Evidence-based Practice Center Systematic Review Protocol

Project title: Behavioral Programs for Diabetes Mellitus

I. Background and Objectives for the Systematic Review

The high burden of diabetes necessitates careful attention to factors contributing to optimal diabetes care and self-management including lifestyle behaviors and medication adherence. Over the past few decades, much of the care and education of people with diabetes in the United States has transferred from hospitals to outpatient settings, and several guidelines and diabetes management programs have been developed to improve diabetes care in the community.[1] However, an evaluation of initiatives to implement guidelines and processes of care in community health centers did not find improved control of hemoglobin A_{1c} (HbA_{1c}) levels for patients with diabetes.[2]

Approaches for supporting patients to change behaviors include interventions such as diabetes self-management education (DSME) and support, lifestyle interventions, and medical nutrition therapy (MNT). However, whether these are effective for type 1 diabetes (T1DM) is not clear. Moreover, although there is a diverse evidence base supporting effectiveness of these approaches for type 2 diabetes (T2DM), it is unknown what combination(s) of program components and delivery mechanisms are most effective for their success. Health providers struggle with how to best support, educate, and work with patients to improve their disease control. To date, it is not clear whether there is (or what constitutes) a set of best practices associated with behavioral programs that can be implemented in the community health setting.

Pathophsyiology

"Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both."[3] T1DM and T2DM are the major classes of diabetes although several others exist. T1DM accounts for 5–10 percent of cases of diabetes and usually results when the body's immune system destroys the beta cells of the pancreas, the only cells that make insulin. The incidence of T1DM peaks in adolescents although it can occur at any age.

T2DM accounts for 90–95 percent of cases of diabetes. It usually begins with insulin resistance in which it takes more than the usual amount of insulin to achieve a given degree of glucose regulation. T2DM occurs if, over time, the pancreas is progressively less able to secrete enough insulin to normalize blood glucose.[3, 4] T2DM is associated with obesity, family history of diabetes, history of gestational diabetes mellitus, impaired glucose metabolism, physical inactivity, and non-white race or ethnicity.

Burden of disease

In the United States, diabetes affects 25.8 million people, or 8.3 percent of the entire population and 11.3 percent of the adult population.[4] About 215,000 people younger than 20 years have diabetes (T1DM or T2DM).[4] Diabetes-related care accounts for 11 percent of all U.S. health care expenditure[5] equating to $174 billion in total costs in 2007.[4] Average medical expenses are more than twice as high for a person with diabetes as they are for a person without diabetes.[6]

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Complications from diabetes include cardiovascular disease, retinopathy, neuropathy, nephropathy, and cerebrovascular disease, as well as comorbidities such as depression and other mental health conditions.[7] In adults, the most frequent first-listed diagnoses among hospital discharges in 2010 were diseases of the circulatory system (24 percent) and diabetes (12 percent). Between 5 and 11 percent of emergency department visits are for diabetes-related complications.[5] For children and young people in 2009, 74 percent of hospital discharges and 42 percent emergency visits had diabetes listed as the first diagnosis. About 64 percent of these discharges and 46 percent of the emergency visits were for diabetes ketoacidosis.[4] Reducing morbidity and mortality and improving quality of life for people with diabetes is a major public health objective.

Disparities in prevalence, care, and outcomes

Older adults (>65 years) are disproportionately affected with diabetes , as are African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Native Hawaiians or other Pacific Islanders.[4] Specific to T1DM, non-Hispanic white youth are affected more often than all other race/ethnicities.[8]

Apart from disparities in disease prevalence, several subpopulations are considered vulnerable to poor health care access and outcomes for a variety of individual and societal reasons. Race or ethnicity and socioeconomic considerations including literacy, educational levels, and household income have been shown to be associated with sub-optimal care[2, 9] and poorer diabetes outcomes for both T1DM and T2DM.[10,11,12]

Diabetes care and self-management

With hyperglycemia defining diabetes, the mainstay of treatment for T1DM is insulin. T2DM patients are often treated progressively through diet (e.g., calorie and fat reduced while controlling carbohydrate intake) and then, if needed, one or more oral hypoglycemic medications. Many T2DM patients eventually require the addition (or sole use) of insulin to obtain good blood glucose control. Landmark trials of T1DM and T2DM patients showed that intensive control of glycemia (average achieved HbA_{1c} was about 7 percent) significantly reduced the incidence of microvascular and neurological complications.[13-15] Reducing the risk for diabetes-related complications often requires lifestyle and/or pharmacological management of body weight, blood pressure, and cholesterol levels.[15-18] The responsibility for this extensive, multicomponent disease management falls to both the diabetes health care team and, most notably, the patient. Patients are encouraged to adopt and adhere to several self-care or self-management and lifestyle behaviors.[19] For many, a key behavior may be self-regulation of carbohydrate intake, physical activity and/or medication doses based on results of monitoring of blood glucose. In addition, lifestyle interventions targeted at weight loss, diabetes nutrition, and physical activity recommendations have been shown to be associated with weight control and improved glycemic control.[20-24]

A critical element of diabetes care is education and support to enable patients to engage in self-care and self-management behaviors. Diabetes self-management education (DSME) is designed to "reduce the burden of diabetes on individuals, families, communities and healthcare systems, and, by supporting good health, prevent or delay the onset of diabetes-related long-term complications."[25] Because knowledge acquisition alone is not enough for behavioral changes,[26,27] the focus of many national and international guidelines and recommendations for diabetes self-management education has shifted from traditional didactic educational services to more patient-

centered methodologies incorporating interaction and problem-solving.[25,28-31] In addition, the national standards for DSME developed by the American Association of Diabetes Educators (AADE) and the American Diabetes Association (ADA) have over the past two revisions[28,29] incorporated the provision of ongoing diabetes self-management support (DSMS) following DSME, "to encourage behavior change, the maintenance of healthy diabetes-related behaviors, and to address psychological concerns."[29] In addition to DSME, a diverse range of interventions and programs have been developed that focus more on supporting patients' efforts in changing lifestyle behaviors in order to better manage glycemia and prevent complications.[23]

Despite the availability of new medications and treatment devices (e.g., insulin pumps, continuous glucose monitoring), several standards for care management and DSME programs, and implementation of lifestyle interventions, the National Health and Nutrition Examination Survey data indicate that 45 percent of adults with diabetes in the United States do not achieve glycemic targets[32] and few (as low as 16 percent[33]) patients carry out self-management recommendations. Further, the Centers for Disease Control and Prevention's Behavioral Risk Surveillance System found that 36 percent of adults diagnosed with diabetes reported no physical activity in the past 30 days. Other reported risk factors for diabetes-related complications included smoking (20 percent), self-reported overweight or obesity (86 percent), hypertension (58 percent), and high cholesterol (58 percent).[3]

Behavioral programs for diabetes

For the purpose of this systematic review we developed an operational definition of behavioral programs that encompasses DSME as well as other programs incorporating interactive components that target important behavioral changes (e.g., diet and physical activity). This definition focuses on *programs*, defined as "…a plan of action for an event or sequence of actions over a period that may be short or prolonged…. A health program is generally long term and often multi-faceted, whereas a health project is usually short-term and narrowly focused."[34] Our operational definition of a behavioral program is as follows. We expand on specific elements of the above operational definition in Appendix A.

An organized, multicomponent diabetes-specific program with repeated interactions by one or more trained individuals, with a duration of ≥4 weeks, to improve disease control and/or patient health outcomes, and consisting of at least one of: a) DSME; or b) a structured dietary intervention (related to any of weight loss, glycemic control, or reducing risk for complications) together with one or more additional components; or c) a structured exercise or physical activity intervention together with one or more additional components. Additional components for (b) and (c) above may include interventions related to: diet or physical activity; behavioral change (including but not limited to goal setting, problem solving, motivational interviewing, coping skills training, cognitive behavioral therapy strategies); relaxation or stress reduction; blood glucose regulation; medication adherence; or self-monitoring for diabetic complications (foot, eye and renal tests).

We include contact with those delivering the program, rather than relying solely on "interactive behavior change technology" (e.g., patient-centered websites, automated telephone calls, DVDs, and touch screen kiosks). While these tools show great promise for helping health systems meet the growing demand for diabetes management and support, they have been shown to be most effective when they support human contact.[35]

Rationale for an evidence review

Health providers working in outpatient and primary care settings in the community struggle with how to best support, educate, and work with patients to improve their disease control. To date, it is not clear whether there is (or what constitutes) a set of best practices associated with behavioral programs that can be implemented in the community health setting. For the purposes of this review, community health settings include ambulatory care (i.e., outpatient) clinics, primary care clinics, family physician clinics, and federally qualified health centers (i.e., Community Health Centers, and Rural Health Centers).

Many previous systematic reviews on topics relevant to this review have included studies of didactic educational interventions (i.e., not meeting current recommendations) as well as behavioral and psychological interventions. Many also included studies evaluating single stand-alone interventions. Multicomponent behavioral programs have been shown to improve glycemic control for T2DM to a clinically significant extent at least in the short term—reductions in HbA_{1c} from -0.36 to -1.4 percent;[36-43] the evidence for these programs in T1DM is less conclusive. For reviews of T1DM or T2DM that conducted meta-analyses, the vast majority only evaluated HbA_{1c} as their primary outcome. Very few simultaneously assessed multiple factors contributing to the success of the interventions[25,37,44,45]—the mediating effects of program content and characteristics have therefore not been fully investigated.

Our focus for T1DM is placed on determining the effectiveness of behavioral programs. For T2DM we will build upon previous systematic reviews by identifying factors contributing to the effectiveness of multicomponent programs. We will conduct multiple variable analyses and will investigate patient-important outcomes in addition to HbA_{1c}. By analyzing potential mediators to effectiveness, such as delivery personnel, effective community linkages, and demographics we will help inform decisions regarding what combination of program components and delivery methods are effective for implementation of these programs in community health settings.

II. The Key Questions

Question 1

For patients with T1DM, are behavioral programs implemented in a community health setting effective compared with usual or standard care, or active comparators in, a) improving behavioral, clinical, and health outcomes, b) improving diabetes-related health care utilization, and c) achieving program acceptability as measured by participant attrition rates?

Question 2

For patients with T1DM, do behavioral programs implemented in the community health setting differ in effectiveness for behavioral, clinical, and health outcomes, their effect on diabetes-related health care utilization, or program acceptability , for subgroups of patients based on: age (i.e., children and adolescents [≤18 years] and their families, young adults [19-30 years], adults [31-64 years], older adults (≥65 years]); race or ethnicity; socioeconomic status (e.g., family income, education level, literacy); time since diagnosis (i.e., ≤1 year vs. >1 year); and, level of glycemic control (e.g., HbA_{1c} <7 vs. ≥7 percent])?

Question 3

For patients with T1DM, does the effectiveness of behavioral programs differ based on the: a) components; b) intensity (i.e., program duration, frequency/periodicity of interactions); b) delivery personnel (e.g., dietitian, exercise specialist, physician, nurse practitioner, certified diabetes educator, lay health worker); c) method of communication (e.g., individual vs. group, face-to-face, interactive behavior change technology, social media); d) degree of tailoring based on needs assessment (e.g., educational/behavioral deficits, age or other demographics, readiness to change); or e) level and nature of community engagement?

Question 4

For patients with T1DM, what are the associated harms (i.e., activity-related injury) of behavioral programs implemented in a community health setting compared with usual care, standard care, or active comparators?

Question 5

Among behavioral programs targeted at adults with T2DM implemented in a community health setting, what factors contribute to: a) their effectiveness for behavioral, clinical, and health outcomes; b) their effect on diabetes-related health care utilization; and c) program acceptability as measured by participant attrition rates? Factors include program components, program intensity, delivery personnel, methods of delivery and communication, degree of tailoring, and community engagement.

Question 6

Do the factors that contribute to program effectiveness for patients with T2DM vary across the following subpopulations: age (i.e., young adults [19-30 years], adults [31-64 years], older adults [≥65 years]); race or ethnicity; socioeconomic status (e.g., family income, education level, literacy); time since diagnosis (i.e., ≤1 year vs. >1 year); and, level of glycemic control (i.e., HbA_{1c} <7 vs. ≥7 percent)?

Summary of Revisions to the Key Questions

Preliminary Key Questions were available for public comment from January 6-27, 2014. Based on the public comments, the following changes were incorporated to the Key Questions presented above:

- The term "alternate behavioral health programs" was changed to "active comparators" because not all comparators will meet our definition of behavioral health programs.
- Key Question 2 was revised to be explicit for what outcomes there will be subgroup analysis performed.
- A factor was added to Key Questions 3 and 5, namely the "degree of tailoring based on needs assessment", to capture a delivery method of programs that may be informative.
- A term was added in Key Question 5 to consider the effects of program factors on program accessibility and acceptability, in addition to the behavioral, clinical and health outcomes and diabetes-related health care utilization.
- The wording "newly diagnosed" was removed when defining the subgroup analyses for time since diagnosis. The review will not include programs targeted to patients at

diagnosis ("newly diagnosed") although it will examine the differential effectiveness of programs for those with shorter (<1 year) versus longer (>1 year) times since diagnosis.

Based on feedback in April 2014 from the Agency for Healthcare Research and Quality Effective Healthcare Program, we combined the preliminary Key Questions 1 and 2 (Key Question 1, above) and added acceptability and accessibility as an outcome in order to be consistent with the outcomes for T2DM. We removed "burden of intervention" from Key Question 4 and incorporated it as an outcome in Key Question 1.

Input from members of the Technical Expert Panel (TEP) in May, 2014 was important in: clarifying the wording and intent of the setting (i.e., community health settings); confirming the change in terminology from "behavioral health programs" to "behavioral programs"; and confirming that the use of participant attrition rates captures the concept of program acceptability but not accessibility. Program accessibility was removed as an outcome although some aspects of this will be incorporated into the factor of degree of tailoring.

PICOTS Criteria

PICOTS (patients, interventions, comparators, outcomes, timing, and setting) frameworks are presented below for the Key Questions that relate to T1DM and T2DM. These frameworks will guide all the stages of the systematic review, including literature searching, study selection, and data abstraction.

Table 1. Type 1 diabetes (Key Questions 1-4)

Population	• Patients with T1DM (any age) who have undergone basic diabetes education
Interventions	• Multicomponent behavioral program that includes at least one of: - Diabetes self-management education; OR - Structured dietary intervention (related to any of weight loss, glycemic control, or reducing risk for complications) together with one or more additional components; OR - Structured exercise/physical activity intervention together with one or more additional components. - Additional components may include interventions related to: diet or physical activity, behavioral change (including but not limited to: goal setting, problem solving, motivational interviewing, coping skills training, cognitive behavioral therapy strategies), relaxation or stress reduction, blood glucose awareness, medication adherence, or self-monitoring for diabetic complications (foot, eye, and renal tests). • Repeated provision by one or more trained individuals • Duration of intervention: minimum 4 weeks
Comparators	• Usual or standard care or an active comparator (e.g. behavioral program or intervention) as reported for studies • Delivery methods (personnel, intensity, communication methods etc.) as reported for studies
Outcomes	• Behavioral outcomes - Self-regulation of insulin based on diet, physical activity, and glucose monitoring results - Change in physical activity (e.g., volume of activity per week) or fitness (e.g. cardiorespiratory fitness, strength) - Change in dietary or nutrient intake (i.e., energy intake, saturated fat consumption) - Adherence to treatment, including self-monitoring and medication • Clinical outcomes - Glycemic control (HbA_{1c}) - Change in body composition (i.e., weight, BMI, waist circumference, % body fat) - Episodes of severe hypoglycemia[46] - Treatment for hyperglycemia (ketoacidosis) - Control of blood pressure and lipids - Development or control of depression or anxiety • Health outcomes

	- Quality of life (e.g., validated tools for health-related quality of life, life satisfaction, psychosocial adaptation to illness, patient satisfaction) - Development of micro- and macrovascular complications (i.e., retinopathy, nephropathy, neuropathy, cardiovascular outcomes) - Mortality (all-cause) • Diabetes-related health care utilization - Hospital admissions - Length of stay in hospital - Emergency department admissions - Visits to specialist clinics • Program acceptability as measured by participant attrition rates • Harms from program as reported for studies - Activity-related injury
Timing	• Any length of followup
Study design	• Prospective comparative studies using a best evidence approach based on hierarchy of evidence: randomized controlled trials, nonrandomized controlled trials, prospective cohort studies, controlled before-after studies
Settings	• Community health setting (i.e. ambulatory care clinics, outpatient clinics, primary care clinics, family physician clinics, Community Health Centers, Rural Health Centers) • United States or other high-income countries with a very high Human Development Index[47]
Language	• English

BMI = body mass index; HbA_{1c} = hemoglobin A_{1c}; T1DM = type 1 diabetes

Table 2. Type 2 diabetes (Key Questions 5-6)

Population	• Adults (≥18 years) with T2DM who have undergone primary diabetes education
Interventions	• Multicomponent behavioral programs that include at least one of: - Diabetes self-management education; OR - Structured dietary intervention (related to any of weight loss, glycemic control, or reducing risk for complications) together with one or more additional components; OR - Structured exercise/physical activity intervention together with one or more additional components. - Additional components may include interventions related to: diet or physical activity, behavioral change (including but not limited to: goal setting, problem solving, motivational interviewing, coping skills training, cognitive behavioral therapy strategies), relaxation or stress reduction, blood glucose awareness, medication adherence, or self-monitoring for diabetic complications (foot, eye, and renal tests). • Repeated provision by one or more trained individuals • Duration of intervention: minimum 4 weeks
Comparators	• Usual or standard care or an active comparator (e.g., behavioral program or intervention) as reported for studies • Delivery methods (personnel, intensity, communication methods etc.) as reported for studies
Outcomes	• Behavioral outcomes - Change in physical activity (e.g., volume of activity per week) or fitness (e.g., cardiorespiratory fitness, strength) - Change in dietary or nutrient intake (i.e., energy intake, saturated fat consumption) - Adherence to medication • Clinical outcomes - Glycemic control (HbA_{1c}) - Change in body composition (i.e., weight, BMI, waist circumference, % body fat) - Control of blood pressure and lipids - Sleep apnea or sleep quality - Development or control of depression or anxiety • Health outcomes • Quality of life (e.g., validated tools for health-related quality of life, life satisfaction, psychosocial adaptation to illness, patient satisfaction) • Development of micro- and macrovascular complications (i.e., retinopathy, nephropathy, neuropathy, cardiovascular outcomes) • Mortality (all-cause) • Diabetes-related health care utilization

	- Hospital admissions - Length of stay in hospital - Emergency department admissions - Visits to specialist clinics • Program acceptability as measured by participant attrition rates
Timing	• Any length of followup
Study design	• Randomized controlled trials
Settings	• Community health setting (i.e., ambulatory care clinics, outpatient clinics, primary care clinics, family physician clinics, Community Health Centers, Rural Health Centers) • United States or other high-income country with a very high Human Development Index[47]
Language	• English

BMI = body mass index; HbA_{1c} = hemoglobin A_{1c}; T2DM = type 2 diabetes

III. Analytical Frameworks

Figure 1 (below) depicts the Key Questions related to patients with type 1 diabetes within the context of the PICOTS described in the previous section. In general, the figure illustrates how behavioral programs implemented in a community health setting, as compared with usual or standard care, or active comparators, may result in behavioral outcomes (e.g., self-regulation of insulin based on diet, physical activity, and glucose monitoring results, change in physical activity or fitness), clinical outcomes (e.g., glycemic control, episodes of severe hypoglycemia), and health outcomes (e.g., quality of life, development of micro- or macrovascular complications); may affect program acceptability; and may change diabetes-related healthcare utilization (e.g., hospital admissions, emergency department visits). Harms related to the intervention (i.e., activity-related injury) may occur at any point during the intervention.

Figure 2 (below) depicts the Key Questions related to patients with type 2 diabetes within the context of the PICOTS described in the previous section. In general, the figure illustrates how program features contribute to the effectiveness of behavioral programs implemented in a community health setting. Program features include program components, program intensity, delivery personnel, methods of delivery and communication, degree of tailoring, and community engagement. Measures of effectiveness include behavioral outcomes (e.g., change in physical activity or fitness, adherence to medication), clinical outcomes (e.g., glycemic control, change in body composition), and health outcomes (e.g., quality of life, development of micro- or macrovascular complications). The effect of behavioral programs on diabetes-related healthcare utilization outcomes (e.g., hospital admissions, emergency department visits) and program acceptability will also be evaluated.

Figure 1. Analytic framework for behavioral programs for type 1 diabetes mellitus

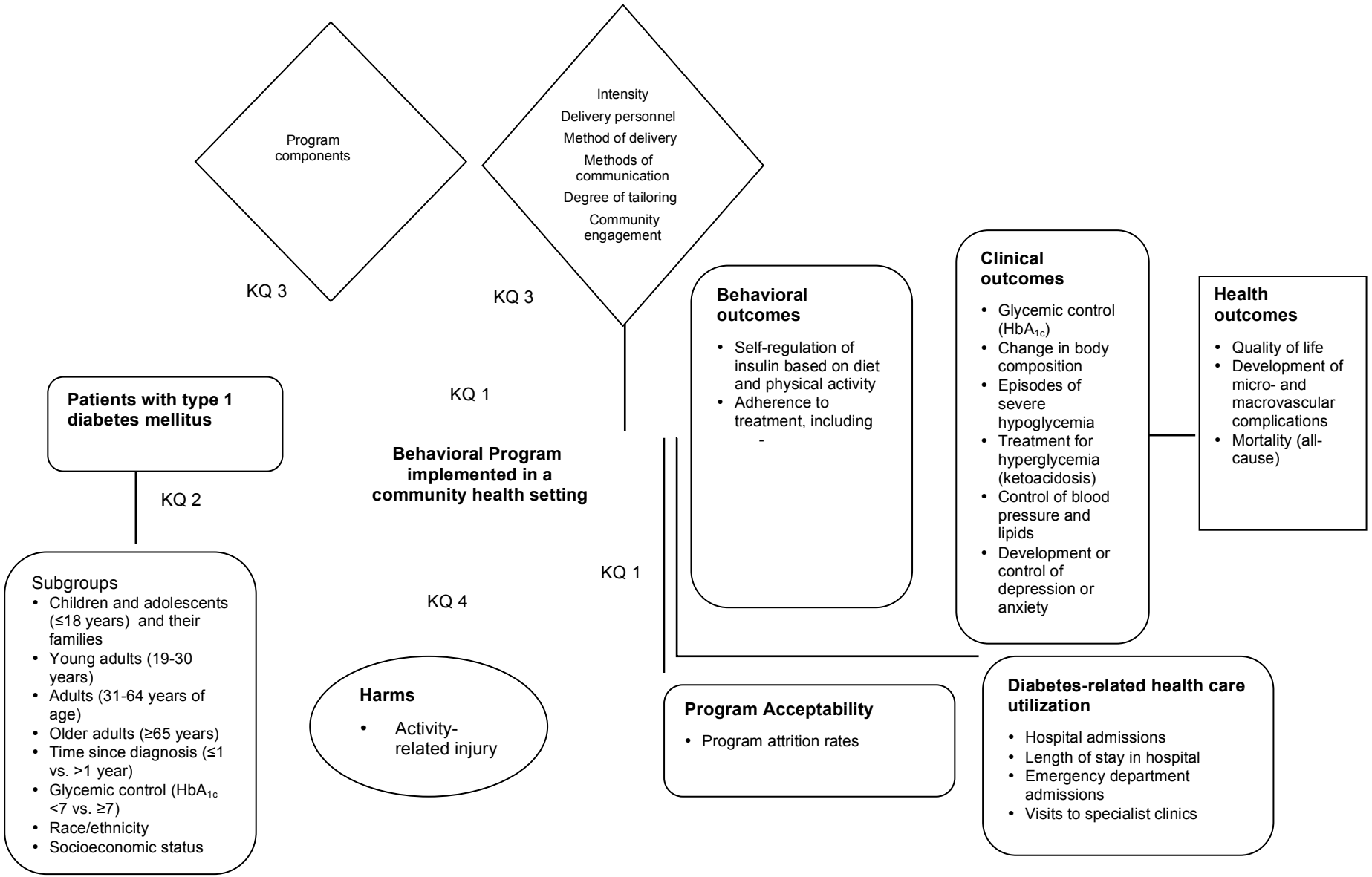

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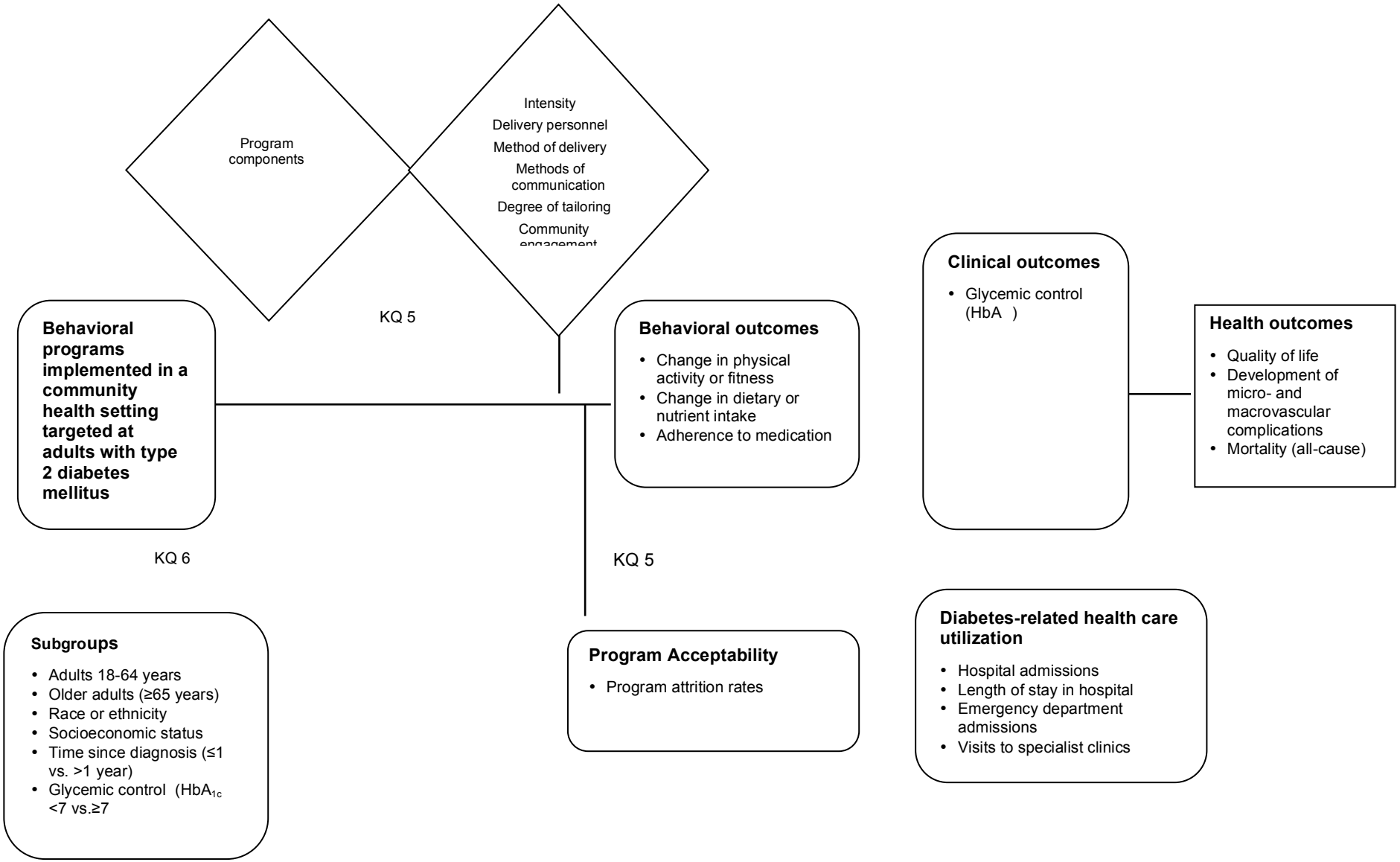
Figure 2. Analytic framework for behavioral programs for type 2 diabetes mellitus



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IV. Methods

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

We will use the eligibility criteria outlined in the PICOTS for T1DM and T2DM as presented above under the Key Questions. We will include RCTs conducted in the United States or other high-income countries[47] (Appendix B) and published in the English language. We are including studies conducted in high-income countries because we believe that the results will be more relevant to community health settings in the United States. We are including English-language publications because we believe it is unlikely that we will miss important data that are reported in non-English articles. The earliest publication date for studies will be 1993. This date was chosen because of changes to standard care (the comparator in most cases in this systematic review) resulting from the findings of landmark trials published from this date onwards.[13-15] With regard to study designs that will be considered, we will use a best evidence approach for T1DM. First, we will include RCTs. If there are not sufficient RCTs to permit a conclusion, we will sequentially include other prospective comparative studies based on a hierarchy of evidence (i.e., nonrandomized controlled trials [NRCTs], prospective cohort studies, controlled before-after studies[48]). For T2DM we will include RCTs. RCTs are the gold standard for determining the effectiveness of interventions[49] particularly when there are multiple potential confounding patient and intervention factors that may bias the results. Our preliminary searches identified over 400 potentially relevant RCTs involving patients with T2DM so we believe that there will be sufficient trials and variability with respect to program factors that may contribute to effectiveness to address the relevant Key Questions.We do not have a minimum sample size for inclusion, nor do we have a minimum threshold for extent of incomplete followup or participant attrition.

To distinguish between the effects of behavioral programs (targeting patient behaviors) and other interventions to improve outcomes for diabetes patients, we will exclude studies where the intervention is a disease/care management program (e.g., consisting of one or more interventions actively adjusting diabetes-related medications, monitoring patient medical data, or coordinating care provision)[50] or other quality improvement programs that incorporate strategies targeting health systems or providers.[51] Other exclusion criteria include: 1) studies focusing exclusively on newly diagnosed patients, because these will not represent our target population; 2) reports of studies where the outcomes are not of interest to this review (e.g., short-term effects on glucose sensitivity, C-reactive protein); 3) studies evaluating behavioral programs targeted at hospital inpatients; 4) studies evaluating community-based programs that are not implemented in affiliation with a community health setting (e.g., independent faith-based programs); 5) studies published exclusively in abstract form (e.g., conference abstracts). Where relevant abstracts are identified we will search for a complete report including contacting authors, as needed.

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

Process for Searching

We will use the same approach and search strategies for T1DM and T2DM. We will conduct a comprehensive search to identify prospective controlled studies conducted over the past two decades. Our research librarian will conduct searches in the following databases from 1993 to present: Ovid MEDLINE and Ovid MEDLINE® In-Process & Other Non-Indexed Citations,

Cochrane Central Register of Controlled Trials via Cochrane Library, EMBASE® via Ovid, CINAHL Plus with Full Text via EBSCOhost, PsycINFO® via Ovid, Scopus®, and PubMed® via the National Center for Biotechnology Information Databases.

Search strategies will include a combination of subject headings and keywords for diabetes, behavioral interventions, and diabetes education. We will apply a validated search filter for RCTs[52] and a search filter to identify prospective comparative studies. Searches will be restricted by English language. The search strategy will be developed in MEDLINE (Appendix C), peer reviewed by a second librarian, and adapted to accommodate the controlled vocabularies and search languages of the other databases.

We will review the reference lists of relevant systematic reviews. We will also review the reference lists of all included studies. We will contact authors of included studies to seek additional data as required (e.g., to clarify details of the interventions). Any additional studies identified during the Federal Register notice process will also be assessed for eligibility.

We will also search the gray literature for unpublished RCTs. We will search the following trial registries: metaRegister of Controlled Trials (includes ClinicialTrials.gov, the International Standard Randomised Controlled Trial Number Register, Action Medical Research, the Wellcome Trust, and UK Trials) and the World Health Organization International Clinical Trials Registry Platform. We will hand search the conference proceedings from the ADA, AADE, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Canadian Diabetes Association (CDA), European Association for the Study of Diabetes (EASD), International Diabetes Federation, Society of Behavioral Medicine, and International Society for Behavioral Nutrition and Physical Activity from 2011 to present.

Process for Selecting Studies

Two reviewers will independently screen the titles and abstracts (when available) using broad inclusion/exclusion criteria. Studies will be classified as "include," "exclude," or "unsure." The full text of studies classed as "include" or "unsure" will be retrieved for full review. For the full-text review, two reviewers will independently assess eligibility using a standard form that outlines the inclusion and exclusion criteria. Disagreements will be resolved through consensus or third party adjudication. In particular, when uncertainty relates to our operational definitions of behavioral programs or community health settings (Appendix A) we will seek input from the TEP. We will pre-test the inclusion/exclusion form on a sample of studies.

All results of the search and selection process will be tracked in an EndNote® database (Thomson Reuters, New York, NY). We will use an internally developed online tool to manage the title and abstract screening and full-text review.

We will update the literature search concurrent with the peer-review process. Abstract and full-text screening will be performed as described above. Any studies suggested by Peer Reviewers or public comment respondents will also be assessed for eligibility. Eligible studies will be incorporated into the final report.

C. Data Abstraction and Data Management

Data will be abstracted directly into the Systematic Review Data Repository™ (SRDR; http://srdr.ahrq.gov/).[53] The data extraction forms will include elements relevant to the Key Questions, including population characteristics, study characteristics, descriptions of the

interventions and comparators, analytic details, and outcome data. Team members will pilot test the forms on several studies to ensure consistency in interpretation and application. The final data extraction form will be reviewed by the TEP to ensure that all items of clinical or research importance are captured.

For RCTs that were included in previous systematic reviews, one reviewer will extract available data from the previous review(s). Where additional data are required for the current review or for studies that were not included in previous systematic reviews, data from the primary studies will be extracted by a single reviewer. All data will be verified by a second reviewer for accuracy and completeness. Disagreements will be resolved by consensus or third-party adjudication, as needed. We will contact authors to clarify information reported in the papers, in particular regarding program components and delivery. Author contact will be by email (to the corresponding author of each study), with a primary contact attempt and up to two reminder emails. We anticipate that there will be multiple publications associated with many of the studies. Relevant data from reports referring to the same study will be extracted to a single data extraction form with clear information provided as to the source of the data.

For studies where it is unclear whether patients have T1DM or T2DM, we will develop decision rules based on mean age of study population, duration of diabetes, and treatment. Where both types of patients are included and results are not separated, if more that 75 percent are one type of diabetes we will include the study with that disease group. Where this information is not provided, we will include studies in both T1DM and T2DM and will conduct sensitivity analyses.

D. Assessment of Methodological Risk of Bias of Individual Studies

We will assess the risk of bias for the RCTs and NRCTs using the Cochrane Risk of Bias tool.[54] The tool examines seven domains of potential bias (sequence generation, concealment of allocation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and "other" sources of data), and a categorization of the overall risk of bias.

Each domain is rated having "low," "medium," or "high" risk of bias. We will assess blinding and incomplete outcome data separately for subjective outcomes (e.g., quality of life) and objective outcomes (e.g., HbA_{1C}). "Other" sources of bias will include comparability of groups at baseline and design-specific risks of bias.

The overall assessment is based on the responses to individual domains. If one or more individual domains has a high risk of bias, we will rate the overall score as high risk of bias. We will rate the overall risk of bias as low only if all components are assessed as having a low risk of bias. In all other situations, the overall risk of bias will be rated as medium.

We will assess the risk of bias for prospective cohort studies and controlled before-after studies using the Newcastle-Ottawa Scale (NOS).[55] This tool uses a star system to assess methodological quality across three categories: selection of participants, comparability of study groups, and ascertainment of the outcome of interest. A star rating system is used to indicate the quality of a study with a maximum assessment of nine. If a study scores eight or nine, we will rate the overall risk of bias as low. We will rate the overall risk as medium if the score is between five and seven. For scores below five, the overall risk of bias will be rated as high.

Two reviewers will independently assess the risk of bias of included studies. Discrepancies will be resolved through consensus or third-party adjudication, as needed.

E. Data Synthesis

We will analyze data separately for T1DM and T2DM. For each condition we will summarize the characteristics of included studies qualitatively and present important features of the study populations, study designs, interventions, comparators, outcomes, and results in summary tables.

Outcomes of interest were finalized with input from the TEP and are listed in the PICOTS. We will calculate mean differences or standardized mean differences for continuous variables, and risk ratios or odds ratios for dichotomous data. Results will be reported with accompanying 95 percent confidence intervals (95% CIs). We will analyze outcomes at different post-intervention time points. A priori we propose the following time points, but will seek input from the TEP to confirm their appropriateness: end of active intervention; <3 months; 3 to 6 months; >6 to 12 months; >12 months to 24 months; 2 to 5 years; >5 to 10 years; and >10 years.

For each outcome we will define a minimum clinically significant difference (MCSD; i.e., the smallest difference between groups that can be considered clinically significant). For $HbA1_c$, the MCSD is 0.4 percent (e.g., 7.6% vs. 8.0%), which is based on the value used by the U.S. Food and Drug Administration.[46] For quality of life measures, we will use an MCSD of one-half standard deviation (0.50 standard deviation) which has been shown to represent a universal, conservative estimate of a meaningful difference.[56, 57] For other outcomes MCSDs have not been established and we will seek input from the TEP.

Based on discussions with Key Informants, TEP members, and our own examination of previous systematic reviews, we anticipate considerable variation in behavioral programs and the comparators (e.g., usual care). To address this we will seek input from the TEP to define groups of interventions and comparators that are "sufficiently similar" for synthesis. The options for grouping them will be based on the various components and delivery methods (e.g., program intensity, method of communication, nature of community engagement). Discussions with the TEP will occur during the later stages of the review after data on the interventions have been extracted from included studies. To guide these discussions, TEP members will be given a list and description of components, delivery methods, duration, and so forth; they will not be given any data on outcome results.

For each comparison of interest, we will assess whether the eligible studies are sufficiently similar to be combined in a meta-analysis on the basis of study design, clinical heterogeneity of patient populations, interventions, comparators, outcomes, and time points. Various approaches to synthesizing the evidence are available including pairwise meta-analysis and methods that combine direct and indirect evidence (i.e., network meta-analysis or mixed treatment comparisons).[58-60] The summary effect from a meta-analysis of behavioral programs (collectively) versus usual care is meaningful as a first approach. To date most systematic reviews have focused on this high-level comparison. We anticipate that pairwise analyses will be used for Key Questions 1, 2, and 4. However, such an approach does not allow examination of the comparative effectiveness of different categories of behavioral programs based on their components or delivery methods. We anticipate that meta-regression or network meta-analyses will be used to answer Key Questions 3, 5, and 6. We will not pool the results of trials and observational studies in the same analysis.

Pairwise Meta-analysis

Direct pairwise meta-analyses will be conducted when more than two studies evaluate the same intervention and comparator and report the same outcome. We will use the random effects model[61-63] for all meta-analyses with Stata 11.2 and Excel 2010 software. We will calculate pooled mean differences, standardized mean differences, risk ratios or odds ratios with corresponding 95% CIs, as appropriate.

Sensitivity analyses (including leave-one-out analyses, assuming a fixed effects model, re-analyses after excluding a group of studies) may be undertaken if appropriate (e.g., in the presence of studies with outlying effect sizes, for studies rated as high risk of bias in some domains such as incomplete [<70%] outcome data). Heterogeneity will be considered substantial when the I^2 statistic is greater than 50 percent.[64] We will attempt to explore between-study heterogeneity using subgroup and meta-regression analyses (where there are at least 10 studies);[65] the decision to pool studies will not be based on statistical tests for heterogeneity.[66] Planned subgroup analyses are those listed in Key Questions 2 and 6.

Meta-regression analysis

We will perform a forward stepwise multiple meta-regression. The following covariates will be considered for inclusion in the model: program components, intensity, delivery mode, delivery personnel, tailoring, and community engagement. The final inclusion of covariates will be decided on the basis of the number of studies (minimum of 10 studies per covariate), information provided in the included studies, and input from the TEP (as discussed above).

Network Meta-analysis

For the network meta-analyses, the grouping of behavioral programs and comparators into categories will be decided on the basis of the information provided in the included studies and input from the TEP (as discussed above). As such, we cannot provide details about the network structure (e.g., number or composition of nodes) at this time except that they may each incorporate a combination of components and other factors (e.g. delivery mode). Based on the final grouping we will examine the network architecture and specify the analysis model.

In general, we expect that we will use a generalized linear model with an appropriate variance structure (e.g., binomial for binary outcomes; normal for continuous outcomes), link function (e.g., logit for binomial outcomes; identify for continuous outcomes), and prior distributions for each outcome of interest.[67] Models will be random effects and account for between-study heterogeneity for each comparison. If the data are sufficient, we will also evaluate the consistency of direct and indirect effects using established methods. All models will be fit using Bayesian methods.

We will obtain estimates of the treatment effects, as well as the rank probabilities for each treatment strategy (e.g., probability that a particular combination of components and delivery methods for a behavioral program is the "best program"). We will also evaluate the consistency of direct and indirect effects, whenever possible (i.e., for comparisons where both direct and indirect estimates are available).

F. Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes

We will follow the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[68] to evaluate the strength of evidence for Key Questions 1 and 2 for all health outcomes (i.e., quality of life, development of micro- and macrovascular complications, all-cause mortality) and selected behavioral and clinical outcomes (i.e., glycemic control, change in body composition, change in physical activity or fitness, and change in dietary or nutrient intake).

We will examine five core domains: study limitations or risk of bias, consistency, directness, precision, and reporting bias. We will also consider additional domains such as dose-response association, plausible confounding, and magnitude of effect. For all domains we will describe the logic and rationale for our judgments. We will define the *risk of bias* (low, medium, or high) on the basis of study design and methodological quality. We will rate *consistency* (consistent, inconsistent, unknown [if there is only one study]) by assessing the direction, magnitude, and statistical significance of all studies. We will assess *directness* of the evidence (direct or indirect) on the basis of the use of surrogate outcomes or the need for indirect comparisons. We will assess *precision* (precise or imprecise) on the basis of the degree of certainty surrounding the effect estimate. A precise estimate is one that allows for a clinically useful conclusion. *Reporting bias* (suspected or unsuspected) will be evaluated with respect to publication bias, selective outcome reporting bias, and selective analysis reporting bias. Publication bias will be assessed both visually and quantitatively using Egger's test.[69] For the selective reporting and analysis biases, we will evaluate the results across studies qualitatively on the basis of completeness of reporting for individual studies and reporting patterns across studies.

We will rate the body of evidence using four strength of evidence grades: high, moderate, low, and insufficient. These describe our level of confidence that the evidence reflects the true effect for the major comparisons of interest. The body of evidence will be graded independently by two reviewers; disagreements will be resolved through discussion, or third-party adjudication, as needed.

We will not grade the body of evidence for Key Questions 3 to 6. Key Question 4 assesses harms, which is a minor focus of this review. The other questions explore factors that may be associated with the effectiveness of behavioral programs using methods that combine direct and indirect evidence; methods to evaluate the body of evidence using this approach have not been fully developed.

G. Assessing Applicability

We will follow the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[68] to evaluate the applicability of the evidence to the delivery setting of interest (i.e., U.S. community health settings). We will consider important population characteristics, behavioral program characteristics, and delivery settings that may limit applicability of the findings. In this review, some factors that may limit the applicability include narrow eligibility criteria, components or delivery elements of behavioral programs that may not be feasible in some settings, and health system differences.

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VI. Definition of Terms

See Appendix A.

VII. Summary of Protocol Amendments

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

VIII. Review of Key Questions

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

IX. Key Informants

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

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

X. Technical Experts

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

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

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for Comparative Effectiveness Reviews and Technical Briefs, be published 3 months after the publication of the Evidence Report.

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

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest which cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA 290-2012-00013-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be

construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A: Definition of Terms

Operational Definitions

Behavioral program

An organized, multicomponent diabetes-specific program with repeated interactions by one or more trained individuals, with a duration of ≥4 weeks, to improve disease control and/or patient health outcomes, and consisting of at least one of: a) diabetes self-management education (DSME); b) a structured dietary intervention (related to any of weight loss, glycemic control, or reducing risk for complications) together with one or more additional components; or c) a structured exercise or physical activity intervention together with one or more additional components. Additional components for (b) and (c) above may include interventions related to: diet or physical activity; behavioral change (including but not limited to goal setting, problem solving, motivational interviewing, coping skills training, cognitive behavioral therapy strategies); relaxation or stress reduction; blood glucose regulation; medication adherence; or self-monitoring for diabetic complications (foot, eye and renal tests).

Interventions must include contact with those delivering the program, rather than sole reliance on "interactive behavior change technology" (e.g., patient-centered websites, automated telephone calls, DVDs, touch screen kiosks). While these tools show great promise for helping health systems meet the growing demand for diabetes management and support, they have been shown to be most effective when they support human contact.[35]

Below, we expand on specific elements of the above operational definition. They are presented in the order in which they appear in the definition.

> **Trained individual**. This can be an individual who has either received formal education and training in diabetes management and/or education, or has received some form of training to provide the specific program offered. There is no requirement to have a certain degree level or certification. This may include what is described as a lay health worker, "expert patient," "promotores" (Spanish term), or peer, as long as training is provided.
>
> **Repeated interaction**. There must be more than one interactive session—via face-to-face or indirect means—with the personnel providing the program.
>
> **Duration of ≥4 weeks**. The minimum duration of 4 weeks does not include post-intervention follow-up assessments for outcome ascertainment.
>
> **Diabetes self-management education.** A program will be considered DSME if the authors state that it meets the standards for DSME in the country in which the program is delivered (i.e., the program does not just cover a set of recommended topics of education). We also will include programs aiming to change patient (not provider) behaviors that are reported to: 1) include individualized assessment of needs/behaviors (performed by the provider and/or patient); 2) provide education on multiple self-care/management behaviors using interactive approaches (these may be combined with didactic and/or collaborative approaches); and 3) incorporate some form of behavior change strategy (e.g., goal setting) whereby patients are trained to make informed decisions to self-manage their disease.

Not all topics must be provided to all patients and not all patients will receive the same duration/number of sessions, that is, there may be some tailoring of topics and delivery based on the needs assessment.

Structured dietary intervention. Dietary interventions may related to weight loss (e.g., caloric restriction), glycemic control (e.g., carbohydrate counting, controlling glycemic index of foods), and/or reducing risk for complications or comorbidities (e.g., reduced saturated and trans fats, increased fiber). The intervention must include interactive education/training methods (i.e., must be more than the provision of information or advice) on more than one occasion. The diet composition may either be personalized to the patient or follow a predetermined composition (e.g., low calorie diet with <30 percent fat).

Structured physical activity intervention. Physical activity interventions must include either 1) personalized programs based on patient assessment and/or a patient's goals to train and facilitate behavior change, or 2) a structured intervention with a pre-determined program of activity (i.e., type, frequency, intensity and duration). The intervention must include interactive education/training methods (i.e., must be more than the provision of information or advice) on more than one occasion.

Activities that do not provide considerable energy expenditure (moderate intensity or more; goal to reach >40 percent aerobic capacity) or strength training potential will not be included (e.g., yoga, tai chi, stretching) but may be considered relaxation or stress reduction interventions.

Blood glucose regulation. This includes self-regulation of medication, diet, physical activity and so forth, based on results of blood glucose monitoring or awareness training. The intervention must consist of more than didactic teaching of blood glucose monitoring, teaching how to use pumps or other diabetes treatment technology, or teaching how to inject insulin. It may, for example, include practicing skills and problem solving on how to use the test results or to increase self-awareness to improve control through behaviors.

Relaxation or stress reduction. This includes interactive training or teaching related to meditation, yoga and other forms of non-aerobic or resistance training, or specific relaxation exercises or techniques (e.g., biofeedback). It may or may not include supervised practice.

Behavior change strategies. These include strategies to change behaviors but are not solely focused on emotional well-being. Strategies include, but are not limited to, motivational interviewing, coping skills training, cognitive behavioral therapy or techniques, problem-solving, goal setting, behavioral contracting, support groups, use of incentives or rewards, environmental change or barrier reduction, parent simulation, family therapy (related to problems with disease management behaviors), or anchored instruction. They must be directed at more than the single behavior in the structured diet or physical activity interventions. For example, a diet intervention with goal setting and motivational interviewing that are only related to diet will not be considered two separate interventions. The strategies do not have to be based on theory but, where they are, this will be noted during data extraction. They do not include interventions limited to screening or therapeutic counseling for mental health diagnoses or emotional issues, although general psychosocial aspects and adaptation to disease will be included.

Medication adherence. Any ongoing or intermittent intervention (i.e., not one-time provision of advice or information) that is intended to increase adherence to medication for hyperglycemia or risk factor reduction (e.g., lipid-lowering medications). This can be technology-based (e.g., text reminders via cell phone).

Self-monitoring for diabetic complications. Any ongoing or intermittent intervention (i.e., not one-time provision of advice or information) that is intended to increase self-monitoring or screening for micro- or macrovascular complications (e.g., training on home foot care, reminders to attend screening appointments). This can be technology-based (e.g., text reminders via cell phone).

Community health setting

A clinical practice setting with the primary purpose of providing health care to community-dwelling individuals (i.e., not hospital inpatients). Community health settings include ambulatory care clinics, outpatient clinics, primary care clinics, family physician clinics, and federally qualified health centers (i.e., Community Health Centers and Rural Health Centers). Programs that will be excluded are those delivered in inpatient settings and those offered in the community but without a link to a health clinic or center.

Comparators

Usual (or routine) care or standard care. These will be defined as they are reported in the studies and we will extract data on them in the same manner as for the interventions.

Active comparator. This includes any intervention not described as usual or standard care to which a behavioral program is compared. The intervention does not have to meet our definition of behavioral program (e.g., it could be a stand-alone diet intervention).

Appendix B: Very High Human Development Index countries

These countries meet the category of Very-high Human Development Index status, as per the United Nations Development Program.[47]

1. Norway
2. Australia
3. United States
4. Netherlands
5. Germany
6. New Zealand
7. Ireland
7. Sweden
9. Switzerland
10. Japan
11. Canada
12. Korea (Republic of)
13. Hong Kong, China (SAR)
13. Iceland
15. Denmark
16. Israel
17. Belgium
18. Austria
18. Singapore
20. France
21. Finland
21. Slovenia
23. Spain
24. Liechtenstein
25. Italy
26. Luxembourg
26. United Kingdom
28. Czech Republic
29. Greece
30. Brunei Darussalam

31. Cyprus
32. Malta
33. Andorra
33. Estonia
35. Slovakia
36. Qatar
37. Hungary
38. Barbados
39. Poland
40. Chile
41. Lithuania
41. United Arab Emirates
43. Portugal
44. Latvia
45. Argentina
46. Seychelles
47. Croatia

Appendix C: Search Strategy

This search strategy was developed for Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present –
It will be modified to the correct terminology for other databases.

1. exp Diabetes Mellitus/
2. exp hypoglycemia/
3. diabet*.mp.
4. (noninsulin depend* or non insulin depend* or insulin depend*).mp.
5. (T1DM or T2DM or IDDM or NIDDM).mp.
6. or/1-5
7. exp Diabetes Insipidus/
8. (diabet* adj3 (insipidus not mellitus)).mp.
9. or/7-8
10. 6 not 9
11. Behavior Therapy/
12. Blood Glucose Self-Monitoring/
13. Cognitive Therapy/
14. Community Health Centers/
15. Disease Management/
16. exp Exercise/ and (counsel* or intervention* or program* or train*).mp.
17. exp Exercise Therapy/
18. exp Directive Counseling/
19. Health Behavior/ and (counsel* or intervention* or program* or train*).mp.
20. Health Education/
21. Health Promotion/
22. exp Nutrition Therapy/
23. "Outcome Assessment (Health Care)"/
24. exp Patient Care Team/
25. exp Patient Compliance/
26. Patient Education as Topic/
27. Program Evaluation/
28. Relaxation Therapy/

29. Self Administration/
30. Self Medication/
31. Self Care/
32. Weight Loss/
33. (behavio?r adj2 therap*).mp.
34. (blood glucose adj2 monitor*).mp.
35. (cognitive adj2 therap*).mp.
36. (communit* adj2 (center* or centre*)).mp.
37. disease management.mp.
38. directive counsel*.mp.
39. ((behavio* or exercis* or diet* or fitness or life style* or lifestyle* or nutrition or physical activit* or problem solving or relax*) adj3 (counsel* or intervention* or program* or therap* or train* or treat*)).mp.
40. motivation* interview*.mp.
41. (self manag* or selfmanag* or self car* or selfcar*).mp.
42. or/11-41
43. 10 and 42
44. randomized controlled trial.pt.
45. controlled clinical trial.pt.
46. randomi?ed.ab.
47. placebo.ab.
48. drug therapy.fs.
49. randomly.ab.
50. trial.ab.
51. groups.ab.
52. or/44-51
53. exp animals/ not humans.sh.
54. 52 not 53
55. 43 and 54
56. cohort studies/
57. follow-up studies/
58. longitudinal studies/
59. prospective studies/
60. (control* adj5 (before adj2 after)).tw.
61. (cohort adj (study or studies)).tw.
62. cohort analy*.tw.
63. (follow up adj (study or studies)).tw.
64. longitudinal.tw.
65. (observational adj (study or studies)).tw.
66. (control* adj5 (pre* adj2 post*)).tw.
67. prospective.tw.
68. or/56-67
69. 43 and 68
70. 55 or 69
71. limit 70 to yr="1993-2014"
72. limit 71 to english language