Principal Investigators: Linda M Delahanty, MS, RD and Deborah J. Wexler MD MSc
Department /Division: Department of Medicine/ MGH Diabetes Center
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I. BACKGROUND AND SIGNIFICANCE

a. Historical background

The Center for Disease Control and Prevention (CDC) estimates that there are currently 29 million people with diabetes and 86 million people with pre-diabetes in the U.S. One in 10 Americans has diabetes now, and, if current trends continue, 1 in 3 Americans will have diabetes by 2050. This chronic disease significantly impacts both quality of life and rapidly rising national healthcare costs. The estimated cost of diabetes in the U.S. in 2012 was $245 billion with $176 billion in direct medical costs and $69 billion in indirect medical costs (disability, work loss, premature mortality). Medical expenses for people with diabetes are 2.3 times higher than for people without diabetes (1).

b. Previous clinical studies leading up to and supporting the proposed research

Studies such as the Diabetes Prevention Program (DPP), Look AHEAD, and the SHIELD study illustrate a gap in the quality of diabetes care and its effectiveness in improving long term medical outcomes in participants with pre-diabetes and type 2 diabetes (T2DM) (2-5). The DPP has demonstrated that a lifestyle intervention aimed at 7% weight loss and 150 minutes of weekly activity reduced the risk of developing diabetes by 58% over 2.8 years, compared to placebo (2). The Look AHEAD study has compared a program of diabetes support and education to a DPP-adapted lifestyle intervention aimed at 7-10% weight loss and 175 minutes of weekly activity in people with type 2 diabetes and demonstrated significantly greater weight loss (8.6% vs. 0.7%) and fitness after 1 year, resulting in improvements in glycemia, blood pressure, and lipids with simultaneous reductions in medications and costs to treat these conditions (3). Yet SHIELD showed that while participants with type 2 diabetes comprehend the severity of their disease, they lack the skills and decision-making support to make a significant lifestyle change (5). These studies highlight a number of behavioral and lifestyle interventions proven to have positive outcomes on patient quality of life, health measures, and healthcare costs (6,7). Many translation projects of the DPP have been implemented in people with prediabetes (8). However, to our knowledge, the Look AHEAD study, which has completed an 11-year efficacious lifestyle intervention program for participants with type 2 diabetes, has not yet been translated to the clinical practice setting.

We performed a pilot translation for this project called the IDOLc (Improving Diabetes Outcomes through Lifestyle change) study. We randomly assigned 57 MGH primary care participants with T2DM and BMI>25kg/m^2 who were taking at least one non-metformin, non-GLP1 diabetes medication to dietitian referral for medical nutrition therapy (RD-MNT) or a 19-week group lifestyle intervention adapted from the published Look AHEAD curriculum. Participants were 61 years old, 59% male, 32% non-white, and weighed 97 kg with mean HbA1c 8.2%. At 6 months, 46% of group lifestyle vs. 21% of RD-MNT lost >5% body weight (P=0.039), with mean weight loss 6.6 (SD 7.0) kg with group lifestyle and 2.1 (3.5) kg in RD-MNT (P=0.004). Eighty-two percent vs. 38% stopped or reduced diabetes medications

(P<0.001), and HbA1c improved by 0.70 (1.13) vs. 0.39 (1.51) in group lifestyle vs. RD-MNT (P=0.38), respectively. There was no difference in blood pressure or lipid levels between interventions; however, 14% in group lifestyle stopped a blood pressure medication vs. none in RD-MNT (P=0.046). Weight loss remained significantly greater in group lifestyle compared to RD-MNT at one year. Group lifestyle program cost was $578 per patient. Including changes in personnel and medication costs, the group lifestyle program cost $146 per patient more than RD-MNT.

c. Rationale behind the proposed research, and potential benefits to participants and/or society

Although it is tempting to directly translate successful research methods into clinical care without a demonstration that the methodology developed and implemented in a clinical trial is effective in a clinical setting, attempts to directly translate such programs can be both ineffective and expensive. The challenge of demonstration translational studies is to ensure that the interventions are practical and effective, and in turn easily applied to clinical practice. If the Look AHEAD lifestyle program proves to be effective in the proposed translation study, subsequent steps will include determining how to expand the program to other clinical settings more broadly. The goal of this study is to translate the lifestyle program proven in the two national clinical studies and the IDOLc pilot study to result in weight loss of 5-10%, increased activity to 175 minutes/week, decreased hemoglobin A1c (HbA1c), blood pressure, lipid levels, and reduced medications used to treat these conditions into usual care at MGH Community Health Centers and practices in communities affected by diabetes and obesity, and to determine the reach, cost-effectiveness, and sustainability of the program. Two intervention modalities, in person group or telephone conference call group, will be tested against referral to dietitians for individual medical nutrition therapy (MNT), the current standard of care.

This project is funded by the National Institutes of Diabetes and Digestive Diseases (NIDDK; grant R18 DK102737, under PAR 12-172, Translational Research to Improve Obesity and Diabetes Outcomes). In addition, it aligns with Partners and MGH's Diabetes Care Redesign initiative, which supported the pilot work under a Clinical Innovation Award to Linda Delahanty, and with MGH's Strategic Plan goal to address obesity in diabetes in the communities MGH serves.

While this project is being funded and conducted as research, it is a true translational effort meant to bridge the gap between what we know to be effective in clinical trials and what is possible in clinical settings. As such, it is a hybrid, with research staff at the MGH Diabetes Center acting as a "coordinating center" for central research activities such as screening and health center provider co-investigators trained and funded to carry out the work in usual care settings. Consequently, there are several novel aspects of this project.

Group conference call arm. Delivering this intervention via group conference call could potentially increase reach by having one central team manage participants across a health system, but it has not yet been attempted. Because this is a novel component, we propose to conduct structured interviews of eligible participants before launch to obtain feedback on the telephone modality and shape the potential use of 3-4 in-person sessions at the beginning of the telephone intervention to increase engagement. The group teleconference intervention will be conducted using "reserved conference calls" in which participants use their own phones to call into the session at a prearranged time using a toll-free number. Participants may apply for reimbursement for excess use of cell phone minutes. There is evidence to support the group telephone delivery

arm. In the SHINE study, the success of the group telephone delivery of the DPP lifestyle intervention program in achieving comparable weight losses to individual phone-delivered intervention at 1 year, and continued, sustained weight losses at 2 year follow up compared to weight regain in individual phone-delivered intervention in the SHINE study represents exciting innovation, effectiveness, and potential for reach but has not been tested using the Look AHEAD intervention (9). In addition, a large proportion of patient population at the community health centers lack internet access to enable implementation of other novel technologies, but 91% of Americans have telephones (10). The telephone intervention is evidence-based, lower cost, and more convenient for participants than in-person groups as they do not have to travel, increasing reach (11-14).

Role of the community health center primary care clinician leaders and staff. The community health center clinicians will provide logistical and medical oversight to the project, anchoring it at each community health center. Dr. Larocca and Dr. Wheeler cross-cover their colleagues as members of a practice group; Ms. Chase ANP APRN runs the diabetes programs at Chelsea health center, collaborating in the care of patients of all of the physicians and nurse practitioners at her practice (inclusion of a nurse practitioner medical leader in the REAL HEALTH-Diabetes project enhances generalizability and reach). They will promote the project to their colleagues and support recruitment efforts by co-signing recruitment letters (which will be created by Diabetes Center Research personnel). More importantly, they will be the supervising medical care providers for participants in the program. They will be trained by Dr. Wexler (Co-PI). Community health center staff will be funded by the REAL HEALTH-Diabetes grant for this work.

A final potential benefit to health center participants is the ability to offer the lifestyle program at no cost to its patients and to train staff in cutting edge lifestyle change strategies.

II. SPECIFIC AIMS

a. Objectives and hypotheses to be tested in the research project

The goal of this project is to translate the Look AHEAD intensive lifestyle intervention for type 2 diabetes and obesity into usual care at community health centers, comparing an in-person group program (IP), a telephone conference call (TCC) group program, and referral to medial nutrition therapy (MNT), the current standard of care.

Aim 1: To evaluate the effectiveness of the REAL HEALTH-Diabetes lifestyle change program comparing in-person (IP) group and telephone conference call (TCC) group intervention to individual dietitian referral for MNT.

H1a. Primary outcome. Weight loss: We hypothesize that the IP and TCC lifestyle groups will demonstrate greater weight loss than MNT at 6 months, and that the lifestyle group participants will have more sustained weight loss at 12, 24 and 36 months. The sample size of 210 provides 80% power to detect a 3.5% difference between any two groups adjusting for three group comparisons, 10% drop-out rate, and intraclass correlation (ICC=0.02).

H1b. Secondary outcomes. Medical outcomes: We hypothesize that compared to individual MNT, participants in the IP and TCC group interventions will maintain or improve HbA1c, blood pressure, and lipids from baseline with reduced medication use

(dose and cost) to treat these conditions, both at the end of the intensive intervention and at follow-up.

H1c. Behavioral and psychosocial outcomes: We hypothesize that compared to MNT, the lifestyle groups will have greater improvements from baseline in health behaviors and the patient-reported outcomes of self-efficacy and health-related quality of life.

Aim 2: To evaluate the reach, adoption, implementation fidelity, and maintenance of the two adapted Look AHEAD lifestyle change programs (IP and TCC) at the three community health centers, comparing factors across centers using the RE-AIM Model Dimension items checklist. We will use a mixed methods approach, first using structured interviews with participants who would be eligible to participate to inform the design of the telephonic intervention, then using provider surveys and participant structured interviews in years 2-4 to assess engagement and adoption by providers and compare responders and non-responders. Participant structured interviews will be conducted when the participant has completed the active intervention at year 2. Structured interviews will be administered by non-blinded study staff, and will follow the same procedures as described for the initial structured interviews that indicate the study design [see V. Study Procedures].We will also collect quantitative indicators of implementation.

Aim 3: To estimate the incremental cost per percentage point decrease in body weight of the implementation strategies assessed in this study compared to usual care. The focus of our analysis will be identifying short-term costs and health effects that are relevant to accountable care organizations and insurers with the goal of informing the design of payment contracts that ensure the adoption of effective and efficient diabetes care, with a particular focus on the tradeoffs between costs and effectiveness of telephone compared to in-person format.

III. SUBJECT SELECTION

a) Inclusion/exclusion criteria

Eligibility criteria for participation include:

- Diagnosis of type 2 diabetes
- Age 18 years or older
- Overweight or obese (BMI >25 kg/m^2) unless of Asian descent then BMI criterion is lowered to BMI > 23 kg/m^2
- HbA1c level 6.5<11.5%
- Systolic blood pressure (SBP) <160 mmHg, diastolic blood pressure (DBP) <100 mmHg
- Willing to lose 5-7% of body weight
- Willing to increase activity to at least 175 minutes/week
- Willing to commit to random assignment to either attend and participate in the lifestyle change program in person or on the telephone or be referred to Nutrition Services for medical nutrition therapy
- Stable health, with no severe comorbidities that might interfere with their ability to participate in a group intervention that includes increasing activity or decreasing calories, such as severe psychiatric illness or significant heart disease
- Ability to understand and communicate effectively in English or Spanish
- Willing to self-monitor blood glucose
- Willing to keep a food, exercise, and blood glucose diary

- Have a primary care physician at MGH Chelsea, Charlestown, Revere Health Centers, or any Partners affiliated practices or be willing to attend sessions, in-person or by phone, and have medications adjusted by a provider based at one of those health centers or the MGH Diabetes Center with communication to the referring primary care provider

Exclusion criteria include:

- Weight greater than 350 pounds
- Pregnant or planning pregnancy in the next year
- Currently seeing a dietitian (regular scheduled follow up appointments) or participating in a weight loss program and unwilling to stop
- Weight change of more than 3% body weight in the previous 1 month.
- Currently enrolled in another diabetes study
- Lack of availability of telephone
- Another member of the household is a study participant or a study staff member
- Overt hypo- or hyperthyroidism, defined as abnormal free T4, who have had thyroid medication adjustments in the last three months
- Long term use (in the 6 months prior to study entry) of medications likely to cause weight gain or inhibit weight loss (e.g. corticosteroids, with the exception of maximum dose of prednisone 10 mg or equivalent)
- Previous or planned gastric bypass
- History of cancer, other than non-melanoma skin cancer, that required therapy in the 5 years prior to randomization.

Participants must have (1) a medical need and willingness to lose at least 5% of body weight and (2) medical clearance to participate safely in the exercise component of the program which has a goal of increasing moderate intensity activity to at least 175 minutes per week. Each participant will be asked to keep a 1-week food, exercise and blood glucose record prior to meeting with the dietitian for a screening appointment. In order to participate in this study, participants must complete at least 5 of the 7 days of the food, exercise and blood glucose diary. Participants will have an intake interview with a dietitian to evaluate readiness to participate in a lifestyle intervention program. This interview will not determine eligibility but rather foster the ability of each patient to determine his/her own readiness to commit to the program and to help him/her decide whether to enroll or defer enrollment until another time when other competing priorities and identified barriers to successful participation are reduced.

b) Source of participants and recruitment methods

Participants will be primarily recruited from health center primary care practices. Participants also will be recruited from MGH primary care practices, MGH Diabetes Center, Newton-Wellesley Hospital and North Shore Medical Center. Others may participate as long as they have a primary care provider or treating provider who can approve their participation. Participants can be identified by their primary care physician, endocrinologist, nurse, or nurse practitioner. Patient registries will also be used to generate lists of potential participants for providers to review and identify eligible participants. Patient registries will also be used to generate lists of patients who have agreed to be directly contacted for research in a clinical care setting.

From this potential pool, we will recruit using the following steps:
1) Conduct an electronic chart review using the TopCare or RPDR diabetes list to verify eligibility criteria and PCP linkage. The current population of each health center is described in Table 1.

Table 1. Characteristics of community health center populations

	Racial/ethnic distribution of population			***Number with DM***	***Prevalence of DM***	***Target n to recruit***
	W	**H**	**AA**			
Charlestown	79%	9%	5%	1085	10%	~45
Chelsea	28%	56%	9%	2691	19%	~85
Revere	64%	16%	5%	2120	15%	~85

2) Obtain permission for initial contact from each potentially eligible patient's primary care or treating physician (PCP) [see "1. PCP Patient Recruitment Email"]. After permission received, study staff will check to see if participant is in the process of being contacted or in the process of enrolling in another study (GRADE) that is recruiting concurrently. If participant has already been contacted and is interested in GRADE, we will not contact.

3) Send an introductory letter [see Introductory Patient Letters] to PCP-approved participants and to patients who have agreed to be directly contacted for research describing the study and procedures to opt out of further contact. The introductory letter will be sent along with a brochure. In the brochure, potential subjects will be able to learn more about the study. The brochure will also include a study phone number and a study email address that participants can call or email to either decline further contact or to request that a study coordinator contact them.

4) If no answer is received after 7 days have passed, the potential research subject will be contacted by study staff to determine his/her willingness to participate.

5) If the subject is willing to participate, he/she will then undergo initial screening [see "3. Screening Phone Call Script"]. During this phone call, the study will be explained in further detail, subject questions will be answered, and an initial screening questionnaire to assess eligibility will be completed. Participants who remain eligible will be scheduled for an initial research visit and/or an introductory orientation session based on preference and mailed a 1-week food, exercise and blood glucose record, an appointment reminder letter, and an informed consent form [see "4. RV1 Appointment Reminder" and "5. Informed Consent Form"] (described below "SUBJECT ENROLLMENT"). We will also send them a link to a video about the study if they have access to email. (See **Figure 1** Recruitment flow).

6) Potential participants who see posters advertising the introductory orientation sessions at the health centers may also attend the informational session. They may participate in an in-person eligibility screen after the orientation or schedule a phone screening appointment at a later time to determine eligibility.

7) At the introductory orientation session, which will be held at their health center, participants will meet with the dietitian interventionist. The dietitian interventionist will describe the study and go through the informed consent document, provide instructions on completing the 1-week

food, activity, and blood glucose diary and answer questions from the group. In individual sessions following the group session, the dietitian will answer individual questions in private.

8) If the subject declines to participate or does not wish to answer the questions at any point during the phone or in-person screening, he/she will be thanked for his/her time and the call or session will be ended.

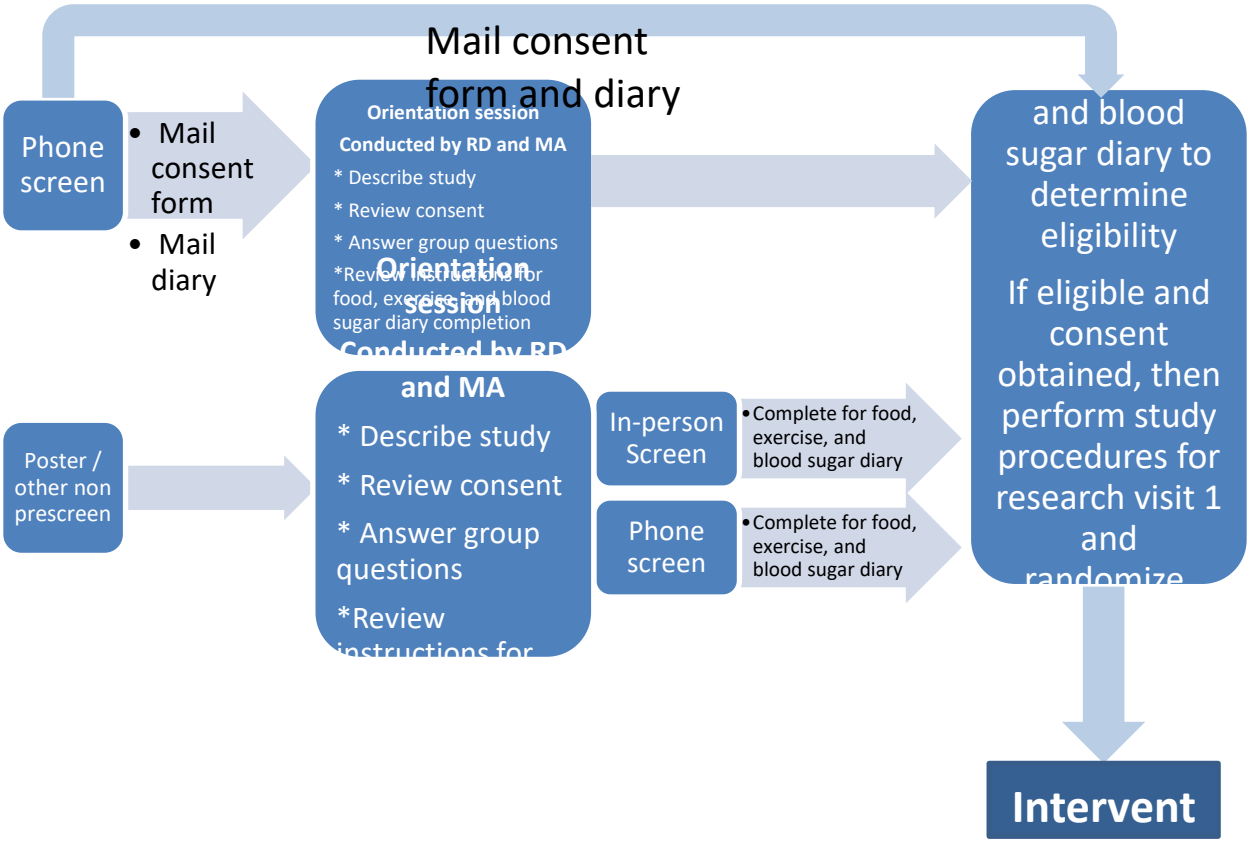

Figure 1. Recruitment flow

In addition to the primary recruitment method described above, we will welcome referrals from MGH Primary Care groups. We will leave pamphlets in the waiting rooms of the MGH Primary Care groups not based at the community health centers as long as participants are willing to attend sessions at the community health centers. We will leave pamphlets in the waiting rooms of the MGH Health Centers to inform patients about the study and put flyers up at approved places at MGH. We will also utilize the Broadcast MGH e-mail system to seek study volunteers if necessary [see "6. Email Broadcast"]. If a study volunteer contacted the Broadcast MGH e-mail system or other posting, we will contact their PCP to make sure it is safe for him or her to participate.

IV. SUBJECT ENROLLMENT

Before the intervention programs can begin, study staff will conduct a 6-week pilot study of the telephone intervention. Study staff will ask participants who participated in the Improving Diabetes Outcomes through Lifestyle Change (IDOLc) study and were randomized to the usual care arm and who consented to be recontacted, if they would like to participate.

For recruitment for structured interviews to be used to inform the design of the telephone intervention, we will send opt-out letters signed by physician or nurse practitioner co-investigators to 20 participants at each health center who meet eligibility criteria (drawn from the TopCare diabetes roster) letting them know they will receive a call to seek their opinion about a diabetes study via telephone interview [See "7. Structure Phone Interview Opt-out Letter"]. Those who do not opt out will receive a phone call. At the beginning of the phone call, verbal permission for the phone interview will be obtained [See "8. Structured Phone Interview]." We will obtain baseline demographic and clinical information on respondents from the electronic medical record.

a. Methods of enrollment for the clinical trial

Participants who call to express interest in the study, or who are contacted in follow up to the introductory letter to determine interest in participation, will first have a phone or in-person screening interview to explain the study protocol, answer questions, determine eligibility and willingness to continue the screening process. Those who qualify according to the phone screen will be mailed the consent form to review and emailed a brief video about the study [See 9. video link]. They will also receive a 1-week food, exercise, and blood glucose diary to complete. Study volunteers will be asked to write down what they eat and the portion size, the amount of exercise they do, and their blood glucose testing results each day for 1 week and bring this diary to the baseline visit, Research Visit 1 (RV1). Ability to keep this log predicts potential participants' readiness for lifestyle change and serves as an eligibility criterion for randomization.
In order to participate in this study, participants must complete at least 5 of the 7 days of the food, exercise and blood glucose diary. If a participant has not completed at least 5 of 7 days of the diary, then he or she will be offered a second chance to complete this behavioral task and will be rescheduled to complete Research Visit 1 (see below).

Potential volunteers may also attend the introductory sessions to learn about the study. In that case, they will subsequently meet with study staff or undergo phone or in-person screen and will take home the consent form to review. They will receive a brief video about the study if they have access to email. They will also receive a 1-week food, exercise, and blood glucose diary to complete for review at Research Visit 1. See Figure 1 for recruitment flow.

b. Procedure for obtaining informed consent

If a subject meets eligibility criteria for the study and expresses a desire to participate, a dietitian or trained member of the research staff will review the consent form and obtain written, informed consent from the subject. This process will occur at the beginning of the initial research visit before any study procedures are performed. At the time of informed consent, participants will receive an explanation of the randomization process so that they are aware that they may or may not be assigned to receive the in person or telephone group lifestyle intervention program or

referral to Nutrition Services. We will make it clear that the study participants can choose to leave the study at any point without providing a reason. We will emphasize that participants declining to enroll and those leaving the study midway will not be jeopardizing their usual clinical care in any way. Before giving consent, every volunteer will be asked if he or she would like to discuss any further questions with the study investigators via telephone.

c. Treatment assignment and randomization

The proposed study is a controlled clinical trial comparing three arms: in-person group lifestyle change program, telephone conference call lifestyle change program, or referral to individual medical nutrition therapy (MNT) for weight loss. The study schema is shown in **Figure 2.**

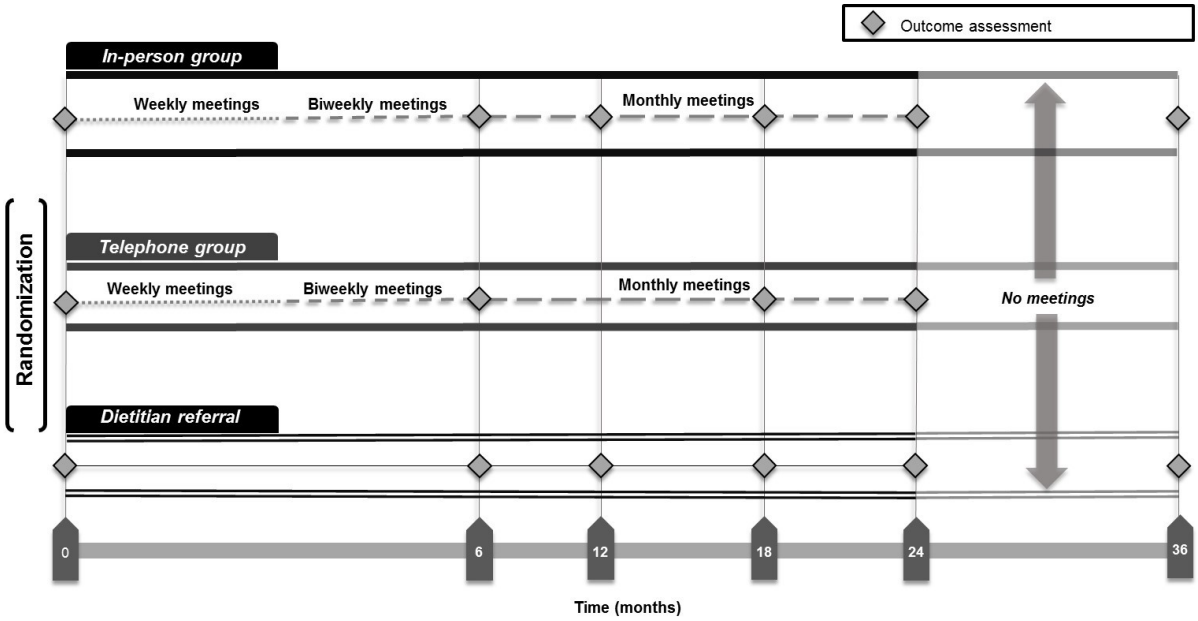

Figure 2. Study design

Lifestyle intervention participants may have up to 5 sessions of individual medical nutrition therapy (MNT); dietitian referral participants have MNT per usual care.

Participants will be randomly assigned to one of these three arms at the end of Research Visit 1 following informed consent, and data will be collected and compared at baseline and Research Visits at 6, 12, 24, and 36 months. For the group-based interventions, dietitians will deliver the adapted Look AHEAD lifestyle intervention. The goals of the diabetes lifestyle intervention program are weight loss of 5-10% of initial body weight and increased activity levels to 175 minutes/week of moderate intensity physical activity over 6 months. The adapted Look AHEAD session materials used for the pilot program are culturally sensitive and have a Flesch Reading Ease score of 74.0 and a Flesch-Kincaid grade level of 5.3. We will have Spanish versions (previously used in Look AHEAD) of all session materials available for those who prefer to read in Spanish. Materials do not focus on foods specific to individual cultures but rather build skills that participants apply to their food preferences. Accomplishment of these goals is expected to lead to improvements in weight, HbA1c, blood pressure, and lipid levels and reductions in medications used to treat these conditions.

The REAL HEALTH-Diabetes program is adapted from the published Look AHEAD program and will include 19 group sessions offered over a six-month period. The first 14 sessions will be delivered weekly and the next 5 sessions biweekly. In the subsequent 18 months,

group sessions will be delivered monthly from 6-24 months. In addition, participants will be offered up to 5 individual MNT sessions over the 2 year intervention period. At these individual visits, dietitians will address diabetes-related issues and discuss tailored goals and behaviors, based on the Look AHEAD model. Dietitians will provide ongoing feedback to participants' own PCPs about patient progress toward goals and will encourage PCPs to reinforce weight loss strategies with their patients. Each group will contain up to 10 participants with type 2 diabetes and will last 1-1.5 hours. The program curriculum focuses on nutrition, activity, and behavioral topics and incorporates the use of meal replacements for the first 4-16 weeks to enhance weight loss success. The program fosters the development of knowledge and lifestyle skills to change diet and exercise habits through use of goal-setting, problem-solving, stimulus control and other behavioral techniques that have resulted in weight loss, weight maintenance and improved glycemic control (7).

In addition to the teaching component, participants who are taking insulin or medications that can cause hypoglycemia will self-monitor blood glucose levels at least 2 times per day and submit self-monitoring records for review each week, either by delivering them at the in-person sessions or by mailing, faxing, or emailing them to the study team. Patients on oral hypoglycemics who are not adjusting medications based on blood sugar will be instructed to do targeted monitoring to determine the effects of exercise and meals on blood glucose. The study provider at each health center will review BG records and make any needed adjustments to insulin or medication doses according to a provided algorithm adapted from Look AHEAD and defined in the Manual of Operations on a weekly basis to maintain glycemic control and prevent hypoglycemia as participants lose weight during the initial 14 weeks and then biweekly and monthly to coincide with the session schedule. This approach was effective and safe in Look AHEAD and in our pilot IDOLc study.

This program is distinct from currently available diabetes group courses based in many of the primary care practices because it focuses on developing skills for weight loss and increased activity as a means to improve glycemic control. The ultimate goal is to translate this program for delivery within the current diabetes self-management education (DSME) group course framework and, ultimately, within the context of an accountable care organization, either in person or by phone to increase reach.

A trained member of the study staff will provide MNT referral participants with an educational handout [see "11. Educational handout"] emphasizing that modest weight loss (5 – 10%) via caloric restriction and gradual adoption of moderate increases in daily physical activity (equivalent to brisk walking for 30 minutes daily) is safe and effective in managing diabetes and schedule them for an appointment with a dietitian from Nutrition Services for follow up. As per usual care procedures, Nutrition Services will bill each participant's health insurer for dietitian services received and participants assigned to usual care will be responsible for the payment of any deductibles and co-payments required by their insurer for this routine care.

If participants have any questions about costs, we will arrange for them to speak with the study doctors and study staff and if necessary someone in Patient Financial Services about these costs.

V. STUDY PROCEDURES

For the structured interview, trained study staff will interview the respondent over the telephone to obtain feedback on the design of the telephone intervention after obtaining verbal

consent, including consent for audiotaping of the interview. The interview will last 15-20 minutes. Questions will be both open and closed ended. Interviews will be audiotaped and responses will be coded using NVivo software. We will interview at least 10 and up to 20 subjects from each health center for a total of up to 60 interviews in English. Of this, we will seek half men and half women, half 65 or younger and half older than 65, and at least 10 Spanish speaking participants, with the remaining 20 distributed across racial and ethnic groups. Once we reach saturation on response items, we will close the interview portion of the project and establish the definitive protocol for the telephone conference call arm. Each respondent will receive $25 for participation (See "8. Structured Interview Script"). Prior to starting both group lifestyle programs in Spanish, we will conduct another 10 structured interviews in Spanish.

For the 6-week pilot study:

After study staff have contacted and discussed the pilot program with the potential participants, those who agree to participate will be mailed a consent form to sign and send back. Participants will review the consent form over the telephone with study staff when signing. A copy of the signed consent will be mailed to the participant. Participants will be informed of how to call in for the telephone conferences as well as the schedule for the 6-week program. The participants will have the same materials and lessons that are described above. Participants will also be asked to maintain a 7-day food, exercise, and blood glucose diary during the 6 weeks with study MD review of blood sugars. Medication adjustments will be made, if necessary, with changes being relayed to the participant and their physician (see above).

For the randomized controlled trial:

1. Initial Research Visit (RV1). Research Visit 1 will last about 2 hours. Participants will need to fast from midnight until the morning of the visit and wait until after their blood samples are drawn to take any diabetes medications [see "4. RV1 Appointment Reminder"]. The participants will be met by a member of the study team at their health center. At this meeting, informed consent will be obtained by a trained member of the research staff. Participants will have the option of speaking with a study MD, RN, or NP if they still have questions after reviewing the consent form with other study members. After enrolling in the study, participants will be asked to provide their contact information [see "12. Contact Information Sheet"] so they can be reached by the study staff throughout the study should they need to reschedule or remind participants about an appointment. Next, participants will be asked to provide a blood sample of 6 cc taken by trained staff. Subject's blood pressure will be taken resting and will be measured in duplicate using an automated device. Height and weight will be measured and then entered into the electronic medical record to derive BMI values. Once blood samples, blood pressure, and height and weight are recorded, participants can take their diabetes medication(s) and will be provided a nutrition bar. Participants will be asked to complete an intake interview with a dietitian (that includes review of the 1-week food, exercise and blood glucose diary) to assess readiness for participation in a lifestyle intervention program [see "13. Readiness Assessment Questionnaires]. They will also be asked to complete a packet of self-administered study questionnaires to evaluate weight loss history, health behaviors, self-efficacy, measures of self-determination, depression, literacy and numeracy, food insecurity, health-related quality-of-life and patient satisfaction with quality of care and to obtain demographic information [see "14. Baseline and Follow-up Questionnaires].

Participants will then be randomly assigned to either dietitian referral for medical nutrition therapy (MNT) or the in-person or telephone group lifestyle intervention program and be assigned study ID numbers. After randomization, participants will be given a scale to self-monitor their weights. Those who are randomly assigned to the MNT arm will receive an educational handout to emphasize that modest weight loss (5 – 10%) via caloric restriction and gradual adoption of moderate increases in daily physical activity (equivalent to brisk walking for 30 minutes daily) is safe and effective in managing diabetes. They will then be referred to Nutrition Services for follow up and be given an appointment card with the time, date and location of their first Nutrition Service appointment.

Participants assigned to one of the group lifestyle intervention arms will receive information about the dates, times and location so that they can plan their attendance at the program [see "15. Look AHEAD's group lifestyle intervention materials]. Upon completion of the visit, participants will have their parking validated, if applicable, or transportation costs reimbursed.

Participants assigned to the telephone conference call arm receive a binder of materials. The binder will contain

1. Directions for accessing the telephone conference call;
2. Handout on recognition and management of hypoglycemia (see safety monitoring);
3. Handout on monitoring blood pressure with weight loss (see safety monitoring);
4. The program materials for sessions 1-19.

The structured interviews will inform the design of the group conference call format.

Survey instruments: Patients will complete survey instruments on their own on paper or via RedCap web interface at the clinic or from a remote location. The instruments will evaluate health behaviors, self-efficacy, measures of self-determination, depression, literacy and numeracy, food insecurity, health-related quality-of-life and patient satisfaction with quality of care [see "14. Baseline and Follow-up Questionnaires]. Instruments that have validated Spanish versions will be administered in Spanish. Study staff will be available to assist with translation of untranslated instruments and with completion for participants of low literacy or with visual impairment that prevents self-completion.

Blood Samples: Blood samples will be obtained to measure HbA1c and fasting lipids, tests that are required in usual care of people with type 2 diabetes. They will be obtained by health center phlebotomists at the health center clinical laboratory. Participants and providers will be notified that these will be obtained and billed to participants' insurance at each research visit (0, 6, 12, 24, and 36 months), since this schedule is less than the recommended frequency for obtaining these results in usual care. Drawing them through the usual channels allows automatic entry into internal tracking systems and reduces workload on practices that may otherwise need to track patients down to meet internal performance framework reporting metrics. Data may be abstracted from clinical visits if that participant is unable to complete fasting labs at a research visit. Any missing data (second blood pressure, second weight, lipid panel) abstracted from clinical data will not be considered a deviation. Participants who are unable to complete their outcome visit in-person due to COVID-19 will have the option to email a picture of their weight, showing their feet on the scale. Participants will use send secure email unless it is documented that they opted out of send secure email at RV1. Instructions on how to measure weight will be sent to participants. For participants who have opted out of email communication, data will be

abstracted from a clinical visit as described above. The self-reported weights will be analyzed separately with sensitivity analyses. This alternative process for collecting weight data will not be considered a deviation.

Blood pressure and weight will be measured and entered by study staff into coded fields in the electronic medical record. This, too, reflects the integration of the program into usual care, and facilitates tracking of these metrics for internal performance framework reporting.

All clinical data will additionally be entered into study databases using RedCap. Survey instrument responses will be entered into RedCap.

2. Research Visits (RV2, 3, 4 and 5).
Research Visits 2-5 will last about 2 hours. Participants will be scheduled for a research visit 6, 12, 24, and 36 months after the initiation of the intervention with a $\pm$ 2 month visit window. Any clinical data or questionnaires that may be collected outside of the window will count for the closest visit window, with the date of data collection documented. The visit may coincide with a usual care appointment. They will receive an appointment reminder letter [see "16. RV2 Appointment Reminder Intervention and Usual Care"]. Participants will need to fast from midnight until the morning of the visit and wait until after their blood samples are drawn to take any diabetes medications. The participants will be met by a member of the study team at their health center. Participants will be asked to provide a blood sample of 6 cc taken by trained phlebotomist in the health center clinical laboratory. Subject's blood pressure will be taken resting and will be measured in duplicate using an automated device. Height and weight will be measured and then entered into the electronic medical record to derive BMI values. Once blood samples, blood pressure and height and weight are taken and processed as outlined above, participants may take their diabetes medication(s) and will be provided a nutrition bar. Then they will be asked to complete self-administered study questionnaires on paper or via RedCap as outlined above. Any changes in medication doses for glycemic control, blood pressure and lipid management will be reviewed and confirmed by cross checking in electronic medical record.

Research visits will be conducted by a health center medical assistant, RN, or LPN who has received CITI certification in Human Subjects research and has been trained and will be funded by the REAL HEALTH-Diabetes study for this purpose. Central study personnel will support health center staff in training and assessment. Health center staff will also be supervised by the health center-based clinician co-investigators.

Participant compensation. Study participants will receive payment of $25 for completing follow up assessments at 6 months and 1 year, $50 at 2 years, and $100 at 3 years to promote retention for outcome assessment.

Study outcomes/ data to be collected

AIM 1 Outcomes and Assessment Protocol
Measures at baseline and follow up assessments
1. Weight/BMI measured in light street clothes (without shoes) using a single calibrated scale at each health center. Height measured using a stadiometer at baseline only.

2. Resting blood pressure measured using a calibrated sphygmomanometer with appropriate cuff sizes based on arm circumference. Average of 2 seated readings at 1 min intervals following a 5 min period of rest.
3. Laboratory: Hemoglobin A1c (HbA1c) and fasting lipids will be drawn on site and run in the MGH clinical laboratories. HbA1c will be measured by the MGH clinical laboratory.
4. Medications and doses prescribed for diabetes, blood pressure and lipid management will be captured by chart review and phone interview at each outcome assessment as well as at 18 months.
5. Health-related quality of life: EQ-5D, a 5-item instrument that is sensitive to health-related quality of life in diabetes, including changes in BMI (15). It measures 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression at 3 levels, "no health problems," "moderate health problems," and "extreme health problems." In addition, there is a 20 cm visual analog scale for self-assessment of current overall health (16).
6. Diabetes-specific quality of life: Diabetes specific quality-of-life will be measured using the Problem Areas In Diabetes (PAID) scale, a 20-item self-report measure of diabetes-related emotional distress that has shown high internal reliability, sensitivity to change and clinical utility (17). The PAID has been rescaled since its first introduction for greater ease of interpretation and is scored from 0 to 100, with higher scores indicating greater emotional distress (18).
7. Depression: Measured using the Patient Health Questionnaire 8 (leaving out the question on suicidality as is common in research protocols (19). MGH primary care practices are currently using the PHQ2 and 9 for depression screening. Participants found to be severely depressed will be connected to mental health services.
8. Health behavior: Dietary behavior will be assessed using the Fat-Related Diet Questionnaire (20,21) and the Restraint subscale of Dutch Eating Behavior Questionnaire which rates frequency of using ten different restraint behaviors (22). Two questions from the Dietary Screener Questionnaire (DSQ) used in the NHANES 2009-2010 series, will be used to assess intake of sweetened beverages (23). Activity behavior will be assessed by the Paffenbarger Physical Activity Survey and self-reported minutes of physical activity (24).
9. Self-determination theory measures:
a. Autonomy: Treatment Self-Regulation Questionnaire (TSRQ). An 18-item tool that measures reasons for engaging in a particular behavior (e.g., diet) to assess the degree to which the individual holds autonomous reasons for this behavior, i.e., a sense of choice vs. a need to comply will be administered at baseline, 6, 24, and 36 month visits (25). It has been shown to predict better attendance, greater weight loss, greater maintenance of weight loss and better exercise regimen, as well as greater adherence and health behavior change for other behaviors (e.g., smoking, medication) (26-29).
Health Care Climate Questionnaire (HCCQ). A 15-item measure that assesses the degree to which respondents find their clinical and weight loss teams to be supportive of their autonomy vs. controlling will be administered at 6 month and 24 month visits. For example, do providers appear to take the patient's perspective, minimize control, and foster flexibility and choice, promoting feelings of respondent competence and motivation to change behavior (25).
b. Competence/self-efficacy will be measured using the Diet Self-Efficacy scale, a 16-item scale scored from 1 to 5 that measures confidence in one's ability to adopt healthy dietary behaviors and the Exercise Self-Efficacy scale, a 5-item scale scored from 1 to 7 that measures confidence

in one's ability to persist with exercise in situations that involve potential barriers, e.g., negative affect and time constraints (30,31).

c. Relatedness. The construct of relatedness from self-determination theory will be measured using the Social Support for Healthy Behaviors scale, a 22-item scale that assesses perceived social support from family and friends that is specific to healthy eating and exercise behaviors, with good test-retest and internal consistency reliabilities and construct validity (32).

10. Health literacy and numeracy will be measured with the NVS (newest vital sign), a 6-item food-label based assessment validated in English and Spanish, at baseline only (33).

11. Food insecurity will be measured at baseline, 12 months, 24 months and 36 months with the U.S. Household Food Security Survey Module: Six-Item Short Form Economic Research Service, USDA, available in English and Spanish (34).

11. Medication adherence will be measured at baseline, 6 months, 12 months, 24 months, and 36 months using the 8-item Morisky Medication Adherence Scale (35).

12. Satisfaction with care will be measured using survey instruments developed for the IDOLc pilot which were adapted for pertinence from the Diabetes Quality of Life Measure (DQOL) (36) and satisfaction surveys used in previous lifestyle intervention research (37). In addition, participants will be asked questions at the end of the 6-month intervention period and at 2 years at the end of the intervention period to rate their level of satisfaction with the program and their interactions during the visits with the dietitian.

13. ***Other Diabetes Care and Costs*** will be assessed at 6 months, 12 months, 18 months, and 24 months to determine the cost-effectiveness of all arms of the study.

Patient-reported outcomes will be completed by participants in a quiet room at the time of outcome assessments either on paper or via RedCap web interface. Every effort will be made to ensure completion at the time of the research visit, but if this is not possible participants may complete assessments later. Outcomes assessors will be trained to review and administer these instruments and to help participants when necessary. Outcomes assessors will be blinded to study arm. Participants will not be eligible for compensation until all elements of a research visit are complete.

These questionnaires typically take about 40-50 minutes to complete.

Table 2. Schedule of questionnaire administration

Questionnaires (S/I)*	RV1 (0 Mos)	RV2 (6 Mos)	RV3 (12 Mos)	18 Mos	RV4 (24 Mos)	RV5 (36 Mos)
Literacy Questionnaire (I)	X					
Demographic information (S)	X					
Medication and Health Service Utilization (I)	X	X	X	X	X	X
Contact Information (S)	X	X	X		X	X
Health History (S)	X				X	X
Weight History (S)	X					
Treatment Self-Regulation Questionnaire (S)	X	X			X	X
Exercise Self-efficacy Scale (S)	X	X	X		X	X
Diet Self-efficacy Scale (S)	X	X	X		X	X

Paffenbarger (S)	X	X	X		X	X
Fat-Related Diet Behavior (S)	X	X	X		X	X
Program Satisfaction (S)		X			X	
Satisfaction Surveys (S)	X	X	X		X	X
Morisky Medication Adherence (S)	X	X	X		X	X
EQ-5D (S)	X	X	X		X	X
Problem Areas in Diabetes (PAID) Scale (S)	X	X	X		X	X
Restraint Subscale of the Dutch Eating Behavior Questionnaire (S)	X	X	X		X	X
PHQ-8 (S)	X	X	X		X	X
Social Support for Healthy Behaviors (S)	X	X	X		X	X
Food Insecurity (S)	X		X		X	X
Health Care Climate Questionnaire (S)		X			X	X
Dietitian Intake Questionnaire (I)	X					
RV4 Structured Exit Interview (I)					X	
Other Diabetes Related Care and Costs Questionnaire (S)		X	X	X	X	
PCP Questionnaire (S)			X		X	

*(S) Self-administered, (I) Interviewer-administered

X = Questionnaire being administered at visit

Aim 2: Implementation analysis

We have designed and will evaluate the project according to the RE-AIM model. The RE-AIM framework includes participant (Reach, Effectiveness, Maintenance) and organization level (Adoption, Implementation, Maintenance) elements to capture the full effect of not only a program's efficacy but also its broader impact and sustainability.

Variables to be collected to gauge overall efficacy of REAL HEALTH-Diabetes are listed after the corresponding RE-AIM element of interest. This section is modeled after a framework proposed in "RE-AIM for Program Planning" by Belza B. et al. (http://www.prc-han.org/docs/RE-AIM_issue_brief.pdf) (38).

Reach

- What percent of your target population (those who are intended to benefit from your program) will participate in the program?
    - Many patients with diabetes are not ready or able to participate in this program. We estimate a maximal eligibility rate of 20% of the population at a given time. This will be the denominator by which we calculate reach.
- Does your program reach those most in need? Are participants representative of the targeted population?
    - Measure: Participation rate at each center and within R/E groups

Effectiveness—see Aim 1.

- Weight loss
- Medication reduction
- Behavior change
- HRQoL and diabetes–specific quality-of-life
- Cost—see Aim 3
- Participation (attendance)

Adoption—Goal: to ensure that the program will be adopted by those settings that have connections to people in the target population. We will achieve this using the central support and study design aiming for the following: 1. Easy-to-understand program communications and materials. 2. Compatibility with organizational values—offering lifestyle change programs for diabetes and obesity is a priority at MGH and its community health centers. 3. Low disruption to organization—the program has been designed to minimally impact general workflow while fitting into the patient-centered medical home model. 4. Minimal start-up time, given the complexity of the intervention. Training components will be delivered in segments to the appropriate audience. 5. Observable results so everyone can see the benefits. We will report on program metrics (though not efficacy outcomes) in real time.

Measures of adoption will be:

- Proportion of PCPs who refer patients
- Structured interview of providers, in years 2-3 of the project. Provider program evaluation questions have been adapted from the SHINE study and from the Provider Questionnaire used in the IDEATel telemedicine study (39). [See "17. Provider questionnaire"].
- Willingness of health centers and MGH to continue program

Implementation—Goal: to ensure that the program is delivered with fidelity

Measures

- Are different components delivered as intended?
    - Measure: Audiotape sessions
- Can different levels of staff implement the program successfully?
    - Measure: Data fidelity/protocol fidelity
- What parts of the program are flexible or adaptable, without decreasing program efficacy?
- Cost of implementation—see cost analysis section

Maintenance occurs on the individual and organizational level.

- Individual: Do participants stay engaged and sustain positive behavior changes over time? Does the program produce lasting effects (1-2 years or longer) at the individual level?
    - Measure: 3-year outcome measurement, with focus group or structured interview comparing sustainers vs. non sustainers, to be developed in years 4-5 of the project and submitted for IRB approval at that time.
- Organization: How is the program incorporated so it is delivered over the long term? Can organizations sustain the program over time—even after initial funding and enthusiasm?
    - Strategies for consideration in years 4-5 of the project

        - Ensure that existing staff have the skills to continue the program; incorporate these skills into job descriptions of designated MAs and providers.
        - Ensure that supervisors and others know how to monitor quality and fidelity and can successfully guide the program.
        - Ensure that organizational leadership, including board members, know about the program and endorse its value to the organization.
        - Ensure that partners are engaged and understand the importance of their various contributions.
        - Reduce level of resources required. Provide incentives and policy supports.
        - Continue contact and technical assistance to participating organizations or settings.
        - Regularly meet with organizational staff, leaders, and participants to learn what they like and what works. Make changes as feasible, attending to fidelity.
        - Monitor which organizations continue the program and which do not. Explore what differentiates these two groups and see if you can do something that would help with sustainability.
    - Measure—continuation of program at each site in out years.

AIM 3: To estimate the incremental cost per percentage point decrease in body weight of the group treatment models assessed in this study compared to dietitian-delivered MNT. Our approach will incorporate the costs and benefits of each intervention, including training and implementation costs, staff and participant time, and the savings from reduced medication use. We will also examine differences in numbers of visits and hospitalization rates for all models as exploratory analyses. We will measure health utility to facilitate subsequent cost-effectiveness analysis comparing the care models.

Evaluation of implementation costs. The focus of our analysis will be identifying short-term costs and health effects that are relevant to ACOs and insurers with the goal of informing the design of payment contracts that align financial incentives ensuring the adoption of effective and efficient diabetes care. At the same time, we will collect a broad range of cost data, including costs that fall exclusively to participants, to build a foundation for future studies of long-term cost-effectiveness taking a societal perspective.

Primary data will be collected for the three study arms. Each study arm has several cost components. These include the **cost of personnel time**, defined by the differential use of time physicians, nurse practitioners, dietitians, and medical assistants will spend on the project, as well as the **cost of services provided**, including medication utilization, health care utilization not included in clinician time/reimbursement, program materials, and office space. We will also track patient time use, as well as telephone minute, transportation, and parking costs to understand the relative financial burden each strategy places on participants.

***Cost of personnel time*.** Provider time use will be monitored using sessions delivered and self-report augmented by limited direct observation. Total time devoted to training, outreach, session delivery, and patient contact will be estimated by multiplying the total number of times a task was performed by the average time devoted to the task. Dietitian referral time will be counted by review of completed visit notes which document time. We will assess the total cost of time, including time spent on record review and between-visit contact, if any, based on the value of each person's time in hourly wages (salary plus benefits). Direct observation will determine how

much time is spent on coordination tasks. Patient time use will be measured using survey assessments and valued using labor statistics data adjusted by age and residence.
***Cost of services provided*.** Cost of services will be estimated using existing data sources, including inpatient and outpatient billing and reimbursement data, patient self-reports (prescriptions filled), and study data on sessions attended. We will compare the total costs in each arm over the study period.

Personnel time, program materials, office space, patient telephone minutes, and parking costs will be derived from study records.

Patient travel costs and telephone minute costs will be collected at RV2, 3, and 4 [see "18. Patient Travel and Phone Use"].

Dose, type, fill rate, and co-pays for medications and use of health care services will be collected by telephone every 6 months until year 3 (RV5) using pre-populated forms mailed to the participant 1 week before the scheduled call to facilitate accurate medication collection. Participants will be given a calendar to track health service utilization with a particular focus on emergency room visits and hospital admissions outside the Partners system, as these cannot be tracked administratively [See "19. Medication and Health Service Utilization"]. Participants will receive postcard reminders at 3 months to remind them to keep their health service utilization calendar record.

VI. BIOSTATISTICAL ANALYSIS

a. Specific data variables (e.g. data collection sheets)

A list of the variables collected via medical chart review, survey instruments (from screening interview, research visits, RE-AIM components, and cost estimates) are listed in the protocol appendix [see "20. Data variables list"]

b. Study outcomes

All outcomes will be assessed at baseline (prior to randomization) and at 6, 12, 24 and 36 month follow up after completion of the lifestyle intervention program. Primary study endpoint will be change in weight from 0 to 6 months after enrollment in the intervention, with secondary outcomes being weight change at other timepoints, glycemia (HbA1c), blood pressure, and lipids and medication prescriptions (number, dose and cost) for these conditions as well as health behavior, self-efficacy, measures of self-determination, depression, food insecurity, health related quality-of-life, patient satisfaction, and cost.

c. Statistical methods

For all continuous outcomes (% weight loss, HbA1c, blood pressure, fasting lipid levels, self-efficacy, health related quality-of-life score, and satisfaction with care), we will compare changes from baseline among groups using a mixed effects model that includes group, follow-up period (6 months, 1 year, 2 years, 3 years), group and period interaction, baseline weight, and community health center. The follow-up period will be modeled as a categorical variable;

average changes at each time point by treatment group as well as the overall change (with all follow-up visits included in the model) will be presented. Since outcomes from participants within the same counseling group might be correlated, all analyses will take into account the clustering effect in the mixed effect models. With three treatment groups, multiple comparisons adjustment will be applied to reduce the inflation of type I error rate. Randomization codes will be generated for each health center and group assignment will occur in a 1:1:1 ratio within each site stratified by sex.

d. Power analysis

Aim 1:

Sample size/power calculation.

H1a. IDOLc preliminary data showed 6.7% mean weight loss at 6 months in the lifestyle intervention group, which was 4.1% greater than the MNT group. The standard deviation of percent weight loss in the pilot cohort was 5.5. Our aim is to detect a clinically meaningful 3.5% difference between any of the two study groups (where weight maintenance is defined as weight change <3%[71]). We use the conservative Bonferroni method to adjust for 3-arm multiple comparisons, which reduces the two-sided significance level to 0.0167 (0.05/3). Assuming a SD of 5.5%, the study will need an effective sample size of 54 per arm to detect a 3.5% difference with 80% power. We assume a conservative intraclass correlation coefficient of 0.02 within each counseling group, which translates into an inflation factor of 1.2, and 10% drop-out rate based on our prior results and the fact that participants receive primary care at study sites. The final sample size will be 210, 70 per arm.

Further analyses:

H1b. We hypothesize that participants in the group interventions will maintain or improve HbA1c, blood pressure, and LDL with reduced medication use (dose and cost) to treat these conditions, both at the end of the intensive intervention and at follow-up, compared to the MNT arm. Medication reduction is an outcome that is meaningful to participants and reduces costs to payors (40,41). Based on our preliminary data, in which 61% of the lifestyle group had improved HbA1c on less medication compared to 31% in the MNT group, we have 81% power to detect a difference of 33% with an effective sample size of 54 per group, adjusting for the 3-arm comparison. We will perform further analyses employing number of medications, insulin use, insulin doses, and Diabetes Medication System Questionnaire, PAM-D or similar weights to model differences in medication intensity among groups (42,43).

H1c. Using the standard deviation estimates from our previous data (44,45), the study will have 80% power to detect a mean difference of 0.35 (on a scale of 1 to 5) in the change of low-fat diet self-efficacy measure between the two lifestyle change arms or between either lifestyle change and the MNT arm, assuming a standard deviation of 0.55. For the change in exercise self-efficacy measure, the study will have 80% power to detect a mean difference of 0.88 (on a scale of 1 to 7), respectively, assuming a standard deviation of 1.4.

Aim 2:

This aim is largely qualitative. For quantitative outcomes we will compare if appropriate but the study is not powered to perform statistical analysis on RE-AIM measures.

Aim 3:
We will estimate the cost of each treatment model, and compare the incremental cost-effectiveness as **(**(total cost[treatment model$_i$]-total cost[treatment model$_j$])/(average % weight loss[treatment model$_i$]-average % weight loss[treatment model$_j$])**)**. A formal cost-utility analysis (cost per QALY saved) is beyond the scope of this project, but we will collect data that may be used for a future effort if the intervention is effective.

The study was not designed to be powered for detecting differences in cost outcomes, but we will use standard modeling methods (e.g. Monte Carlo analyses) to account for uncertainty in cost outcomes when calculating incremental cost-effectiveness.

VII. RISKS AND DISCOMFORTS

The risks to the participants will be minor, and be limited to 1) blood drawing, 2) discomfort answering questions 3) risks of intervention 4) risks of exercise 5) loss of confidentiality. We will address these sequentially.

Blood drawing will be minimal. Five blood draws (total 6 cc) will be taken, one at baseline and one each at 6, 12, 24, and 36 months. Results of these blood draws will also be used for usual care. Participants may experience a small amount of pain. Occasionally a bruise may be produced. There is also a small risk of infection, lightheadedness, and/or fainting. Fasting overnight will be required, however a snack will be offered after the blood draw.

Discomfort answering questions. Some participants may feel uncomfortable answering questions about their diabetes, health, nutrition and daily activity. Participants will be told that that they may skip over the questions in the questionnaires that they do not want to answer.

Risks of the intervention: Changing diet and exercise and losing weight may cause hypoglycemia or hypotension. Participants in the group lifestyle intervention will be asked to submit weekly food, activity and blood glucose records which will be reviewed by the study provider who will make any needed adjustments in diabetes medications to prevent hypoglycemia. With every 10 lbs of weight loss, it will be recommended to patients to have their blood pressure monitored according to the protocol outlined below. Participants receiving usual care will continue to be managed by their primary care physician.

Risks of exercise: There is a risk in all exercise of pulling or straining a muscle. Participants will be advised to slow down or stop if they experience any pain and advised to inform their dietitian if they have muscle pain from the exercise at the next appointment. Some participants may feel tired or become short of breath from the exercise. Participants will be advised to stop exercising if they experience any pain or pressure in the chest or have moderate shortness of breath and to call 911 if they feel there is any risk of having a heart attack.

Subject confidentiality will be protected. In order to protect the privacy of the participants, they will be assigned a coded, anonymous numerical identifier at enrollment. Study specific data (mostly from the survey instruments) will be linked to this anonymous coded identifier only, and will not be part of the medical record. Routine diabetes labs and weight, along with medication

changes, will be entered into the electronic medical record by the study MA and provider at each site to promote safety and integration of the intervention with usual care.

For study-specific data, the key will be stored in the Diabetes Research Center in a locked cabinet and in her password-protected hard drive. Only study personnel who have undergone appropriate human research training and signed standard confidentiality agreements will have access to these data. All subject-related documents will be stored in locked file cabinets within locked offices. However, it cannot be guaranteed that a breach will not occur.

VIII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals

Participants will receive usual nutrition and lifestyle care at MGH Nutrition Services or a free group in-person or telephone conference call group based nutrition and lifestyle intervention program. Based on our pilot data it is likely that participants in all arms will lose weight and experience improvements in blood glucose control, blood pressure, and lipid levels and reductions in some medications to treat these conditions.

b. Potential benefits to society

On a societal level, this proposal will be a next step in translating an evidence-based lifestyle intervention into high-value clinical care of type 2 diabetes participants in the community health center setting. Results and materials from this project will be freely available on a study website.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data

A Data Safety Monitoring Plan will be implemented. The PI will review the safety and progress of this study on a monthly basis. In addition, the PI will include results of the review in the annual progress reports submitted to the IRB. The annual report will include a list of adverse events. It will address: 1) whether adverse event rates are consistent with pre-study assumptions; 2) reason for dropouts from the study; 3) whether all participants met entry criteria; 4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and 5) conditions whereby the study might be terminated prematurely.

b. Safety monitoring

The study will employ a Data Safety Monitoring Board of three independent clinical investigators (a primary care physician, an endocrinologist, and a psychologist) not affiliated in any way with the REAL HEALH-Diabetes study. The DSMB will be charged with overseeing rates of recruitment, eligibility criteria, protocol adherence, and the tracking of patient safety. The DSMB will establish its own independent meeting schedule and will determine what, if any, safety stopping rules will be necessary. At a minimum, the DSMB will meet with the PI (s) and co-investigators bi-annually the first year and then annually to evaluate the progress of the study and any safety concerns.

The major safety issues in this low-risk study will be the potential for participants to experience hypoglycemia and/or hypotension as weight loss occurs in those taking sulfonyureas and/or insulin and blood pressure medication. Based on our pilot trial (in which no severe hypoglycemia

was reported) and 11+ years experience in the Look AHEAD study during which cases of self-reported/self-treated hypoglycemia were rare, and no episodes of severe hypoglycemia were reported in the lifestyle intervention group at our center, we do not anticipate any substantive hypoglycemia issues in the proposed study. Severe hypoglycemia is defined as any episode of loss of consciousness/ seizure or documented hypoglycemia (glucose < 70 mg/dl or 3.9 mmol/l) that prevents self treatment, or requires hospitalization or treatment by emergency personnel. Minor hypoglycemia is defined as self-reported transient symptoms such as lightheadedness, tremor, shaking, sweating, tingling, blurry vision, trouble concentrating etc., in combination with a documented low blood sugar value that are self-treated by ingestion of carbohydrates and resolved on their own or within 15 minutes of such self-treatment.

As a precaution, we will require the participants to self-monitor blood glucose and report any incidences of hypoglycemia. In such cases, the study providers will review the records and incidences of hypoglycemia and decrease/adjust medications as needed. In addition, the study provider will review glucose logs of all participants taking medications that cause hypoglycemia (insulin and sulfonylurea) weekly during the first 14 weeks of the study and then bi-weekly in weeks 15-26 so that they may pro-actively reduce those medications as participants lose weight and blood sugars hit 80-100 mg/dl, the low end of the ADA target range of 80-130 mg/dl. The hypoglycemic management guidelines are attached and based on the Look AHEAD trial algorithm. [See "10. Look AHEAD algorithm for medication adjustment based on blood glucose results"]

Since the need for blood pressure medications decreased in both Look AHEAD and our pilot study in the active lifestyle intervention group, we will monitor blood pressure at baseline and at data collection visits as well as evaluate any symptomatic orthostasis reported by participants during the course of the study. For patients on blood pressure medication, it is recommended that for every 10 lbs of weight loss, participants obtain a seated blood pressure measurement either at a pharmacy and/or a visit to the health center. If a seated blood pressure is less than 100/70, or participant complains of lightheadedness with blood pressure less than 110/70, either at a research outcome visit or by self-report, one blood pressure medication will be held under the supervision of the study provider with notification of the referring provider and instructions to follow up with the referring provider for blood pressure measurement.

All participants will be given a handout on recognition of management of hypoglycemia and the protocol for blood pressure monitoring in their study materials [See "21. Handouts"].

Study staff will report all adverse events to the PI who will document and log them. The Log will include the PI's evaluation of each event based on severity, whether it is related/unrelated to the study intervention, and if the event is anticipated/unanticipated. Based on that determination, the PI will follow the reporting requirements to the IRB within the required time frame. The Adverse Events Log will be provided to the DSMB on a quarterly basis.

Study staff will have each completed an IRB-required course in ethics and confidentiality in clinical research. Data will be gathered in a subject file that will be identified by number only, kept in a locked cabinet, and be made available only to authorized, trained study staff.

c. Adverse event reporting guidelines
Each subject is evaluated for any adverse events. Any event that is reported to either the PIs, co-investigators, or the study staff by the subject or medical staff caring for the subject and which meets the criteria will be documented as such. Any event that is reported will then generate an adverse event report, which will be submitted to the IRB. The report will include a description of the event, when and how it was reported, as well as any official chart records or documentation to corroborate the event or the reporting of the event. Any severe and/or unanticipated adverse event will be immediately reported to the IRB. All other adverse events will be reported in a timely fashion to the IRB preferably within 2 weeks of the date of the event. All adverse events will be summarized annually and submitted to the IRB.

d. Data integrity
The research team will ensure that the documentation of all consent forms, questionnaires and diaries are adequate and accurate. Electronic data capture will be stored on RedCAP, the Partners Research Computing HIPAA and research-compliant electronic data capture system. The research team will also ensure that all paperwork is securely stored in locked drawers. Documents that include participants' PHI will be kept separately from documents that include the participants' study code.

The research team will maintain confidentiality of data. All study demographic and survey data will be entered by study staff to RedCap. Each participant will be given a coded ID. A master key of the coded IDs and participant MRNs will be kept in a secure and password protected file by the PI as well as within RedCap. Only study staff that requires access to the password protected file or RedCap will be given access to it.

Separation of subject names and identifiable health information from the data will be done through the use of unique identifiers. All information transferred via the Internet will be done using at least 128-bit SSL encryption. All email sent out of the Partners firewall will be sent through Send Secure if any medication or diagnoses are included. Virus and password-protected facilities will be provided for the research team. All mobile devices will be encrypted to the standard defined by the Partners Laptop and Portable device encryption policies.

X. REFERENCES

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XI. STUDY SCHEMATIC

Table 3. Study Timeline

	Year 1		Year 2		Year 3		Year 4		Year 5	
Completion / revision of protocol	X									
Finalize IRB approval	X									
Train project staff	X									
Participant recruitment	X	X	X	X	X					
Conduct of the intervention		X	X	X	X	X	X	X	X	
Analysis of results								X	X	
Cost analysis								X	X	X
Publication and dissemination									X	X

XII. APPENDICES

1. PCP Recruitment E-mail
2. Introductory Patient Letter
3. Screening Phone Call Script
4. RV1 Appointment Reminder
5. Informed Consent Form
6. Email Broadcast
7. Structured Phone Interview Opt-out Letter
8. Structured Phone Interview
9. **http://youtu.be/BMBHV5i_yMc**
10. Educational Handout
11. Contact Information sheet
12. Readiness Assessment Questionnaires
13. Baseline and Follow-up Questionnaires
14. Look AHEAD's 19 session group lifestyle intervention materials
15. RV2 Appointment Reminder-Intervention and Usual Care
16. Provider Questionnaire
17. Other Diabetes Care and Costs
18. Medication and Health Service Utilization
19. Data Variables List
20. Handouts

18. Data Variables List (to be collected/confirmed from electronic medical record)

1. Age (date of birth)
2. Height
3. Weight
4. Hba1c 6.5< 11%
5. Blood pressure <160/100
6. Diabetes medications and doses
7. Blood pressure medications and doses
8. Lipid medications and doses
9. Any severe comorbidities
10. Any weight change of more than 3%in past 3 months
11. Type 2 diabetes
12. Billing charges

RV1 Content Domains (and corresponding survey items)

1. Demographic information (race/ethnicity, income, educational attainment)
    a. Health history
    b. Medication and Health Service Utilization
2. Readiness for lifestyle change questionnaires
3. Health behavior
    a. Dietary behavior
        1. Fat-related Diet Questionnaire
        2. Restraint Subscale of the Dutch Eating Behavior Questionnaire
        3. Dietary Screener Questionnaire (2 questions)
    b. Activity behavior
        1. Paffenbarger
4. Depression
    a. PHQ-8
5. Quality-of-life
    a. Diabetes–specific quality of life
        1. Problem Areas in Diabetes (PAID) Scale
    b. Health-related quality of life
        1. EQ-5D
6. Self-determination theory measures:
    a. Autonomy
        1. Treatment Self-Regulation Questionnaire
    b. Competence/Self-efficacy
        1. Diet Self-efficacy Scale
        2. Exercise Self-efficacy Scale
    c. Relatedness
        1. Social Support for Healthy Behaviors scale
7. Health literacy
8. Food insecurity
9. Satisfaction Surveys
10. Participant Travel and Phone Use

11. Medication adherence
    a. Morisky Medication Adherence

RV2 Content Domains (and corresponding survey items)

1. Medication and Health Service Utilization
2. Health behavior
    a. Dietary behavior
        1. Fat-related Diet Questionnaire
        2. Restraint Subscale of the Dutch Eating Behavior Questionnaire
        3. Dietary Screener Questionnaire
    b. Activity behavior
        1. Paffenbarger
3. Depression
    a. PHQ-8
4. Quality-of-life
    a. Diabetes–specific quality of life
        1. Problem Areas in Diabetes (PAID) Scale
    b. Health-related quality of life
        1. EQ-5D
5. Self determination theory measures:
    a. Autonomy
        1. Treatment Self-Regulation Questionnaire
        2. Health Care Climate Questionnaire
    b. Competence/Self-efficacy
        1. Diet Self-efficacy Scale
        2. Exercise Self-efficacy Scale
    c. Relatedness
        1. Social Support for Healthy Behaviors scale
6. Satisfaction Surveys
7. Other Diabetes Care and Costs8. Medication adherence
    a. Morisky Medication Adherence

RV3 Content Domains (and corresponding survey items)

1. Medication and Health Service Utilization
2. Health behavior
    a. Dietary behavior
        1. Fat-related Diet Questionnaire
        2. Restraint Subscale of the Dutch Eating Behavior Questionnaire
        3. Dietary Screener Questionnaire
    b. Activity behavior
        1. Paffenbarger
3. Depression
    a. PHQ-8
4. Quality-of-life
    a. Diabetes–specific quality of life

1. Problem Areas in Diabetes (PAID) Scale
    b. Health-related quality of life
        1. EQ-5D
5. Self determination theory measures:
    a. Competence/Self-efficacy
        1. Diet Self-efficacy Scale
        2. Exercise Self-efficacy Scale
    b. Relatedness
        1. Social Support for Healthy Behaviors scale
6. Food insecurity
7. Satisfaction Surveys
8. Other Diabetes Care and Costs
9. Medication adherence
    a. Morisky Medication Adherence

18 Month Content Doman (Telephone Call)

1. Medication and Health Service Utilization
2. Other Diabetes Care and Costs

RV4 Content Domains (and corresponding survey items)

1. Health history
2. Medication and Health Service Utilization
3. Health behavior
    a. Dietary behavior
        1. Fat-related Diet Questionnaire
        2. Restraint Subscale of the Dutch Eating Behavior Questionnaire
        3. Dietary Screener Questionnaire
    b. Activity behavior
        1. Paffenbarger
4. Depression
    a. PHQ-8
5. Quality-of-life
    a. Diabetes–specific quality of life
        1. Problem Areas in Diabetes (PAID) Scale
    b. Health-related quality of life
        1. EQ-5D
6. Self determination theory measures:
    a. Autonomy
        1. Treatment Self-Regulation Questionnaire
        2. Health Care Climate Questionnaire
    b. Competence/Self-efficacy
        1. Diet Self-efficacy Scale
        2. Exercise Self-efficacy Scale
    c. Relatedness
        1. Social Support for Healthy Behaviors scale
7. Food insecurity

8. Satisfaction Surveys
9. Other Diabetes Care and Costs
10. Medication adherence
    a. Morisky Medication Adherence

RV5 Content Domains (and corresponding survey items)

1. Health history
2. Medication and Health Service Utilization
3. Health behavior
    a. Dietary behavior
        1. Fat-related Diet Questionnaire
        2. Restraint Subscale of the Dutch Eating Behavior Questionnaire
        3. Dietary Screener Questionnaire
    b. Activity behavior
        1. Paffenbarger
4. Depression
    a. PHQ-8
5. Quality-of-life
    a. Diabetes–specific quality of life
        1. Problem Areas in Diabetes (PAID) Scale
    b. Health-related quality of life
        1. EQ-5D
6. Self determination theory measures:
    a. Autonomy
        1. Treatment Self-Regulation Questionnaire
        2. Health Care Climate Questionnaire
    b. Competence/Self-efficacy
        1. Diet Self-efficacy Scale
        2. Exercise Self-efficacy Scale
    c. Relatedness
        1. Social Support for Healthy Behaviors scale
7. Food insecurity
8. Satisfaction Surveys
9. Participant Travel and Phone Use
10. Medication adherence
    a. Morisky Medication Adherence