU) on hypoglycaemia in Muslim patients with type 2 diabetes mellitus fasting during Ramadan.

Study	N	Objective
Mendivil, 2014[44]	3773 patients	To assess the proportion of patients on vildagliptin add-on dual therapy who respond to treatment over a 12 month follow-up, relative to comparator oral anti-diabetes dual therapy, in a usual care setting.
Al-Arouj, 2013[45]	1300 patients	To assess, in a real-world setting, the effect of vildagliptin compared with sulphonylurea (SU) treatment on hypoglycaemia in Muslim patients with type 2 diabetes mellitus (T2DM) fasting during Ramadan.
Mathieu, 2013[46]	45,868 patients	To assess the effectiveness and tolerability of vildagliptin add-on vs. other oral antihyperglycaemic drugs (OADs) added to OAD monotherapy in a real-life setting
Reaney, 2013[47]	2388 patients	We examined PROs in patients initiating injectable treatment in the CHOICE (CHanges to treatment and Outcomes in patients with type 2 diabetes initiating InjeCtablE therapy) study.
Sicras, 2013[48]	2067 patients	We have analyzed the clinical (diabetic treatment adherence, metabolic control, hypoglycemia and macrovascular complications) and economic (resource use and costs) consequences of the combination of metformin with dipeptidyl peptidase inhibitors (DPPIV) in patients with type 2 diabetes.
Case-Control Studies		
None	–	–
Other Study Designs		
Cook, 2014[49]	1961 patients	To test the effectiveness and safety of saxagliptin 5 mg/d in patients with type 2 diabetes mellitus (T2DM) with and without history of cardiovascular disease (CVD) or cardiovascular (CV) risk factors.
Digenio, 2014[50]	33,810 patients	To document the characteristics and clinical outcomes of patients with T2DM initiating prandial insulin or a glucagon-like peptide-1 (GLP-1) receptor agonist while on basal insulin.
Mintz, 2014[51]	858 patients	To compare characteristics of hypoglycemic episodes in patients with type 2 diabetes receiving saxagliptin or glipizide add-on therapy to metformin.
Morgan, 2014[52]	33,983 patients	To compare the risk of major adverse cardiovascular events (MACE) and mortality for combination therapies with metformin and either sulphonylurea (SU) or dipeptidyl peptidase-4 inhibitor (DPP-4i).
Yang, 2014[53]	56,536 patients	To assess and compare all-cause mortality rates between pioglitazone (PIO) and insulin (INS).
Gitt, 2013[54]	3810 patients	DPP-4 inhibitors (DPP4-I) have been shown to provide non-inferior glycaemic control compared with sulfonylureas (SU), but result in a reduction of body weight and a significantly lower risk of hypoglycaemia in patients with type 2 diabetes. We aimed to validate these results in a large real-world sample of patients participating in the prospective DiaRegis registry and to assess prognostic implications.

Study	N	Objective
Grimm, 2013[55]	263 patients	The efficacy and tolerability of exenatide once weekly (EQW) were compared with those of b-INS in patients with type 2 diabetes mellitus and a baseline HbA1c level 8.5% who were undergoing treatment with metformin +/- a sulfonylurea.
Ongoing Studies (ClinicalTrials.gov)		
Individually Tailored Treatment of Type 2 Diabetes (NCT02015130)	2246 patients	Ongoing (Estimated completion October 2025). This study proposes a new approach to treatment of type 2 diabetes, where the patients' individual characteristics are considered. The aetiology of the diabetes can be different, which warrants different treatment. Many patients have concomitant illness which can affect the way the patient is treated. A tight regulation of blood glucose can in some patient constitute a risk of adverse effects, especially hypoglycemia. In that sense individual targets for the treatment are important. Effective lifestyle treatment has importance for a successful outcome and the study therefore offers an application that can help the patient and the physician organizing activity individually.
Surgery or Lifestyle With Intensive Medical Management in the Treatment of Type 2 Diabetes (NCT01073020)	88 patients	Ongoing (Estimated completion April 2017). This trial investigates the utility of currently practiced and available bariatric surgical procedures as compared with multidisciplinary intensive medical and weight management for the treatment of T2DM with class 1 and 2 obesity.
Early Intermittent Intensive Insulin Therapy as an Effective Treatment of Type 2 Diabetes (RESET-IT Main Trial) (NCT02192424)	148 patients	Ongoing (Estimated completion September 2018). The investigators propose a randomized controlled trial to determine whether intermittent intensive insulin therapy is an effective therapeutic strategy that can preserve pancreatic beta-cell function and maintain glycemic control early in the course of type 2 diabetes.
Early Intermittent Intensive Insulin Therapy as an Effective Treatment of Type 2 Diabetes (RESET-IT Pilot Study) (NCT01755468)	24 patients	Ongoing (Estimated completion December 2017). The investigators propose a pilot randomized controlled trial to determine whether intermittent intensive insulin therapy is an effective therapeutic strategy that can preserve pancreatic beta-cell function and maintain glycemic control early in the course of type 2 diabetes.
Sleeve Gastrectomy and Roux-en-Y Gastric Bypass in the Treatment of Type 2 Diabetes Mellitus. (NCT01984762)	134 patients	Ongoing (Estimated completion September 2020). The principal aim of this study is to compare two types of bariatric procedures, the Roux-en-Y gastric bypass (RYGBP) and sleeve gastrectomy (SG). The study hypothesis is that these procedures have equal efficacy with regard to resolution of type 2 diabetes.

Study	N	Objective
Prospective Controlled Trial on Surgical Treatment of Type 2 Diabetes Patients With BMI 25-30 by Means of Biliopancreatic Diversion (NCT01046994)	40 patients	Ongoing (Estimated completion December 2016). A new prospective study was planned with the aim to gain insight in the mechanism of action of BPD in T2DM patients in the 25-30 BMI range.
A Comparative Effectiveness Study of Major Glycemia-lowering Medications for Treatment of Type 2 Diabetes (NCT01794143)	5000 patients	Ongoing (Estimated completion not reported). The GRADE Study is a pragmatic, unmasked clinical trial that will compare commonly used diabetes medications, when combined with metformin, on glycemia-lowering effectiveness and patient-centered outcomes.
Prevention and Treatment Of Diabetes Complications With Gastric Surgery or Intensive Medicines (NCT01974544)	150 patients	Ongoing (Estimated completion December 2016). The investigators are proposing a prospective randomized trial comparing RYGB, SG and the best medical treatment availed for the T2DM in poorly control patients with the primary endpoint being 36 month glycemic control (patients achieving HbA1C < 6.5%, normal glucose levels not requiring medication).
A Study to Evaluate ITCA 650 Compared to Sitagliptin as add-on Therapy for the Treatment of Type 2 Diabetes (NCT01455870)	500 patients	Ongoing (Estimated completion July 2015). Phase 3 study to compare treatment with ITCA 650 to sitagliptin when added to metformin monotherapy in patients with type 2 diabetes.
Efficacy and Safety of Mitiglinide vs Acarbose in Patients With Type 2 Diabetes Mellitus (NCT02143765)	248 patients	Ongoing (Estimated completion not reported). The purpose of this study is to evaluate the efficacy and safety of Mitiglinide vs Acarbose in patients with type 2 diabetes mellitus.
Effects of Liraglutide in Young Adults With Type 2 DIAbetes (LYDIA) (NCT02043054)	90 patients	Ongoing (Estimated completion January 2016). The aim of this research is to investigate the cardiometabolic effects of Liraglutide (GLP1 analogue) compared to that of its clinically relevant comparator Sitagliptin (DPP IV inhibitor).
Efficacy and Safety Comparative Study of Sitagliptin,Vildagliptin and Saxagliptin (NCT01703637)	300 patients	Ongoing (Estimated completion not reported). The purpose of this study is to explore the differences in efficacy and safety of sitagliptin,vildagliptin and saxagliptin and to find which one is more better in treating type 2 diabetes mellitus.
Alliance of Randomized Trials of Medicine vs Metabolic Surgery in Type 2 Diabetes (NCT02328599)	302 patients	Ongoing (Estimated completion December 2017). The aim of this study is to combine data from the 4 studies and continue to follow the original randomized subjects for an additional 2 years of follow-up. The purpose of the study is to determine the longer term durability and effectiveness of bariatric surgery compared to medical/lifestyle intervention on the treatment of type 2 diabetes.

Study	N	Objective
Triple Therapy in Type 2 Diabetic Patients (NCT01895569)	64 patients	Ongoing (Estimated completion June 2016). The aim of the study is to evaluate the effects of a triple therapy with metformin, pioglitazone and sitagliptin on glycemic variability compared to metformin monotherapy, and compared to a combination of metformin and pioglitazone. To assess glycemic variability a continuous glucose monitoring system will be used.
Novel Model for South Asian Treatment in Diabetes (NaMaSTe-Diabetes) Trial in Primary Care (NCT02136654)	600 patients	Ongoing (Estimated completion June 2019). We propose to conduct a randomized controlled trial to assess the impact of a novel culturally tailored lifestyle and medication adherence intervention in SA patients with poorly controlled diabetes.
Efficacy and Safety of Semaglutide Once-weekly Versus Sitagliptin Once-daily as add-on to Metformin and/or TZD in Subjects With Type 2 Diabetes (NCT01930188)	1200 patients	Ongoing (Estimated completion October 2015). The aim of the trial is to evaluate efficacy and safety of semaglutide once-weekly versus sitagliptin once-daily as add-on to metformin and/or TZD (thiazolidinedione) in subjects with type 2 diabetes.
Efficacy and Safety of Semaglutide Once Weekly Versus Insulin Glargine Once Daily as add-on to Metformin With or Without Sulphonylurea in Insulin-naÃ¯ve Subjects With Type 2 Diabetes (NCT02128932)	1047 patients	Ongoing (Estimated completion September 2015). The purpose of the trial is to compare the effect of once-weekly dosing of two dose levels of semaglutide versus insulin glargine once-daily on glycaemic control after 30 weeks of treatment in insulin-naïve subjects with type 2 diabetes.
Efficacy and Safety of Semaglutide Once-weekly Versus Exenatide ER 2.0 mg Once-weekly as add-on to 1-2 Oral Antidiabetic Drugs (OADs) in Subjects With Type 2 Diabetes (NCT01885208)	798 patients	Ongoing (Estimated completion July 2015). The aim of the trial is to investigate the efficacy and safety of semaglutide once-weekly versus exenatide ER (extended release) 2.0 mg once-weekly as add-on to 1-2 oral antidiabetic drugs (OADs) in subjects with type 2 diabetes.
The Inova Type 2 Diabetes Mellitus Study (NCT02222623)	115 patients	Ongoing (Estimated completion April 2016). The purpose of this study is to compare the safety and effectiveness of the two different basal insulins commonly used for basal blood sugar control in the treatment of type 2 diabetes mellitus in patients who are hospitalized and require low doses of insulin: neutral protamine Hagedorn (NPH) insulin and glargine (Lantus®) insulin.

Study	N	Objective
A \Real World\" Trial to Determine Efficacy and Health Outcomes of Toujeo (ACHIEVE CONTROL REAL LIFE STUDY PROGRAM)" (NCT02451137)	3270 patients	Ongoing (Estimated completion March 2017). Demonstrate clinical benefit of Toujeo in achieving individualized HEDIS HbA1c targets (<8% if age 65 years or with defined comorbidities or otherwise <7%) at 6 months without documented symptomatic (BG 70mg/dl) hypoglycemia at any time of day from baseline to 6 months in uncontrolled insulin naive patients with type 2 diabetes initiating basal insulin therapy in a real world setting.
Calorie Reduction Or Surgery: Seeking Remission for Obesity And Diabetes (NCT01295229)	40 patients	Ongoing (Estimated completion June 2015). The investigators propose a feasibility study to demonstrate our capacity to identify, recruit, randomize, and track outcomes for 40 adult Group Health members identified as having T2DM and a BMI between 30-40 kg/m2.

Abbreviations not defined above: BMI=body mass index; DPP=diabetes prevention program; N=number of studies/patients; NR=not reported; RCTs=randomized controlled trials; T2DM=Type 2 Diabetes Mellitus; VADT=Veterans Affairs Diabetes Trial

Appendix Table C-3. Published and ongoing studies potentially relevant to Research Question 4 *[What is the comparative effectiveness of different strategies for determining diabetes treatment success (for both metformin and second-/third-line treatments)? Specifically, how do treatment choices, treatment adherence/persistence, diabetes control, other patient-centered outcomes (e.g., weight, hypoglycemia rates, quality of life), and maintenance of clinical gains differ with hemoglobin A1c goal-driven decision making versus approaches that formally consider additional factors (e.g., patient values, overall diabetes complication risk, preservation of the body's ability to produce insulin, avoidance of overtreatment, and/or new technologies like continuous glucose monitoring)?]*

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
He, 2013[56]	24 patients	To assess whether there is a difference in the effects of vildagliptin and glimepiride on glucose fluctuation in patients with type 2 diabetes mellitus (T2DM) using continuous glucose monitoring (CGM)
Kim 2013[26]	33 patients	To compare the effects of sitagliptin on glycemic change and 24-h blood glucose variability with those of the sulfonylurea glimepiride
Cohort Studies		
Bramlage, 2014[57]	3810 patients	To intensify and optimise antidiabetic treatment due to insufficient glucose control.
Case-Control Studies		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		

Study	N	Objective
Triple Therapy in Type 2 Diabetic Patients (NCT01895569)	64 patients	Ongoing (Estimated completion June 2016). The aim of the study is to evaluate the effects of a triple therapy with metformin, pioglitazone and sitagliptin on glycemic variability compared to metformin monotherapy, and compared to a combination of metformin and pioglitazone. To assess glycemic variability a continuous glucose monitoring system will be used.
Efficacy of a Chronic Care Model Supported by Self Monitoring of Blood Glucose With BGStar Over Usual Care in Improving Glycemic Control in Patients With Type 2 Diabetes Not Treated With Insulin (NCT02082028)	238 patients	Ongoing (Estimated completion July 2015). To demonstrate the superiority of a chronic care model (SINERGIA model) supported by the Self Monitoring of Blood Glucose with BGStar over usual care in improving glycemic control at 12 months in patients with type 2 diabetes not treated with insulin.

Abbreviations not defined above: DPP=diabetes prevention program; N=number of studies/patients; RCTs=randomized controlled trials

Appendix Table C-4. Published and ongoing studies potentially relevant to Research Question 5 *[What is the comparative effectiveness of approaches for enhancing diabetes treatment adherence and persistence in real-world settings (for both metformin and second-/third-line treatments)? How can efficacious approaches to fostering adherence (e.g., diabetes self-management education, diabetes self-management support, treatment of comorbid mental illness, care delivery strategies that utilize communications technology to facilitate frequent contact, and approaches used in the setting of clinical trials) be feasibly implemented under real-world conditions?]*

Study	N	Objective
Systematic Reviews		
Antoine, 2014[58]	6 studies	To analyze the effectiveness of adherence-enhancing pharmacist interventions for oral medication in type 2 diabetes mellitus.
RCTs		
Fall, 2013[59]	80 patients	To test the effects of brief psychological interventions based on diabetes threat and mastery perceptions in terms of adherence, acceptance and motivation
Cohort Studies		
Thorens, 2015[60]	13,428 patients	To estimate the effects of insulin adherence and delivery device on real-world health outcomes.
Case-Control Studies		
None	–	–
Other Study Designs		
Adhien, 2013[61]	36 patients	A modular pharmacy intervention, named 'Support for Diabetes', was developed to improve adherence to type 2 diabetes treatment.
Quilliam, 2013[62]	NR	To quantify the relationship between adherence to oral anti-diabetic drugs and incident hypoglycaemia in Type 2 diabetes

Study	N	Objective
Ongoing Studies (ClinicalTrials.gov)		
Nutritional Therapy and Education With Multimedia Application in Patients With Type 2 Diabetes (NCT02441023)	306 patients	Ongoing (Estimated completion December 2015). The purpose of this study is to evaluate the effectiveness of nutrition therapy in combination with education in diabetes using a multimedia application for improving indicators of metabolic control in patients with type 2 diabetes.
Lifestyle Intervention for Treatment of Diabetes (NCT01806727)	260 patients	Ongoing (Estimated completion August 2017). This study is evaluating two approaches to improving the control blood sugar, and other risk factors for heart disease in overweight and obese adults with type 2 diabetes. The first approach has participants focus on weight loss via reducing food intake and increasing physical activity, while attending weekly group sessions led by trained community health workers for 12 months. The second approach has participants receive education on diabetes self management, which focuses primarily on glucose control, while attending monthly group sessions led by a study staff member for 12 months.
Effectiveness and Cost-effectiveness of a Telemonitoring Program for Diabetic People at Home (NCT01955031)	282 patients	Ongoing (Estimated completion September 2017). The objective of EDUC@DOM is to help people with diabetes to improve lifestyle and equilibrium of glycaemia in order to avoid or delay chronic complications of diabetes. Our main goal is to assess effectiveness of our telemonitoring program in type 2 patients' care compared to a usual care of diabetes, on the glycaemia of the patients.
Two Years Maintenance of Structured Group Self-management Education in Type 2 Diabetes : a Randomized Controlled Trial (NCT01425866)	240 patients	Ongoing (Estimated completion December 2016). The hypothesis of the ERMIES study is that a structured group self-management education maintained at the community level for 2 years in patients with insufficiently controlled type 2 diabetes has better metabolic results (as attested by improvement in HbA1c level) at 2 yrs, compared to an initial short term (< 3 months) self-management program, based on the same theoretical basis and framework (learning nests empowerment). A total of 240 adults living in Reunion Island, with type 2 diabetes mellitus with HbA1c ≥ 7.5% on a stable treatment for at least 3 months will be randomly allocated to 2 intervention arms: either a short term (< 3 months) program (1 to 7 thematic 2-hr long sessions depending on individual assessment), or a long term program including the same initial program as 1st arm, but with group self management education sessions, maintained for 2 years (4-monthly assessment, empowerment, and contextual action planning; facultative additional specific thematic sessions being delivered if needed).
Mobile Health Technology as an Intervention for Diabetes Self-Management (NCT01546844)	500 patients	Ongoing (Estimated completion February 2013). This purpose of this is study is to evaluate the effectiveness of an interactive mobile health information service, Care4Life, in supporting patient self-management of Type II Diabetes Mellitus.

Study	N	Objective
Novel Model for South Asian Treatment in Diabetes (NaMaSTe-Diabetes) Trial in Primary Care (NCT02136654)	600 patients	Ongoing (Estimated completion June 2019). We propose to conduct a randomized controlled trial to assess the impact of a novel culturally tailored lifestyle and medication adherence intervention in SA patients with poorly controlled diabetes.

Abbreviations not defined above: DPP=diabetes prevention program; N=number of studies/patients; NR=not reported; RCTs=randomized controlled trials

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