I. Background

A. Historical Background

Physical inactivity among patients with type 2 diabetes (T2D) is a major clinical and public health problem. Roughly 18 million Americans with T2D do not follow recommended guidelines for physical activity,[1] and inactivity is independently associated with major diabetes-related complications and mortality.[2-4] Intensive multicomponent programs for physical activity and other health behaviors in T2D have had positive results in research trials but may be less feasible and effective when applied in front-line clinical settings.[5-8]

Motivational interviewing (MI) is a more widely applied technique that can improve physical activity in T2D. MI is a patient-centered approach used to address ambivalence and promote change,[9] and it can be effectively delivered in person and by phone.[10-12] MI can be used with patients at any stage of change, from those who currently are not ready to become active, to those who are highly motivated to make change.[9] MI has been used in many settings for >30 years and has resulted in increased physical activity in patients with T2D.[13] However, MI alone may not be enough. Though MI is associated with increased physical activity in T2D, the effect size has been relatively small (~0.2 in 3 recent trials),[14] and these somewhat limited effects on physical activity may not translate to fewer adverse clinical events. Also, specific subgroups may be less likely to benefit from MI, such as those who have low expectation of improvement, low overall optimism, or low perceived social support.[15-17] Fortunately, MI has integrated well with other treatments in research and clinical settings.[18,19]

Positive psychology (PP) interventions have the potential to promote physical activity in T2D. Baseline levels of optimism and positive affect are associated with greater subsequent improvements in physical activity (and medical outcomes) in patients with T2D and other chronic illnesses, controlling for baseline physical activity, medical illness severity, and depression.[20-22] This suggests a prospective, independent role of positive constructs on physical activity. PP interventions use structured exercises to boost the frequency and intensity of positive states, and have reduced distress and improved well-being in >3000 study participants.[23,24] PP is well-accepted, requires little staff training, and can be delivered remotely.[24,25] PP programs have increased physical activity and related behaviors in randomized trials of patients with medical illness,[26,27] bolstering the scientific rationale for PP to improve physical activity in chronic medical conditions like T2D. PP also addresses psychological distress and low motivation, which are common in T2D and impair self-care.[28] Despite these features, there has been minimal use of PP in T2D.[29]

A novel physical activity intervention combining PP and MI in T2D may be very effective. MI represents an established health behavior intervention to increase motivation, boost confidence, and reduce ambivalence related to physical activity. A PP intervention could enhance the effects of MI by promoting factors (optimism, perceived support, and confidence) linked to superior outcomes in health behavior interventions,[19,30] and PP could have direct effects on physical activity mediated by increased well-being and confidence.[23,29,31] Such a combined PP-MI intervention could be delivered by phone, allowing inclusion of patients who are unable to attend regular in-person visits. Novel components that focus on social connection, built environment, and reducing sedentary time could further improve outcomes while maintaining a phone-based individual intervention.

B. Preliminary Data. This project continues our progress in developing a PP-MI intervention in T2D.

Positive psychological states and physical activity. In 164 patients with an acute coronary syndrome (ACS), we found that optimism 2 weeks post-ACS predicted greater 6-month physical activity (measured by accelerometer), controlling for baseline physical activity, medical factors, sociodemographics, depression, and anxiety (β=102.5; p=.026).[32] We also completed a mixed methods project with ACS patients (N=32), finding that optimism and positive affect led to initiation of physical activity and predicted overall future health behavior adherence.[33,34]

PP intervention studies in cardiac patients. We tested PP in two controlled trials in patients with heart disease. In a small pilot (N=28), PP was associated with more improvement in mental health outcomes than either attentional control or mindfulness interventions.[25] We then used the above qualitative interviews to refine the PP intervention and studied the revised intervention in 48 post-ACS patients. The intervention was well-accepted and led to improvements in psychological status (positive affect, depression, and anxiety), compared to usual care.[35] We are now examining the effects of PP on activity after ACS.

PP-MI intervention studies. In concert with Dr. Elyse Park, who has much experience testing MI in medical cohorts,[10-12] we have developed a combined PP-MI intervention that is now being studied in a trial (N=128) comparing PP and PP-MI for ACS patients with low physical activity.[36] In the first 50 participants, both conditions were associated with increases in physical activity. However, PP-MI participants had even greater physical activity improvement (12.6 metabolic equivalent [MET]-hours; effect size difference: *d*=.33) at 16 weeks, compared to PP. This data further supports the idea that PP, and especially PP-MI, can improve physical activity in medical populations.

Expansion to T2D. We have spent the past 3 years developing PP and PP-MI in T2D patients using the NIH-supported Rounsaville[37] and ORBIT[38] models of iterative behavioral intervention development. We completed a review of positive psychological states and outcomes in diabetes[22] and published a theoretical model for PP-MI in T2D.[39] Empirically, we completed a single-arm pilot (N=15) of a 12-week PP-alone intervention to assess its feasibility in T2D.[39,40] PP exercise completion rates were high, and participants rated the exercises as useful (mean ratings: 7.8/10). PP was associated with improvements in optimism, depression, diabetes self-care, and health behavior adherence, with a large pre-post effect (Cohen's *d*=.81) on physical activity. We have completed qualitative interviews in 20 T2D patients with low physical activity that focused on relationships between psychological issues and health behaviors, and gathered feedback about a proposed PP-MI intervention to adapt it to the nuances of T2D. Compared to ACS patients, T2D patients reported more unsuccessful attempts to become active, and they showed the most interest in PP activities that focus on the use of personal strengths to meet new health goals.[41] We are currently completing a single-arm pilot (N=12) of a 16-week PP-MI intervention to evaluate its feasibility and acceptability in T2D.

Relevance to proposed project. In sum, we have identified relationships between positive states and physical activity, generated PP and PP-MI interventions in cardiac patients, and begun to develop a PP-MI intervention for T2D using feedback from a PP-alone pilot trial and qualitative interviews in T2D patients. The T2D projects also provided valuable experience recruiting from the Massachusetts General Hospital (MGH) Diabetes Center where the proposed project will occur, making us well-positioned to successfully complete the proposed trial.

C. Rationale/potential benefits/overview of proposed research

Given: (a) the relationship between psychological well-being and physical activity, (b) the potential for combined PP and behavioral interventions to improve physical activity more than either alone, and (c) the great need for effective activity interventions in T2D patients, the use of a combined PP and MI intervention has the potential to increase physical activity and reduce adverse events in a high-risk, high-yield population of patients. This would have direct benefits to patients and would impact public health, given that >18 million Americans have T2D. This project could represent a key first step in determining the feasibility and efficacy of such a program.

II. Specific aims. In a randomized trial of 60 T2D patients with low baseline physical activity, our goal is to complete the following specific aims:

Specific Aim 1 (*feasibility and acceptability*): To determine whether the PP-MI intervention is feasible (assessed by % of total PP-MI phone sessions completed) and well-accepted (assessed by participant ratings of the ease and utility of each PP-MI session) among T2D patients with low baseline activity.

Specific Aim 2 (*physical activity*): To assess whether PP-MI is associated with larger increases in moderate to vigorous physical activity (MVPA), and less sedentary time, on accelerometer at 8 and 16 weeks, compared to standard MI.

Specific Aim 3 (*additional outcomes*): To explore whether the PP-MI intervention is associated with greater improvements on other psychological, behavioral, and medical outcomes, compared to MI.

Hypotheses: Our primary hypotheses are that a majority of the PP-MI participants (n=30) will fully complete at least 6 of 8 PP-MI sessions (feasibility) and provide mean ratings of over 7/10 for the ease and utility of PP-MI sessions (acceptability). We also expect participants in PP-MI to have larger improvements in MVPA (minutes/day) and other key outcomes, warranting further testing in a well-powered efficacy trial.

III. Subject selection

A. Inclusion/exclusion criteria

Inclusion criteria. We will enroll adults who are seen in an outpatient clinic at MGH (including the MGH Diabetes Center) and meet the following criteria:
(1) T2D. Eligible patients will meet American Diabetes Association (ADA) criteria[42] for T2D (e.g., HbA1c [A1C] ≥6.5%, fasting glucose ≥126 mg/d), with diagnosis confirmed by their diabetes clinician and/or medical record review. We will include patients with well-controlled T2D if they have low physical activity because inactivity still puts them at risk for complications.
(2) Low physical activity. We will define low physical activity as ≤150 minutes/week of MVPA (corresponding to ADA recommendations for moderate or greater intensity aerobic physical activity). Physical activity will be measured using a brief questionnaire adapted from the International Physical Activity Questionnaire (IPAQ) which has been used and validated in medical cohorts.[44,45] Patients will complete the brief IPAQ regarding their activity in the past

week (or a typical week, if the past 7 days atypical) to assess # of minutes spent performing MVPA. Patients reporting ≤150 minutes/week of MVPA will be eligible for inclusion in the study. We chose this cutoff in order to ensure adequate room for improvement over the course of the study.

Exclusion criteria:
(1) Cognitive impairment precluding consent or meaningful participation, assessed using a six-item screen developed for this purpose.[54]
(2) Lack of phone availability.
(3) Inability to read/write in English. We are excluding other languages for this initial pilot trial to maintain consistency but will expand to additional languages (e.g., Spanish) if the intervention proves to be effective.
(4) Additional medical conditions (e.g., severe arthritis) that preclude physical activity.
(5) Enrollment in mind-body programs, lifestyle intervention programs (e.g., cardiac rehabilitation), or other clinical trials.

B. Source of subjects and recruitment methods

The outpatient MGH Diabetes Center and MGH primary care clinics will serve as the source of study participants. Recruitment and informed consent procedures for this trial will be highly similar to those outlined in our IRB-approved protocol (Partners Healthcare System IRB #2016P-002523) for the pilot PP-MI study in T2D patients at the same outpatient location with similar inclusion and exclusion criteria. The procedures to protect enrolled and non-enrolled participants outlined below are being used in the pilot PP-MI study to good effect.

Potential participants will be adult outpatients in these clinics with a diagnosis of T2D for >1 year who have ever had an A1C of at least 6.5%. Algorithms in *TopCare* (a population-based information management system that is used in clinical care) and RPDR, as well as customized Epic reports (including but not limited to PHS One View Report Diabetes PCP and 2012p002605-222010), will be used to generate lists of potential patients for providers to review and individually approve eligible patients. In addition, we will use the D4Q data warehouse, a tool commonly used at MGH for clinical outcomes research and operations improvement, in our search for eligible participants. After these lists are generated, study staff will conduct a manual electronic chart review to verify eligibility criteria and physician linkage.

For potentially eligible patients who are enrolled in the MGH Research Options Direct to You (RODY) Program, we will send them an opt-out letter and call 10 days later to inform them about the study. Otherwise, we will next obtain permission for initial contact from each potentially eligible patient's physician or other health care provider (e.g., nurse practitioner). We will send provider-approved patients opt-out letters using the following two-letter approach:

For these patients, a study coordinator will send an opt-out letter packet composed of two letters. The mailing will have a cover letter (see attached sample) with their clinician's name at the bottom generally informing the recipient why they are being contacted about this study. The cover letter will also explain that their participation is completely voluntary and whether they enroll or not will have no bearing on their ability to receive care. The opt-out letter, signed by the study PI, will briefly explain this optional study and will describe that if they do not wish to receive a call explaining the study, they can call the study team opt-out line to inform the study team. If the team does not receive an opt-out call after 10 days, a study coordinator will call the

potential participant and describe the study. The study coordinator will further describe details regarding the study, including its goals (to improve physical activity), study procedures (e.g., a total of 3 in-person visits, a total of 8 weekly sessions), and a review of risks and benefits. If patients do not meet criteria, they will also be asked for their permission to be contacted about participation in future studies.

In addition, we will reach out directly to physician groups, and patient referral will be encouraged. For directly referred patients, we will send opt-out letters as above. Finally, we may use hospital press releases, RSVP for Health, and/or the MGH Diabetes Research Center website to publicize the study.

IV. Subject enrollment

A. Methods of enrollment

If the patient is interested in the study during the phone discussion outlined above, the study staff member will evaluate for inclusion criteria, first assessing for physical activity using the brief IPAQ. Staff will similarly assess for exclusion criteria (e.g., cognitive deficits on six-item screen) via interview.

B. Procedures for obtaining informed consent

If patients, as identified above, meet study criteria and remain interested in the study, the coordinator or other study staff will mail, or email, the patient a written IRB-approved consent form for their review, and will schedule an in-person visit that will take place at MGH. This will allow patients to have adequate time to read the consent form. Upon arrival at the hospital, the study coordinator will review the consent form and allow the patent to ask any questions he or she may have; the study PI will also be available to answer any questions. To ensure that participants have the capacity to provide informed consent, we will ask potential participants to describe their understanding of the study's purpose and their role (i.e., that they understand the purpose of the study, timing of study visits/ accelerometers/phone calls and their purpose, confidentiality and its limits, our focused review of medical records, recording of phone sessions, and their ability to end participation in the study at any time for any reason). Participants will also complete a release of information to allow the study team to speak with their primary medical providers about safe physical activity goals. They will also be asked for their permission to be contacted about participation in future studies. We will not exclude patients on the basis of race, ethnicity, or gender.

If a potential subject is a patient in an investigator's clinical practice (e.g., a patient of Co-I Dr. Wexler), we will ensure that this investigator will not be involved in recruitment, obtaining informed consent, or other aspects of the enrollment process. Patients will be given as much time as they desire to consider study participation and review the consent form, and enrollment will be deferred to a future appointment if desired.

Upon signing informed consent, participants will complete baseline self-report assessments and a blood draw (for A1C) by a trained phlebotomist in the MGH Corrigan Minehan Heart Center. A total of 5 ml/cc of blood will be drawn (this is equivalent to 1 tablespoon of blood). We will collect basic de-identified information (e.g., age, race, gender, living alone, medical diagnoses) on eligible patients who decline participation to assess the representativeness of patients who enroll; such data will only be recorded, analyzed, and reported

in aggregate in comparison to enrollees, with no personal identifiable information collected. We will also measure the participant's weight at this initial visit.

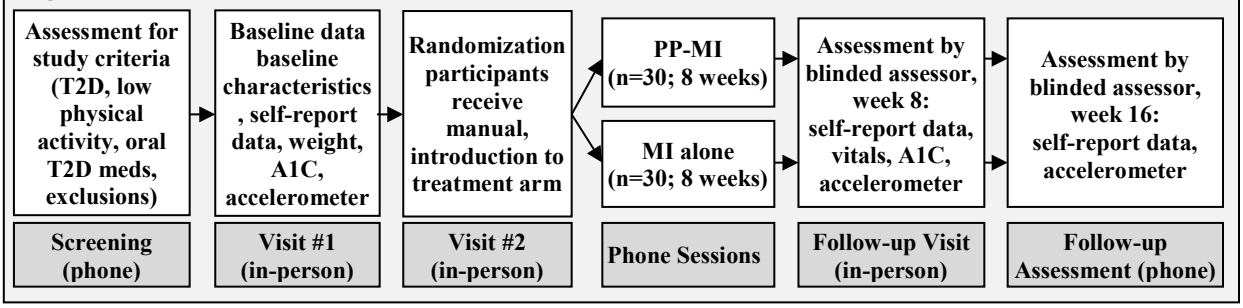
C. Treatment assignment/randomization

Regarding randomization, we will utilize treatment allocation by minimization[55] under the direction of biostatistician Dr. Brian Healy to reduce accidental bias/chance imbalance of key participant variables between the two groups. Minimization is a dynamic randomization technique for achieving a balance of prognostic factors across treatment groups that allows balancing over a larger number of covariates than in stratification.[56,57] Initially, slips of paper detailing study condition (with assignments generated using a random number generator; 30 per condition) will be generated by a research coordinator who is not otherwise involved in the project. The slips will be placed into sealed, opaque, and identical envelopes, and these will be allocated to numbered study binders by a study coordinator. Participants will be assigned to a study condition via this simple randomization method initially. Once at least 8 participants have been enrolled in each group (to allow initial population of both groups prior to balancing via minimization), we will activate the minimization procedure. For all subsequent enrollees, allocation of participants to study condition using a dynamic automated minimization algorithm[55] will occur to ensure balance on dichotomized age, gender, baseline physical activity, and medical comorbidity (Charlson index[58]) variables, using established methods.[55,57,59] These covariables will also be included in the statistical models used to analyze study outcomes as per published methods using this technique.[60] No study staff or investigators will be aware of a participant's condition until consent and all baseline assessments have been completed; participants and study staff will learn of the participant's study condition contemporaneously (via envelope [initial 16 enrollees] or computer assignment [subsequent enrollees]).

V. Study procedures

A. Study visits/assessments (See Figure, below)

Figure. Assessment procedures.



Overview. At baseline, we will obtain self-report measures (see below), height and weight, a blood sample for A1C, and accelerometer data for physical activity. At each intervention phone session, interventionists will collect feasibility and acceptability data (see below). At the follow-up visit (8 weeks), a blinded assessor will obtain repeat self-report data, vitals, A1C, and accelerometer data. At 16 weeks, a blinded assessor will obtain self-report data by telephone, and an accelerometer will be mailed to the participant to measure physical activity. All participants will receive pedometers, free parking or public transportation at all visits, $20

after the second visit, $40 after the 8-week follow-up visit, and $40 after the 16-week phone assessment, after all devices have been returned.

Initial/Enrollment Visit (in-person visit #1). We will collect data on basic sociodemographic variables (age, gender, race/ethnicity, living alone, duration of T2D, medical/psychiatric comorbidities, medications) needed to characterize our population (and to be used as part of randomization by minimization). Next, participants will complete self-report measures, and we will draw blood for A1C if participants did not have these procedures completed as part of a clinical visit (if they had A1C in the last 3 weeks, including this visit, we will use that value to prevent subjecting participants to the blood draw). This visit will occur on site, partially in offices in the Warren building and partially in the MGH Corrigan Minehan Heart Center. Finally, participants will be given an accelerometer, which will be worn over the subsequent week (prior to visit #2) to measure baseline physical activity.

Objective physical activity assessment and in-person visit #2. In order to gather baseline physical activity data, participants will take home and wear accelerometers for 1 week prior to visit #2. During in-person visit #2, participants will return their accelerometers and will begin the study intervention, as outlined below.

Intervention (PP-MI vs. MI alone: 8 weekly phone sessions).

PP-MI intervention. Participants randomized to PP-MI will receive a treatment manual. For each session, a PP exercise will be described in the manual, with instructions and space to write about the exercise and its effects. Next, an MI section will outline specific MI-based topics (e.g., pros/cons, managing slips) and facilitate physical activity goal-setting. Following randomization (in-person visit #2), interventionists will introduce PP exercise #1 and MI session #1 to participants to aid engagement. Following visit #2, participants will engage in weekly, 30-minute phone calls for the next 8 weeks. Participants will independently complete PP exercises and MI-based goals between phone sessions and review them during phone sessions over 8 weeks. PP and MI components will be delivered stepwise within sessions (rather than intertwined) based on our experience, participant feedback, and pilot work.

PP component details. The PP portion of phone sessions (15 mins) will be structured to include: (i) review of the prior PP exercise, (ii) discussion about how to translate the PP exercise skills to daily life (e.g., related to physical activity goals or other activities), including a specific focus on how such skills can be used to foster social support and interactions, and (iii) assignment of the next exercise via guided review of the treatment manual.

Table 1. PP exercises	
Session 1: Counting blessings[61]	Participants recall three events, small or large, in the preceding week that were associated with satisfaction, happiness, pride, or other positive states
Session 2: Gratitude letter[24]	Participants write a letter of gratitude thanking a person for their support or kindness.
Session 3: Enjoyable and meaningful activities[64]	Participants complete three activities: an enjoyable activity alone, an enjoyable activity with another person, and a meaningful activity completed alone or with others.
Session 4: Implementation	Participants focus on implementing positive psychology skills into daily life.
Session 5: Recalling past success[63]	Participants recall an event in which they experienced success. They next write about the event, their contribution to the success, and positive feelings elicited by recalling it.
Session 6: Using personal strengths, part 1[24]	Participants identify a signature strength, then find a specific new way to use that strength in the next 7 days.

Session 7: Using personal strengths, part 2[24]	Participants identify a second signature strength, then find a specific new way to use that strength in the next 7 days.
Session 8: Acts of kindness[62]	Participants complete three acts of kindness, planned or spontaneous, in a single day.
Session 9: Planning for the future	Participants review the positive psychology skills they learned in the program, then make a plan to use their skills in the future.

MI component of PP-MI. This will be adapted from our PP-MI program in ACS patients, Dr. Park's MI interventions,[10-12] and data from T2D patients. The MI portion of calls (15 mins) will assess participant motivation to increase physical activity (safe, specific activity goals will be obtained from their medical providers), and plan action steps or cognitive work to boost motivation. We will use established models of goal-setting and feedback based in social cognitive theory[67,68] and the transtheoretical model of behavior change[69] that utilize setting of proximal, attainable, explicit goals and specific feedback to reinforce progress and enhance self-efficacy. We will typically focus on walking, as brisk walking is feasible as a first step in becoming active for T2D patients[70] and can improve health.[71] The ultimate physical activity goal in nearly all cases will be moderate physical activity for ≥150 min/week, per ADA guidelines.[43] Gradual, safe physical activity progression will be ensured via a stepwise approach, symptom monitoring, and coordination with participants' physicians. Participants will also be given a digital pedometer (Omron) that clips on a belt or other article of clothing, to promote and track physical activity. Finally, this enhanced MI program will also focus on reduction of sedentary time by helping participants to track sitting time and develop strategies to reduce such episodes,[72-74] using the framework for increasing physical activity and our team's experience with sedentary time interventions.[75] Participants will be mailed a graph of their weekly step counts two times over the course of the study. The graph updates will be sent at the middle and end of the study (i.e. following sessions 4 and 8).

Table 2. **MI sessions**.	
5A's model (all sessions)	Interventionists: (a) Ask about progress on the prior cognitive (e.g., pros/cons of becoming active) or physical activity goal, (b) Advise about the benefits of physical activity on health and function, (c) Assess current stage of change and barriers/facilitators to change, (d) Assist with setting a goal, and (e) Arrange the next phone session.
Session-specific topics	Session 1: Introduction to MI tools and tracking of physical activity Session 2: Setting a SMART (Specific, Measurable, Attainable, Relevant, Time-based) activity goal Session 3: Identifying barriers and problem-solving around them Session 4: Using social and equipment resources Session 5: Finding new walking routes (neighborhood walkability audit) Session 6: Using neighborhood resources Session 7: Managing slips Session 8: Reducing sedentary time/taking breaks Session 9: Planning for the future

Walkability audit. Built environment audits (see attachment) can promote physical activity by helping participants find new opportunities for physical activity, manage environmental barriers, and change perceptions about their environment.[76,77] PP-MI participants will complete the 15-item Microscale Audit of Pedestrian Streetscapes-Mini (MAPS-Mini),[78] a walkability audit that has participants identify walkways, parks, traffic, and other features in their neighborhood and usual walking routes by completing checklists as they explore these areas. Participants will be oriented to MAPS-Mini administration in session 5 and complete it in the

next week. Information from this audit will be used during MI sessions to facilitate the setting of practical physical activity goals based in participants' local areas.

Training and fidelity. All team interventionists have delivered PP-MI. Once the intervention is refined for T2D, they will receive additional training via didactics, role play, and supervised interviews. During the study, weekly interventionist supervision will be led by PI Dr. Celano (PP content) and Dr. Millstein (MI). All sessions will be recorded; supervising study staff (Drs. Huffman, Celano, Millstein, or Park) will rate a random selection (20% at minimum) for fidelity using scales for the PP and MI components, respectively, and provide feedback.

MI-based health behavior education condition (time matched). The MI-based health behavior education intervention was selected as the control condition for several reasons. The inclusion of MI and education regarding key diabetes health behaviors aims to increase the retention of participants included in this condition. However, the focus of this intervention on multiple health behaviors and the lack of specific physical activity goal-setting make it less likely that this control intervention will significantly impact physical activity (our primary health behavior outcome). Finally, as an attentional control, it has a parallel structure to the experimental arm with a treatment manual, weekly exercises, and weekly calls to review exercises.

Each week, participants will learn about a different health behavior topic related to diabetes health. They will also be introduced to motivational interviewing topics in concert with the health behavior education topics. The intervention is divided into four sections, focusing on different important diabetes health-related topics:

<u>Part One: Diabetes Self-care</u>

How to Take Care of Your Diabetes *(Session 1)*

Participants will review information about the importance of self-care (e.g., glucose monitoring, foot checks, eye exams) to reduce the risk of T2D complications.

<u>Part Two: Medication Adherence</u>

Taking Medications Regularly *(Session 2)*

Participants will review the importance of medication adherence and learn about medications typically prescribed for T2D. Participants will be encouraged to create a list of their current medications, as well as any questions they have for their physicians about their medications.

Barriers to and Resources for Taking Medications Regularly *(Session 3)*

Participants will identify barriers to taking medications, problem-solve those barriers, and identify resources to help them maintain adherence to medications.

<u>Part Three: Staying Active</u>

The Importance of Staying Active *(Session 4)*

Participants will review the cardiovascular benefits of physical activity, questions to ask their physician prior to starting physical activity, and ways to set goals related to physical activity.

How You Can Stay Active *(Session 5)*

Participants will identify one way in which they wish to change their physical activity. They will discuss the importance of making the change and their confidence about being able to do so. Finally, they will create a list of pros and cons for behavior change.

Barriers to and Resources for Activity *(Session 6)*
Participants will identify barriers to physical activity in their life and brainstorm ways to problem-solve around those barriers. Furthermore, they will identify social, community-based, and equipment resources available to help them with physical activity.

Part Four: Having a Healthy Diet

Making Dietary Changes *(Session 7)*
Participants will learn about the importance of reducing sugar, fat, and cholesterol in their diet. Next, they will identify one way in which they wish to change their diet. They will discuss the importance of making the change and their confidence about being able to do so. Finally, they will create a list of pros and cons for behavior change.

Barriers to and Resources for a Healthy Diet *(Session 8)*
Participants will review how to properly read a food label and learn techniques to make healthy decisions while food shopping. They also will identify barriers to a healthy diet, problem-solve those barriers, and identify resources that can help to improve their diet.

Planning for the Future *(Session 9)*
Participants will review the information learned over the course of the program and think of ways to remain healthy after the end of the program.

Follow-up assessments (weeks 8 [in-person] and 16 [by phone]). After completion of the intervention, participants will wear the Actigraph accelerometers for 1 week (they will have had the devices [which have no identifying information outside of a serial #] mailed to them prior to the visit and will return them at the in-person session), then return to the TCRC for an in-person session (8 weeks). At this session, height and weight, hemoglobin A1c, and self-report data will be obtained. These visits will occur on the MGH main campus (TCRC). At 16 weeks, a follow-up phone session will be performed to obtain self-reported outcome data, and participants will be asked to wear an accelerometer for one week. We will allow a window of 3 weeks, to allow flexibility of scheduling such in-person appointments in Boston (and to allow coordination with other medical visits at MGH) while maintaining integrity of study findings. Follow-up assessments will be completed by a study staff member who is blinded to the participant's study condition.

B. Drugs to be used
There are no drugs used in this study.

C. Devices to be used
To measure physical activity, we will use the ActiGraph GT3X+ accelerometer,[82] a small, silent device without readout that is worn at the hip and stores data for several weeks; it has been validated and used in many populations, including T2D, to measure habitual physical activity.[83] The GT3X+ is a half-dollar-sized device that is very lightweight, clips to a belt or

shoe, and has no sharp edges, shock risk, or visible readout (or any identifying data). Participants will wear the devices for 7 days. We will consider 5 valid days of wear (8+ hours per day) to be sufficient; participants will re-wear devices if needed. In a recently completed PP-MI study in ACS patients (n=128; PHS IRB# 2014P001756), we used these devices/methods with good results. Sedentary time will also be measured with Actigraphs, using protocols to differentiate between sedentary time and device non-wear.[84,85] Data will be downloaded onto our study team's local computers without need to transmit data to external servers.

D. Procedures

A single venous blood sample will be collected at baseline and 8 weeks by study staff trained in phlebotomy, for A1C. No other procedures will be performed.

E. Data collected and when the data is to be collected (see Table 1, below)

Baseline characteristics. To allow us to better understand our study population (and to allow for limited/qualitative accounting for covariates, we will record subjects' baseline characteristics (age, gender, race/ethnicity, duration of diabetes diagnosis, medical and psychiatric comorbidities, medications, and baseline lipids, and hemoglobin A1c). Data will be obtained at the initial interview and supplemented with information from medical records.

Feasibility and acceptability (*Aim 1; # of PP-MI sessions completed, participant ratings of PP-MI ease and utility*). Interventionists will record completion of PP-MI sessions at each session (weeks 1-8). A completed PP-MI session requires both: (i) PP exercise completion and phone discussion, and (ii) the MI portion of the call must end with a specific physical activity-based goal for the next week. In addition, at intervention calls, participants will separately report ease and utility (0-10 scales) of the prior week's PP exercise and MI-based goal-setting, for 4 total ratings per session.

Physical activity (*Aim 2; moderate to vigorous physical activity (MVPA) and sedentary time, in mean minutes/day*). As noted, we will follow established protocols[86] for ActiGraphs. Participants will wear the devices for 7 days and we will consider 5 valid days of wear (8+ hours per day) to be sufficient; participants will re-wear devices if needed. We will use standard cutoffs (in counts/minute) for MVPA and non-wear time per the literature[87,88] and Dr. Kerr. Sedentary time will also be measured with Actigraphs.[84,85] This data will be collected at baseline and 8 weeks.

Self-report measures (*Aim 3; psychological, behavioral, and functional measures*). These measures, except for the AUDIT-C and Cigarette Use Questionnaire (baseline only), will be collected by blinded study staff at baseline, 8 weeks, and 16 weeks:

- Positive affect (our main psychological outcome given its links to health outcomes and sensitivity to change[53,65]) will be assessed using the relevant items from the PANAS.[50]
- Additional psychological measures will include the well-validated Life Orientation Test-Revised (LOT-R)[89] for optimism, the Self-Efficacy for Exercise scale[90-92] (SEE) for physical activity self-efficacy, and the Hospital Anxiety and Depression Scale (HADS) for depression and anxiety;[93] the HADS was designed for medically ill cohorts. We will also include validated measures that may mediate connections between PP-MI and PA; these include the Brief Resilience Scale (BRS), the Self-Efficacy for Exercise (SEE) scale, and the Multidimensional Scale of Perceived Social Support (MSPSS).
- Overall diabetes self-care (e.g., diet, medication, foot care), will be measured using we will use the 11-item Summary of Diabetes Self-Care Activities (SDSCA),[94] a well-

validated self-report measure associated with clinical outcomes.[95,96]

- For T2D medication adherence, we will use a %-based self-report measure[97] found to correlate highly with pillcap measurement in T2D patients, allowing us to include patients with varied medications/dosing schedules.
- For dietary adherence, we will analyze the dietary items in the SDSCA as a separate outcome.[95]
- For physical function, the PROMIS 20-item short form (PF-20) will be used. The PF-20 has strong item clarity,[98] and it has been highly responsive to change in patients with a wide range of physical function.[98-100]
- For pain-related disability, we will use the Pain Disability Index (PDI), validated in medical settings.
- For self-reported physical activity, we will use the IPAQ, well-validated in diverse settings.
- For self-reported smoking history, we will use the Cigarette Use Questionnaire.
- For self-reported alcohol use, we will use the Alcohol Use Disorder Identification Test – Consumption (AUDIT-C).

Medical outcomes (*Aim #3; exploratory*). At baseline and follow-up, we will also measure weight and A1C.

Table 1. Schedule of study events/assessments.

	Pre-enrollment	Enrollment	Weeks 1-**8**	Week **8**	Week **16**
Assessment for inclusion criteria (T2D, IPAQ)	X				
Assessment for exclusion criteria (e.g., cognitive screen, other medical conditions limiting activity)	X				
Interview and chart review for baseline characteristics		X			
Self-report measures		X		X	X
Vital signs (weight) and A1C*		X		X	
Accelerometer (MVPA and sedentary time)		X		X	X
PP-MI exercise sessions			X		
Session ratings by participants (ease/utility)			X		

***Will use values from clinical visit (or within 3 weeks in the case of A1C) if available.**

VI. Biostatistical analyses:

A and B. Specific data variables and study endpoints

Specific Aim 1 (*feasibility and acceptability*): To determine whether the PP-MI intervention is feasible (assessed by % of total PP-MI phone sessions completed) and well-accepted (assessed by participant ratings of the ease and utility of each PP-MI session) among T2D patients with low baseline activity.

Measures:

- Rates of completion of exercises (recorded by study trainer)

Specific Aim 2 (*physical activity*): To assess whether PP-MI is associated with larger increases in MVPA, and less sedentary time, on accelerometer at 8 and 16 weeks, compared to MI.

Measures:
- MVPA in mean minutes per day
- Sedentary time in mean minutes per day

Specific Aim 3 (*additional outcomes*): To explore whether the PP-MI intervention is associated with greater improvements on other psychological, behavioral, and medical outcomes, compared to MI.

Measures:
- Psychological measures: PANAS, LOT-R, SEE, HADS, BRS, MSPSS
- Behavioral measures: SDSCA, % medication adherence, IPAQ, PF-20**,** PDI
- Medical outcomes: Weight, BMI, and A1C

C. Statistical methods

All analyses will be performed under the direction of biostatistician Dr. Brian Healy. All analyses will be performed using Stata 14.0. Alpha for between-group comparisons will be set at p=.05. We will use descriptive statistics (means, standard deviations, proportions for the Aim 1 feasibility/acceptability outcomes. For Aim 2, we will compare between-group improvement from baseline in mean minutes/day of MVPA (and sedentary time) at 8 weeks using a random effects regression model, with a random intercept for each patient, allowing us to include participants with some missing data.[101] For Aim 3, we will likewise compare change from baseline on all measures (e.g., self-care, A1C) at 8 weeks, using random effects models. We will secondarily compare outcomes at 16 weeks, and will complete sensitivity analyses by sex. All variables used in minimization (age, gender, baseline MVPA, Charlson index) will be included as covariates in these models as per protocol using this method.[60] We will also measure pre-post effect size (Cohen's *d,* defined as change in the outcome measure divided by the standard deviation of the measure across all time points) of PP-MI for each Aim 2/3 outcome. If there are significant between-group differences in physical activity outcomes, we will use mediation analyses[102] to evaluate a pathway from PP-MI to proximal targets (positive affect/optimism/self-efficacy) to physical activity.

D. Power analysis

For our primary aim (feasibility/acceptability), in our prior work, 75% of subjects completed three-quarters of sessions.[25,35] Using the same rate, with 30 PP-MI participants we will have 80% power (two-sided α=0.05, binomial proportion test) to demonstrate that the proportion who complete $\geq$8 of 11 PP-MI sessions is larger than 50% (i.e., a majority). Likewise, mean PP ease/utility scores were 7.8+/- 1.8 in prior work;[35] with n=30 (and 4 weekly ratings per participant), we will have 93% power (using a within-person correlation of 0.5 for ratings across exercises) to detect a true mean score of >7.0 on composite ratings. This initial trial is not powered to definitively test group differences on physical activity and other Aim 2/3 outcomes, but it will allow us to gather data on PP-MI's impact on these outcomes at this key early stage.

VII. Risks and discomforts

A. Complications of surgical/non-surgical procedures

Blood sampling. We will obtain A1C data at baseline and 8 weeks. Risks of venous blood sampling include pain, bruising at the phlebotomy site, and emotional discomfort from the process. More rarely, participants may become lightheaded or experience syncope, or have an infection at the site. We will minimize these risks by: (1) ensuring that blood samples are drawn by study staff who have received specific training in phlebotomy (TCRC research protocol nurse) and have specific experience with this procedure, and (2) if A1C is drawn at the clinical visit or was obtained within the prior 3 weeks, that value will be used rather than subjecting the participant to an additional blood draw. Procedurally, we will make sure participants are seated comfortably during and after the sampling, and we will temporarily (or permanently) halt blood draws if patients voice pain or discomfort. If participants experience problems after blood draws (e.g., concerns about infection), they will be able to reach a study physician at any time, who can help to assess the situation over the phone or arrange to have the participant seen by their own physician or by study physician staff to assess any problems.

B. Drug side effects and toxicities

No medications are being used in this study.

C. Device complications

Accelerometer. The devices used to measure physical activity should pose minimal risk to subjects. The accelerometer (ActiGraph G3TX+) used to measure activity as a formal study outcome is small, lightweight, and without sharp edges. Immersing the device in water for a prolonged period may render it unusable, but does not pose a shock risk. We will provide explicit instructions regarding the use of this device to ensure safety and proper use, and to reduce inconvenience/distress associated with uncertainty about their use. Participants will also have study staff contact information if they have questions about the devices; project staff will be well-versed in the use of these devices given their experience from our prior projects that have used the G3TX+.

D. Psychosocial risks

Confidentiality. To minimize confidentiality-related risks, we will use participant ID numbers—as opposed to identifiable personal data or medical record numbers—on all study documents. We will discuss only information that is related directly to the study with subjects' clinicians, and we will use locked cabinets and offices as well as password-protected databases to store personal information. Information from self-report assessments will be collected and stored using the secure, HIPPA-compliant, firewalled, and password-protected REDCap system. REDCap is a free web-based application developed for management of research and clinical data; it has separate password-protected data collection repositories for each trial. We have used this system for numerous prior studies without difficulty. Accelerometers will be labeled only with participant numbers; they will be connected to staff computers via USB and staff will utilize the password-protected Actigraph software downloaded onto our local computers to obtain activity data. No personally identifiable information will be recorded physically or electronically onto the accelerometers or within the software program.

Finally, digital recordings of PP-MI and MI sessions will be completed using portable recorders. Randomly-selected sessions will be reviewed for competence and adherence to the protocol by supervising study staff members (e.g., Project Director, PI) using PP and MI fidelity rating scales. For sessions in the MI alone condition, supervising study staff will complete fidelity ratings with additional rating items to ensure that interventionists are not delivering PP content or other content (e.g., related to sedentary time) specific to PP-MI. All recordings will be downloaded immediately from the recorders and the electronic files will be kept within the firewalled, password-protected shared file area for fidelity review. Recordings will contain no personally identifiable information (and study interventionists will be specifically trained not to use names or other identifying information on the recordings) and will be erased following review. We have used all of these methods to maintain confidentiality in prior projects using the same measures, data repository, accelerometers, and recorders.

We will ensure that contact with subjects is confidential by using only the phone numbers and other contact information that are specifically allowed by the subjects and not leaving study-related messages for subjects unless expressly allowed by subjects. Upon enrollment, we ask all participants if it is acceptable to leave voice messages on their phones, as well as the appropriate times to call them. We adhere to any and all patient requests regarding contact.

Medical/psychiatric issues. If there is an urgent medical or psychiatric condition that becomes apparent during in-person or phone-based sessions or at follow-up assessments, a study physician will assess the patient's situation and ensure that the patient is seen immediately for an assessment in an emergency department or other urgent care setting if this is necessary; the PI (Dr. Huffman) and study internist/endocrinologist (Dr. Wexler) are available 24/7 by page for emergencies and have arranged emergent evaluation for patients as part of studies on several occasions in the past.

Hypoglycemia. Some medications for T2D (i.e., insulin, sulfonylureas, repaglinide, nateglinide) can lead to hypoglycemia, and patients increasing their activity may become hypoglycemic. To address this for all participants who are on medications that can lower glucose, we will provide specific verbal and written guidance about symptoms of hypoglycemia, self-monitoring of blood glucose, and management of hypoglycemia, using handouts and protocols adapted from the NIDDK-funded Look AHEAD and REAL HEALTH-Diabetes (Look AHEAD implementation) studies focused on increasing activity in patients with T2D.[103,104] Participants in both groups will also be given contact information for the study team and will be asked to contact the study team if hypoglycemia occurs during exercise. At all calls and follow-up assessments, interventionists and study staff will also query participants who are currently taking medications known to predispose patients to hypoglycemia during exercise (i.e., insulin, meglitinides, or sulfonylureas) about signs and symptoms of hypoglycemia. If such symptoms arise, the study endocrinologist (Dr. Wexler) will coordinate with participants' medical care providers (and evaluate participants by phone or in-person as needed) to assist in making medication and other care adjustments to address these episodes, utilizing the approach used by Dr. Wexler when managing T2D participants on glucose-lowering medications in REAL HEALTH-Diabetes. Patients who are not currently taking medications known to increase risk of hypoglycemia during physical activity will not be asked about hypoglycemia symptoms at every call, in order to minimize participant burden. However, these participants will still be encouraged to notify their interventionist should they experience any symptoms of hypoglycemia.

Physical activity safety. To ensure that patients can safely participate in physical activity, we will confirm with the patient's clinician (physician or nurse practitioner) that the patient is

able to participate in a physical activity promotion program prior to approaching the patient. For those who enroll in the program, we will discuss the patient again with the clinician. Specifically, for participants in either condition, we will describe to the clinician the plan for setting goals to increase physical activity, and will ask if there are any specific instructions or cautions to be conveyed to participants, including specific warning signs such as atypical presentations of angina that may be common in T2D patients, such as dyspnea or nausea. This information will be recorded in the REDCap system so interventionists can use this information when developing plans with the patient at phone sessions. If participants have concerning symptoms, interventionists will contact the study physicians (e.g., Dr. Wexler), who will reach out to the participant's clinician to inform them, obtain direction, and alter the physical activity plan as needed; she will also reach out to participants as needed. As noted above, participants will sign a release of information to allow such contact with clinicians (diabetologist, primary care physician) during the informed consent process.

Depression/anxiety symptoms and suicidal ideation. Participants will complete the Hospital Anxiety and Depression Scale (HADS)[93] as part of assessments; although this is a symptom measure and is not used to make a diagnosis of depression or an anxiety disorder, for participants with HADS depression or anxiety subscale scores of 10 or more, we will complete an assessment for suicidal ideation using our standardized, published protocol[105] and inform patients' primary providers of the elevated depression/anxiety score. For participants who have active suicidal ideation or are otherwise considered to be at high risk (e.g., due to combinations of depression symptom severity, history of prior attempt, and passive suicidal ideation), a study psychiatrist will perform a separate assessment and will arrange for urgent evaluation (e.g., in an emergency department) if clinically indicated.

We will ask subjects to report adverse events related to study participation they may have experienced at any time throughout the study. Any adverse events will be reported to the PI and to the IRB according to Partners HRC guidelines.

VIII. Potential benefits

A. Potential benefits to participants

Participants in the project may not benefit from their participation. All participants (in either study condition) will receive serial assessments of medical, psychiatric, and functional status, allowing them access to emergent care if required. Participants in the control condition will receive MI, an established health behavior intervention associated with improvements in physical activity in patients with T2D, as well as T2D-specific education.[14] Participants in this study arm therefore have the potential to increase their physical activity and to experience associated benefits in mood, energy, and health.

Participants randomized to the PP-MI arm may obtain additional benefit. Along with receiving MI as above, participants will also receive PP content. Our preliminary studies have suggested that PP exercises are associated with lower depression and anxiety, greater positive affect, and improved mental health-related quality of life in other medically ill patients. Along with these possible psychological benefits, a prior randomized trial of a PP-based intervention in medically ill persons led to increased physical activity,[27] and our pilot PP project in T2D showed a moderate-large effect on physical activity over 12 weeks. Furthermore, the PP intervention component may lead to improved engagement in MI, potentially leading to greater efficacy of

MI techniques on physical activity. For these reasons, the PP-MI intervention may lead to increased physical activity (and reduced distress) in participants randomized to PP-MI. PP-MI participants will also have additional novel content, including systematic encouragement to utilize social supports, use of a neighborhood walkability audit to identify local physical activity opportunities, and a focus on reducing sitting time. These may further promote physical activity and reduce sedentary time, which has been associated with adverse medical outcomes in T2D independent of MVPA.[106,107]

B. Potential benefits to society

Participation in physical activity (and other health behaviors) is crucial in preventing adverse events in T2D.[1-3,108] However, the majority of T2D patients do not complete recommended amounts of physical activity.[5,109,110] Existing complex health behavior interventions can be difficult to implement in real-world settings, and more straightforward interventions, like MI, may require additional components to increase engagement and boost efficacy. We postulate that a combined PP-MI intervention has the potential to increase physical activity in inactive T2D patients through the combined effects of its two components. However, a PP-MI intervention has never been studied in patients with T2D prior to our team's exploratory work. At this stage, there is still much knowledge to be gained about the feasibility, efficacy, and optimal implementation of this innovative intervention for T2D patients who are at elevated risk of adverse outcomes and mortality due to their inactivity.

By completing this project, we will learn whether this intervention is feasible and well-accepted by T2D patients who have low physical activity at baseline. We will also examine whether the intervention is associated with increased physical activity (objectively measured by accelerometer) in this cohort compared to those receiving standard MI. Finally, we will be able to explore whether this PP-MI intervention may have
effects on additional psychological, adherence-related, and medical outcomes.

This knowledge could be of substantial importance. If the PP-MI intervention proves to be feasible, well-accepted, and effective in this study and larger follow-up studies, it may be possible to implement this easily-delivered program as part of a clinical care package for T2D patients who have low physical activity. This, in turn, could lead to better glycemic control, greater self-care, and fewer complications in a vulnerable population at high risk of complications and mortality. Therefore the knowledge gained from this initial study may ultimately translate to substantial benefit for future patients and public health.

VIII. MONITORING AND QUALITY ASSURANCE

A. Independent monitoring of source data

Entry of data into REDCap will be reviewed by the PI and study biostatistician at intervals to ensure that data is being correctly captured/entered into this system. They will also review downloading of data from REDCap into Stata to ensure that the data is being accurately transmitted to the study database for study analyses.

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B. Safety monitoring

We will utilize an Data Safety Monitoring Board (DSMB) for this study. The following procedures will be followed to ensure participant safety and the validity and integrity of data:

Functions of the DSMB. The DSMB will review proposed amendments to the study

protocol, complete expedited monitoring of all serious adverse events, monitor drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality.

Membership of the DSMB. The DSMB will consist of members with extensive research experience in diabetes, mental health, and biostatistics of clinical trials. Three members will be Dr. Andrew Nierenberg (Psychiatry), Dr. Enrico Cagliero (Diabetes/Endocrinology), and Dr. Lee Baer (Biostatistics); all have agreed to serve in this role throughout the study. The DSMB Chairperson (Dr. Nierenberg) will communicate by email and phone with the other members, and will coordinate formal, scheduled meetings of all members of the study and the PI.

Monitoring of Safety Data by the DSMB. Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the unblinded review of safety by the DSMB. Unblinded data will not be released to investigators unless necessary for safety reasons.

Range of Safety Reporting to the DSMB. It is considered necessary that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.

Serious Adverse Events. Expedited review will occur for all events meeting the definition of Serious Adverse Events (SAEs); i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, or event requiring or prolonging inpatient hospitalization. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, study group assignment, medications, the subject's medical history and current conditions, and any relevant laboratory data. Notification by e-mail and FAX transmittal of all related study forms shall be made to the DSMB. Information will be reviewed and a determination made of possible relevance to the study.

Non-Serious Adverse Events. At periodic intervals determined by the DSMB (e.g., quarterly during the study and then again at its completion), the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.

Other Safety-Related Reports. At quarterly intervals, the DSMB will also receive unblinded summary reports of treatment retention and reasons for drop-out, by treatment arm and study phase.

Study Stopping Rules. If at any time during the course of the study, the DSMB judges that risk to participants outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

Monitoring of Data Quality by the DSMB. At least on a quarterly basis during the course of the study, the DSMB will receive a report on data quality and completeness. Dr. Brian Healy (study biostatistician) will prepare these reports in collaboration with Dr. Huffman. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with evaluations as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients,

study interventions, and primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annual DSMB Report to NIH/NIDDK. During the course of the study, the DSMB will prepare annual summary reports (two reports in total) of its findings regarding safety and quality based on data received to that point in the study. If there are more specific concerns about data quality, study safety, or other issues, the DSMB can elect to generate reports more frequently. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in this DSMB report. A copy of this DSMB report will also be sent to the PHS IRB along with the annual renewal report.

In addition to the work of the DSMB, the research team will meet on a weekly basis to review study progress. During these weekly meetings, the principal investigator will review informed consent documents, study forms, and procedures completed that week. The study team will also discuss any procedural difficulties, recruitment issues, and adverse events at this meeting (and before if needed). If there are consistent issues with the logistics, feasibility, or acceptability of recruitment, enrollment, follow-ups, or the intervention (e.g., participant complaints about length of follow-ups), we will review our methods and alter the study protocol as needed.

Patient Alert System. MGH has an electronic system that lets the study team know if a participant is admitted to a Partners Hospital, or if they visit a Partners Hospital Emergency Department for any reason. This alert will let the study doctors know why a participant is there, to make sure the study doctors know about any possible problems or side effects participants experience while taking part in the study.

C. Outcomes monitoring

For this initial randomized pilot trial, we will not plan to perform interim analyses beyond the analyses performed by the DSMB. However, given the feasibility and acceptability focus of this study, we will review ratings of intervention ease/utility after 10 and/or 20 participants if our weekly team meeting reviews suggest that there are substantial barriers to acceptability (e.g., reports from participants at follow-ups/interviews, high rates of dropout) and consider changes to the protocol as indicated.

D. Adverse event reporting guidelines

We will follow all PHRC guidelines with respect to reporting unanticipated problems, including adverse events. Specifically, when a serious or nonserious adverse event occurs, the PI will review the event to determine if it was possibly or definitely related to participation in the research. For all unanticipated problems and adverse events deemed related or possibly related to the research, we will complete and submit an Other Event report through Insight/eIRB as soon as possible and within 5 working days / 7 calendar days (as defined in the March 2014 Reporting Unanticipated Problems Including Adverse Events report). At Continuing Review, we will provide a summary of all unanticipated problems as per PHRC protocol. Finally, if there are unanticipated problems, especially if serious or recurrent, the PI (Dr. Huffman) will amend the protocol if it is deemed necessary to protect the safety and welfare of the participants.

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