Practical Telemedicine to Improve Control and Engagement for Veterans With Clinic-Refractory Diabetes Mellitus

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Purpose

This randomized trial will evaluate the effectiveness of a novel telemedicine intervention, Practical Telemedicine to Improve Control and Engagement for Veterans with Clinic-Refractory Diabetes Mellitus (PRACTICE-DM). Based on extensive pilot work,(1,2) this novel approach is designed for practical delivery within the Veterans health Administration (VHA). PRACTICE-DM bundles telemonitoring, self-management support, diet/activity support, medication management, and depression support – each of which targets a critical factor underlying persistently poor diabetes control – into a single, comprehensive telemedicine intervention specifically developed for practical delivery using existing VHA Home Telehealth (HT) workforce, infrastructure, and technical resources. We constructed PRACTICE-DM to be: 1) potent enough to reduce HbA1c in clinic-refractory diabetes; and 2) suitable for practical delivery using existing VHA HT services. We will randomize 200 Veterans with persistently poor diabetes control from two VHA sites to receive one of two strategies over a 12-month period: 1) the comprehensive PRACTICE-DM telemedicine intervention; or 2) an active control, HT care coordination and telemonitoring (which is available as part of VHA standard care). All Veterans will continue to receive care from their primary clinicians during the study. This study has three Specific Aims:

- **Specific Aim 1**: Determine PRACTICE-DM's clinical effectiveness for Veterans with persistently poor diabetes control versus standard HT care coordination and telemonitoring
- (**H1**) Mean HbA1c in the intervention group will be ≥0.6% lower at 12 months than in the control group
- **Specific Aim 2**: Evaluate PRACTICE-DM's acceptability and mechanisms of effect using a mixed-method process evaluation, in order to refine the intervention for future implementation
- **Specific Aim 3**: Understand intervention and health care costs associated with PRACTICE-DM as compared to standard HT care coordination and telemonitoring

Background and Significance

Background

For the Veterans Health Administration (VHA), diabetes is a daunting problem. Diabetes prevalence among Veterans is higher than in the general population (~25% of 23 million US Veterans), and has risen sharply in recent years.(3,4) As in the general public, diabetes is the leading cause of kidney failure, non-traumatic lower limb amputations, and blindness in VHA. Veterans with diabetes have higher rates of heart attacks and strokes, along with a two-fold higher mortality rate versus other Veterans (~5% vs. 2.6%).(5) As the fourth most expensive disease afflicting Veterans, diabetes is extremely costly to VHA.(6,7)

Both within and beyond VHA, the complications and costs of diabetes rise exponentially as hemoglobin A1c (HbA1c) increases.(8-10) Landmark research has shown that interruption of poor glycemic control reduces diabetes complications and costs,(11-13) even when glycemic improvements are not sustained.(14) While recent studies targeting near-normalization of HbA1c have suggested that overly tight glycemic control may be associated with increased mortality,(15,16) continuous maintenance of an HbA1c ≥8.5% confers a clearly elevated level of risk for most Veterans – a risk that would be reduced with improved glycemic control.(17,18)

While some patients with persistently poor diabetes control have not received regular healthcare, many maintain elevated HbA1c despite clinic-based diabetes management. We have operationalized this group as having persistent poorly-controlled diabetes mellitus (PPDM), which we define as the continuous maintenance of an HbA1c ≥8.5% for >1 year despite clinic-based management during this period by Primary Care or Endocrinology. Our work suggests that, within VHA, approximately 12% of all Veterans with type 2 diabetes meet our definition for PPDM.(19) Given their ongoing poor control in the face of clinic-based VHA care, Veterans with PPDM are likely to be the highest-risk, highest-cost diabetes patients in the VHA system. Because diabetes control has a greater absolute impact preventing complications and costs in patients with high HbA1c,(13,20) addressing PPDM should be a priority for VHA.

By definition, patients with PPDM remain poorly-controlled despite receiving regular clinic-based diabetes care. Factors associated with poor diabetes control include unreliable or unavailable blood glucose data, self-management nonadherence, suboptimal diet, inadequate physical activity, complex insulin-based treatment regimens, and comorbid

depression.(21-30) These factors are particularly difficult to address with the infrequent patient-provider contact achievable in the clinic setting, leading to PPDM.(31,32) Care delivery approaches are needed that can more effectively counter factors that lead to PPDM.

Telemedicine, or use of electronic information for medical purposes,(33) enhances outcomes versus clinic-based diabetes management. Telemedicine may utilize various technologies, such as telephone, smart phone-, and computer-based platforms, to facilitate synchronous (e.g., real-time voice or video contact) or asynchronous (e.g., store-and-forward data transmission) interactions.(34) Telemedicine-based approaches are well-tolerated by patients and improve access, cost-efficiency, and quality.(33,35)

Table 1. Telemedicine strategies for diabetes.

Strategy	Factor addressed
Telemonitoring	Unreliable/unavailable blood glucose data (21)
Self-management support	Self-management nonadherence (24)
Diet/activity support	Effects of poor diet and inactivity on control (25)
Medication management	Complex insulin-based treatment regimens (28)
Depression support	Impact of depression on diabetes self-care (29)

Telemonitoring, self-management support, diet/activity support, medication management, and treatment of comorbid depression are examples of telemedicine-based treatment strategies that address specific factors underlying poor diabetes control (Table 1). Though data are of variable quality, these approaches appear moderately effective versus clinic-based usual care (UC):

- Telemonitoring: Facilitates blood glucose data collection, lowers HbA1c by 0.48% versus UC (36)
- Self-management support: Fosters self-management adherence, lowers HbA1c by 0.44% versus UC (37)
- Diet/activity support: Counters effects of poor diet and inactivity, lowers HbA1c by 0.6% versus UC (38)
- Medication management: Addresses complex treatment regimens, lowers HbA1c by 0.51% versus UC (39)
- Depression support: Reduces depression's impact on diabetes, lowers HbA1c by 0.33% versus UC (40)

Though effective versus clinic-based care, each of these strategies individually reduces HbA1c to a degree that is insufficient for most of the PPDM population. However, a comprehensive telemedicine intervention combining elements of each of these approaches could address multiple factors underlying PPDM and help these high-risk, clinic-refractory patients meet their HbA1c targets. In our recent pilot work, combining telemonitoring, self-management support, medication management, and depression support improved HbA1c by 1.0% on average versus clinic-based UC and by ~2.0% for highly-engaged patients.(1)

VHA currently utilizes telemonitoring for diabetes as part of its Home Telehealth (HT) program, as do some other health care organizations.(34,41) However, neither VHA nor other systems have successfully combined telemedicine-based monitoring, self-management support, diet/activity support, medication management, and depression support in practice; this shortfall stems from the fact that comprehensive telemedicine-based diabetes care has not been designed for practical delivery under real-world conditions.(42,43) The lack of practical alternatives to clinic-based care is particularly damaging to those clinic-refractory patients with PPDM.

In order to maximize a telemedicine intervention's eventual impact, early consideration should be given to its potential for practical use in the target context.(44) To this end, key factors to consider during intervention development include the workforce requirements for intervention delivery, the organizational infrastructure required for implementation at scale, and the required technical resources.(43) Because these key factors vary according to the health care context, designing an intervention around the target context's available workforce, infrastructure, and technical resources could enhance prospects for eventual real-world use within that context.

VHA's unique HT program makes it a national leader in telemedicine. For diabetes, however, this capacity is used primarily for care coordination and telemonitoring, without integrated self-management support, diet/activity support, medication management, or depression support. Data regarding the effect of VHA HT care coordination and telemonitoring on HbA1c are limited;(45-50) this effect is likely similar to that seen with telemonitoring in other settings (~0.5%). As currently configured, VHA's HT services are therefore unlikely to achieve sufficient HbA1c-lowering for Veterans with PPDM. As such, VHA's nation-leading HT program is currently underutilized for this high-risk population.

If a comprehensive telemedicine intervention for PPDM could be delivered via existing HT workforce, infrastructure, and technical resources – which are ubiquitous at VHA centers nationwide – it could offer a practical, effective alternative for Veterans who are refractory to clinic-based diabetes care. VHA's HT program provides a unique opportunity to develop comprehensive telemedicine for PPDM that can be used in real-world VHA practice.

Current objective

If telemedicine is to fulfill its potential to address VHA's diabetes burden, it must be both effective enough for clinic-refractory Veterans with PPDM and explicitly designed for practical delivery using VHA workforce, infrastructure, and technical resources. Without such an intervention, clinicians and patients will continue without recourse when clinic-based care proves insufficient for PPDM.

This randomized, controlled trial (RCT) will evaluate PRACTICE-DM, a comprehensive telemedicine intervention for Veterans with PPDM combines telemonitoring, self-management support, diet/activity support, medication management, and depression support – 5 evidence-based approaches that target factors underlying PPDM – and is designed for delivery using existing VHA HT workforce, infrastructure, and technical resources. We constructed this innovative intervention to be: 1) potent enough to meaningfully reduce HbA1c in PPDM; and 2) suitable for practical delivery using widely available VHA resources, enhancing its potential for real-world use within VHA. PRACTICE-DM will leverage VHA's unique HT program to deliver effective, comprehensive, telemedicine-based management for PPDM in a practical manner, with the goal of improving outcomes in this high-risk, high cost population.

Significance

This study has high clinical and strategic significance for VHA. Clinically, PRACTICE-DM will reduce VHA's diabetes burden by generating a practical management option for high-risk Veterans with PPDM. Strategically, this project aligns with key VHA and HSR&D priorities, as well as the goals of the VHA Office of Connected Care (OCC), which oversees the HT program nationally.

Design

In order to evaluate the effectiveness and feasibility of delivering PRACTICE-DM within two distinct VHA contexts, we will enroll from Veterans Affairs Medical Centers (VAMCs) in Durham, NC and Richmond, VA. We will enroll/consent up to 300 Veterans per site in order to randomize 200 Veterans with PPDM (type 2 diabetes only) to receive: 1) PRACTICE-DM; or 2) an active control (HT care coordination and telemonitoring), which is available as part of standard VHA care. All participants will receive their assigned intervention for 12 months, during which time they will also continue to receive usual VHA care.

Selection of Subjects

Study sites

The Durham, NC Center of Innovation (COIN) will be the organizing site for this study. Durham is an appropriate setting for this study because of our COIN's extensive experience with research conduct, our racially and socioeconomically diverse patient population, and our high prevalence of PPDM (15% of Veterans with type 2 diabetes).(19) We have chosen the Hunter Holmes McGuire VAMC in Richmond as our second site for several reasons: 1) like Durham, Richmond has a diverse population with a high incidence of PPDM (14% of Veterans with type 2 diabetes); 2) Richmond's strong HT program is keenly interested in adding comprehensive telemedicine for PPDM to its services (see Letter of Support from Richmond site PI Dr. Phillip Tarkington); 3) Richmond, though not a COIN, has research experience that will assure the feasibility of this study; 4) Durham and Richmond have a history of successful research collaboration involving members of this team;(51) 5) Durham and Richmond are only 150 miles apart, which will facilitate collaboration and minimize travel costs.

In developing this study, we have worked closely with the Durham and Richmond HT programs. Both are enthusiastic participants in this evaluation of PRACTICE-DM, and each program's leadership endorses an adequate

capacity to randomize the Veterans needed to conduct study activities at their site (see Letters of Support from Dr. Tarkington of Richmond and Brian Hayes/Oliver Massey of Durham).

Population

In order to assure a representative population, we will proactively recruit Veterans with type 2 diabetes managed for >1 year at each site, including Community-Based Outpatient Clinics (CBOCs). We will identify subjects with PPDM by reviewing the VHA electronic health record (EHR) and soliciting referrals. Inclusion criteria are:

- Diagnosis of type 2 diabetes (diagnosis codes or prescription of diabetes medication)
- ≥1 HbA1c values of ≥8.5% during the prior year, with no readings of <8.5%
- ≥1 appointments with a VHA Primary Care Provider (PCP) or Endocrinology during the prior year

Because there are >1000 potentially eligible Veterans at Durham VAMC and >1000 at McGuire VAMC, we anticipate no difficulty reaching our randomization goal of 200 Veterans. We will proactively identify and purposefully oversample women from our pool of eligible patients, with the goal of achieving a population that is 20% female. With respect to minority Veterans, we will carefully monitor recruitment to assure a population that is at least 50% African-American and 10% Hispanic/Latino, surpassing local demographics. No children or prisoners will be included in the proposed project. Current/prior use of VHA HT, Endocrinology, or other services will not exclude Veterans from participation. Exclusion criteria include:

- Age >70, or life expectancy <5 years
- History of severe hypoglycemia documented in chart in the past 12 months
- Inability to communicate by telephone
- Dementia or psychosis
- Active alcohol or substance disorder
- Current pregnancy or report of new pregnancy during study
- Prior hypoglycemic seizure or coma in the past 12 months
- Refusal to perform self-monitored blood glucose (SMBG) at baseline evaluation
- Use of continuous subcutaneous insulin infusion pumps
- Hospitalized for stroke, heart attack or had surgery for blocked arteries in the past 12months
- Receiving kidney dialysis
- Diagnosed with metastatic cancer
- Use of a continuous blood glucose monitor (due to HT equipment constraints) unless the subject is willing to perform standard finger stick blood glucose monitoring and submit blood glucose values per study protocol.
- Primary provider requests patient not participate in the study
- Primary medication management for diabetes is performed by a non-VAMC provider.

Enrollment/Randomization

Using a proactive process, eligible Veterans at each site will receive an invitation letter signed by the study PI, which will include instructions on opting out of further contact if desired. If a Veteran does not opt out within a week, study staff will initiate telephone contact to gauge interest in participation, explain the study, briefly screen for eligibility, and if appropriate, arrange an in-person appointment for further evaluation. Further screening and informed consent will be performed at this appointment by the site research assistant (RA) or project coordinator (PC). After consent, baseline assessment will include: 1) survey of demographics, clinical history, medications, and measures of relevant psychosocial constructs (Table 2); 2) measurement of BP and body mass index (BMI); and 3) laboratory HbA1c testing. Baseline assessment will take <60 minutes. Veterans will receive a study packet and depart to await contact

from HT. HT will enroll Veterans using local processes; all will receive standard HT equipment, for which all Veterans with PPDM qualify and which is similar across sites (Cardiocom®, Chanhassen, MN).

Randomization will follow Veterans' baseline appointment (Figure 1). Participants will receive information on both study arms during the consent process, we will not attempt to blind participants to randomization assignment. However, in order to assure blinding of our RAs, who manage outcome data collection, randomization will be managed by the PC. Using a computer-generated, blocked sequence, we will allocate Veterans into the two study arms in equal numbers. Randomization will be stratified by site, pre-enrollment use of HT services, and pre-enrollment receipt of Endocrinology care. Notification of randomization assignment will occur within 1 week of enrollment and will be communicated with the veteran via telephone call from the study team. Patients with a baseline HbA1c value below the study inclusion criteria of 8.5% will not be randomized for study participation.

Table 2. Constructs/measures assessed at study baseline.

Construct	Instrument (Reference)	Time
Diabetes burden*	Diabetes Distress Scale	3 min.
Diabetes self-care*	Diabetes Self-Management (DSMQ)	3 min.
Medication adherence*	Voils Medication Nonadherence Measure	2 min.
Self-efficacy*	Perceived Competence Scale	1 min.
	PROMIS Self-Efficacy – SF4a	1 min.
Diabetes knowledge*	Diabetes Knowledge Questionnaire	4 min.
Depressive symptoms*	Personal Health Questionnaire-8	2 min
Health literacy/numeracy	Newest Vital Sign	5 min.
Pain*	PROMIS Pain Interference – SF8a	2 min.
Autonomy*	Healthcare Climate Questionnaire	2 min.

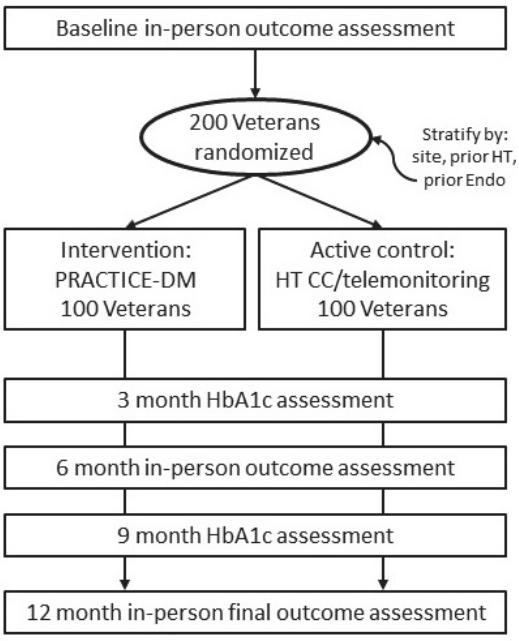
**Also assessed longitudinally*

Study Procedures/Interventions

Intervention group

For Veterans randomized to PRACTICE-DM, each intervention component will be administered by HT nurses, as would be the case in real-world practice. Two HT nurses from each site will work with the intervention group. These nurses will be distinct from the HT nurses that work with the active control group. HT nurses conduct telemonitoring as part of their standard practice; based on our pilot work, HT can deliver PRACTICE-DM with minimal additional training. Intervention HT nurses at both sites will complete training during a single session, which will be led by the study PI, with follow-up/refresher sessions as needed. All HT nurses will receive a hardcopy PRACTICE-DM intervention manual containing study materials and procedures, and will use online software to track intervention activities (e.g., attempted/ completed phone calls, modules delivered, medication changes). PRACTICE-DM research staff will not participate in intervention delivery, but will manage only study-specific tasks like enrollment, randomization, and outcome assessment. Of note, while receiving PRACTICE-DM, intervention-group participants will continue to receive care from PCPs and other VHA providers.

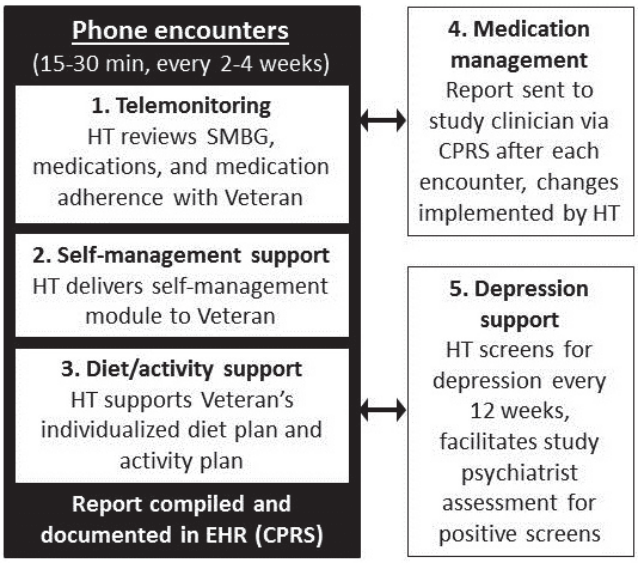
Figure 1. Patient flow through study.



HT will deliver the 5 intervention components during telephone encounters (Figure 2) according to a schedule (see intervention schedule). Each encounter will be documented in an intervention database, as well as in the EHR. Based on feedback from our pilot work, we will allow a degree of flexibility in the encounter schedule for patients who achieve goal HbA1c. The standard encounter frequency will be every two weeks, but may be extended to every 4 weeks for participants achieving their HbA1c goal. Per VA guidelines,(17) HbA1c goals will be individualized based on age, comorbidities, and hypoglycemia risk; most Veterans' goal will be between <7.0% and <8.0% (as will be the case in the control group). Because HbA1c will be assessed every 3 months, the 3-month outcome visit will be the first chance for participants to transition to every-4-week encounters. Should Veterans relapse while receiving the lower encounter

frequency, HT will return to every-two-week encounters until the next HbA1c assessment. The 5 intervention components are described below:

Figure 2. PRACTICE-DM intervention components.



- Telemonitoring: Per HT policy, Veterans receive daily prompts to transmit data using their HT-issued equipment. Failure to submit data for 3 days triggers a call from HT, followed by a letter at 5 days. Per ADA guidelines, and based on their medication regimen and corresponding allocation of glucometer supplies, participants are initially asked to perform SMBG up to four times per day before meals and at bedtime;(18) patients on stable medication doses at goal HbA1c may monitor less frequently at the discretion of the study clinician. At each intervention encounter, HT contacts participants by phone to review SMBG data, reconcile medications, and assess self-reported medication adherence. Following each encounter, HT compiles this information in a report documented in the HER (see report templates). At each intervention encounter, HT contacts participants by phone to review SMBG data, reconcile medications, and assess self-reported medication adherence. Following each encounter, HT compiles this information in a report documented in the HER (see report templates).
- Self-management support: PRACTICE-DM's self-management support component utilizes behavioral strategies rooted in social cognitive theory, and content refined during >10 trials by co-investigator Hayden Bosworth, including recent trials in diabetes.(52-55) We have further adapted this evidence-based content for Veterans with PPDM through our pilot work.(1,2) This component builds patients' self-management capacity by focusing on knowledge and self-efficacy, two key determinants of diabetes control.(56) As PRACTICE-DM is delivered by existing VHA Home Telehealth (HT) nurses, our self-management support component addresses common issues underlying PPDM using a module-based approach appropriate for HT training. Our modules incorporate Veteran-centric strategies such as tailoring and goal setting; all material is at ≤8th grade reading level. At the first intervention encounter, HT nurses work with each participant on individualized goal setting. At subsequent encounters, HT delivers modules according to a schedule (see intervention schedule and modules). HT works with Veterans during some encounters to review and revise goal-setting.
- Diet/activity support: PRACTICE-DM's diet/activity support component is designed to help overweight/obese Veterans (BMI ≥25) achieve >5% weight loss by targeting a 500-750 Calorie/day deficit as per ADA guidelines.(25) Because diets providing equivalent caloric restriction are equally effective in diabetes regardless of macronutrient composition,(57,58) each Veteran's diet plan is individualized based on personal preferences and likelihood of adherence. As per ADA guidelines,(59) our diet/activity support component encourages patients to maintain ≥150 minutes of moderate-to-vigorous-intensity physical activity per week, spread over at least 3 days with no more than 2 consecutive days without activity. Diet and activity are addressed during each phone encounter throughout the intervention period. At the outset of the intervention, the PRACTICE-DM dietitian conducts a baseline call with each Veteran at both sites in order to develop the individualized diet plan. The dietitian also conducts a follow-up call at four weeks to discuss progress and adjust each participant's plan as needed. HT documents each Veteran's individualized diet plan, activity recommendations, and weight loss goals in every intervention encounter note. During each every-two-week PRACTICE-DM encounter, HT reviews participants' goals, follows up progress with regard to diet and physical activity, and records self-reported weight data (a digital scale is standard HT equipment for all overweight/obese Veterans). For Veterans who are

not progressing toward their weight loss goal, additional follow-up may be arranged with the PRACTICE-DM dietician.

- Medication management: Our medication management approach has two key features associated with high impact; it facilitates frequent contact between Veterans and study staff, and allows study clinicians to modify diabetes medications.(39) After each intervention encounter, HT generates an EHR report summarizing participants' SMBG data, reconciled medications, self-reported medication adherence, and the delivered self-management and diet/activity content. HT relays this report to the study clinician via EHR, who considers treatment changes based on our medication protocol. Our protocol targets fasting blood glucose 90-150 mg/dL and preprandial blood glucose 140-180 mg/dL; these liberal goals may be further tailored for individualized HbA1c goals or hypoglycemia. The study clinician notifies HT of any recommendations via addendum to the EHR report (see report templates), and HT contacts the Veteran by phone to implement the changes. PCPs are alerted to changes via EHR. We will use two study clinicians per site, each a doctor-level provider that is well-versed in diabetes medication management. To assure homogeneity in management, we will utilize a medication protocol (see medication protocol) with regular case review meetings to assess protocol fidelity.
- Depression support: Consistent with VA/DOD guidelines,(60) our depression support protocol offers both pharmacologic and non-pharmacologic options. Veterans without baseline depressive symptoms (including those without diagnosed depression AND those with well-controlled depression) do not enter the protocol, but receive screening with the Personal Health Questionnaire-8 (PHQ-8) by HT every 12 weeks.(61) For all intervention subjects with PHQ-8 ≥10, HT arranges an expedited appointment with the site's study Psychiatrist or their existing MH provider, at which the Veteran reviews and chooses between pharmacotherapy and non-pharmacologic options. For those choosing pharmacotherapy, the recommended first-line agent for antidepressant-naïve patients is sertraline (50 mg daily for 4 weeks, titrate to 100 mg for incomplete response),(62) and the alternative is bupropion SR (150 mg daily for 2 weeks, titrate to 150 mg twice daily as needed).(63) For Veterans with a baseline PHQ-8 ≥10 already on an antidepressant, initial options are to increase the current agent, switch to sertraline, or add sertraline to current therapy (or bupropion SR if already on sertraline). For Veterans that opt for a non-pharmacologic approach, the study psychiatrist presents available therapy options and arranges appropriate referrals. The response to the therapeutic intervention will be assess by the study psychiatrist or existing MH provider who will determine whether the subject requires an alternative medication (e.g., bupropion SR if no response to sertraline), combined pharmacotherapy, an alternative non-pharmacologic approach, or combined medication/non-pharmacologic treatment. Patients with symptom remission (PHQ-8 <10) are monitored by HT for recurrence every 12 weeks. Emergency Psychiatric services (suicide hotline and VAMC emergency clinics) are available throughout the study. Please see the PRACTICE-DM Depression Support Algorithm for additional study practice guidelines.

Control group

Veterans randomized to the active control group at each site will receive standard HT services; the HT nurses assigned to these Veterans will be distinct from those working with the intervention group. As per the "Telemonitoring" subsection above, participants will be instructed to transmit SMBG data daily using their HT-issued equipment. Per HT policy at both sites, Veterans will receive daily prompts for data transmission, and failure to submit data for 3 days will trigger a call from HT, followed by a letter at 5 days. Participants will not have study encounters, but will receive standard VA HT care coordination in addition to telemonitoring. Care coordination at both sites will include pre-appointment compilation of SMBG data for review by PCPs or other providers, as well as communication with Veterans as needed between appointments. Control group participants will continue to receive care from PCPs and other providers.

Study follow-up

Veterans will receive their assigned intervention for 12 months. At 6 and 12 months, all will attend in-person outcome assessment visits (Figure 1), at which they will complete a follow-up survey, BP/BMI measurement, and HbA1c testing. The estimated time required for these visits will be 45 minutes. At 3 and 9 months, all Veterans will have interim HbA1c assessment, which can be performed at the nearest CBOC or VAMC. At study completion, all participants at each site will continue routine HT management, with subsequent disposition per HT policy. Responsibility for diabetes care will return to PCPs and other providers.

In order to further examine PRACTICE-DM's acceptability and mechanisms of effect, we will also conduct phone-based, semi-structured, qualitative interviews with 20-30 randomly chosen intervention arm subjects (approximately 10-15 from each site) following their 12-month study visits. Patients will be asked to provide consent to be contacted for these interviews at the time of study enrollment.

Outcomes

Effectiveness outcomes

Our primary effectiveness outcome will be HbA1c difference between groups (baseline to 12 months). We will also examine multiple secondary outcomes. We will use the Self-Care Inventory-Revised (SCI-R) to examine Veteran engagement with PRACTICE-DM.(64) We will examine diabetes burden as a marker for perceived workload using the Emotional Burden/Regimen Distress subscales of the Diabetes Distress Scale (DDS).(65) We will use the Perceived Competence Scale (PCS) to examine patient capacity.(66) We will examine weight and depressive symptoms as secondary clinical outcomes using BMI and PHQ-8.(61)

Process evaluation outcomes

We will examine PRACTICE-DM's acceptability and mechanisms of effect through a mixed-method process evaluation, which will help refine the intervention for future implementation. Using a qualitative approach, we will conduct phone-based, semi-structured interviews with approximately 20-30 intervention arm subjects (approximately 10-15 from each site) following their 12-month study visits. Interview guide questions will probe patients' explanatory models of diabetes, general perceptions of what did and did not work well with PRACTICE-DM, and impressions of the 5 intervention components (see draft interview guide). We will also seek consent to conduct phone-based, semi-structured qualitative interviews with the 2-3 HT nurses that participate in delivering PRACTICE-DM at each site, as well as with 2-3 administrators/medication managers at each site. As with the patient interviews, these interviews will help refine the intervention and will also provide data to guide future implementation. Along with this qualitative work, we will quantitatively examine possible moderators and mediators of PRACTICE-DM's effect. In addition to guiding intervention refinement and implementation, these analyses will help us explore how the individual PRACTICE-DM components contribute to the overall intervention effect.

In order to explore the need for possible refinements to the current PRACTICE-DM intervention design, we are interested in examining clinical information related to diabetes complications and comorbidities associated with PPDM, including retinopathy, nephropathy, neuropathy, dyslipidemia, hypertension, and nonalcoholic fatty liver disease. This clinical information will include only data that are available in the EHR and will not require prospective data collection or new patient contact. Specifically, we will examine medications, laboratory data (e.g., lipid profiles, gastrointestinal panels, kidney function and urine microalbumin), and data related to imaging and procedures associated with diabetes complications and comorbidities.

Additionally, we will ask four program acceptability questions at the completion of the 12-month program with all participants receiving the PRACTICE-DM Intervention or Standard Home Telehealth programs. The four questions were already approved as part of our quantitative evaluation but were not administered to all patients at the time of program completion. In order to collect these acceptability data, we will query all study participants at either the 12-month interview, on a brief follow-up telephone call (if the 12-month interview has passed), or via a mailed survey (if we are unable to reach via telephone call after 3 attempts). These questions will be optional and will take less than 5 minutes to complete. When telephone contact is made or when mailed materials are sent, we will remind the

participants that their participation is optional. No additional compensation will be provided for responding to the questions. The four survey questions can be found in the survey files.

Cost outcomes

We will assess intervention-related and VHA health care costs associated with delivering PRACTICE-DM and our active control. Labor and capital costs will both be captured in calculating intervention costs. Labor will include HT nurse and study clinician time as determined using daily logs documenting engagement in study tasks, with salaries based on VHA Human Resources salary data. For each arm, we will distinguish research-specific costs (e.g., staff time spent preparing regulatory documentation or in research meetings) from intervention costs (e.g., HT nurse time spent interacting with patients, HT time spent documenting reports and communicating with study clinicians, study clinician time). Capital costs will include HT telemedicine equipment, telephone service costs, overhead costs, and supplies.

VHA health care costs will include costs for all health care utilization (clinic visits, Emergency Room visits, hospitalizations, procedures, laboratory, pharmacy, radiology, nursing, and all other clinical costs) that occurs in VHA facilities or facilities reimbursed by VHA (e.g., fee basis) during the 12-month intervention period. Along with tracking local utilization of services (e.g., different types of clinic visits, use of ancillary clinical services, Emergency Room visits, and hospitalizations), we will take a VHA payer perspective to this analysis, so we will obtain cost data from Managerial Cost Accounting National Data Extracts and fee basis files.

Adverse Events

All adverse events will be reported per Durham VAMC requirements. All Serious, Unanticipated and Related adverse events will be reported to IRB within 5 business days of hearing of the event. All other adverse events will be reported at continuing review.

Expected adverse events associated with study participation in both arms may include hypoglycemia (as a result of glucose-lowering treatments) and reactions to commonly-used diabetes or depression medications (e.g., diarrhea with metformin or sertraline, injection site irritation from insulin). Because PRACTICE-DM utilizes approaches that are common in standard practice, we anticipate that adverse events will be similar to standard care in quality and rate. We will assess adverse events in both arms by structured self-report,(67) and as hypoglycemia is the most common side effect of diabetes therapy, we will examine the incidence of blood glucose <70 in both groups by reviewing SMBG data transmitted to HT during the study.

Due to the age and comorbidities of our study cohort (e.g., risk of vascular disease, existing depression), hospitalizations and other health events (e.g., development of new medical conditions, surgeries, ER visits, MI, stroke, falls and death) unrelated to the study are expected. Any events that fall into one of these categories will be reported at continuing review/per the current SOP. Participants may miss study encounters or follow-up assessments during the conduct of the project. We will not consider such events to be protocol deviations, as they will not impact participants' healthcare or impose any additional risks.

At study outset, Veterans will be instructed to seek immediate emergency services for any adverse events that require urgent in-person evaluation. As some recruited patients may have diagnosed or undiagnosed depression, all patients will be given the national suicide hotline number at study outset for use as needed.

Risk/Benefit Assessment

Medical risks associated with study participation in both arms are similar to standard diabetes care, and include hypoglycemia and reactions to commonly-used diabetes/depression medications. PRACTICE-DM combines 5 strategies: 1) telemonitoring, which is available as part of standard VHA care for Veterans with poor diabetes control; 2) self-management support, which is central to effective diabetes care in any setting; 3) diet/activity support, which is a front-line treatment approach for all patients with diabetes; 4) medication management, which is also a requirement for effective diabetes management; and 5) depression support, which enhances patients' ability to self-manage their diabetes. It is possible that combining these multiple standard diabetes management strategies into a single intervention may increase the risk of hypoglycemia versus standard care, but we have mitigated this possibility by

utilizing relatively liberal blood glucose targets (fasting blood glucose 90-150 mg/dL, preprandial blood glucose 140-180 mg/dL) and individualized HbA1c goals, which may be further relaxed for evidence of hypoglycemia. Further, all Veterans will be provided with detailed instructions for hypoglycemia management at study outset, and will also be prescribed a glucagon emergency kit for complicated hypoglycemia if deemed appropriate by study staff. Our active control, HT care coordination and telemonitoring, is available as part of routine VHA care, so risks will not exceed standard care.

Of note, patients in both study arms will receive HT telemonitoring. Because HT nurses are uniquely suited to identifying and managing hypoglycemia and other therapeutic risks in Veterans with diabetes, overall detection and amelioration of medical risks could actually be enhanced relative to standard care. Further, all Veterans will continue to receive their regular VHA care with PCPs and other providers during the study, which will provide an added layer of risk protection. At study outset, Veterans will also be instructed to seek immediate emergency services for any adverse events that require urgent in-person evaluation.

Risks specifically associated with study procedures, such as venipuncture, are minimal. As with any study, risk exists for breach of confidentiality and loss of protected health information (PHI), but steps will be taken to minimize this risk as per the "Privacy and Confidentiality/Information Security" section below.

Direct benefits associated with study participation may include improved diabetes control (which is particularly elusive for Veterans with PPDM). Improved control could translate to reduced rates of future complications (which are particularly common for Veterans with PPDM). Veterans may also experience reduction in weight and improved control of depressive symptoms. Potential benefits to study subjects include improved glycemic control and avoidance of future diabetic complications. Benefits for Veterans not enrolled in this study may include the development of an effective, practical treatment option for Veterans with PPDM, which is currently not available within or beyond VHA.

Costs and/or Payments to Subjects

Participating Veterans will receive compensation for travel and time for all outcome visits. Since the baseline, 6-, and 12-month visits require travel to a VAMC, participants will receive $50 per visit. The 3- and 9-month assessments will require less time/travel, so Veterans will receive $25 per visit (maximum total compensation $200/Veteran).

Data and Safety Monitoring

Fidelity assessment

We will conduct a fidelity assessment in order to assure the intervention is delivered in a manner consistent with our protocol across sites. Nurses will use a database to track all intervention activities, and this documentation will be reviewed weekly by the study coordinator in order to assure that intervention components due at each encounter were delivered. The overall study PI (Dr. Matthew Crowley) and overall project coordinator (Ms. Susanne Danus) will randomly tape record or listen to approximately 10% of calls at each site in order to ensure consistency in intervention delivery. Should we encounter interventionist-specific problems, we will work with local HT to enhance the quality of the nurse-patient interactions. Finally, we will assure fidelity to our medication management protocol through quarterly case review meetings, which all study clinicians will attend through VHA conferencing.

Data monitoring committee

We will also utilize a Data Monitoring Committee (DMC) for this study in order to monitor sample enrollment/randomization and safety issues at both sites. The DMC will consist of the overall PI (Dr. Matthew Crowley), the Richmond site PI (Dr. Phillip Tarkington), the other study clinicians, the study statistician, the overall project coordinator, and in order to provide an independent perspective, 2 Durham VAMC diabetes providers (e.g., Endocrinologist, PharmD) not affiliated with the study. The DMC will carry out the following functions:

- The DMC will monitor enrollment/randomization at both sites to assure that the study adheres to the proposed timeline. Although we do not anticipate any difficulty meeting our enrollment/randomization goal in the time

allotted, should slower-than-expected recruitment occur, the DMC will consider site-specific options to bolster enrollment/randomization, and if necessary, the replacement of an underperforming site.

- The DMC will also review both individual adverse event reports and aggregated safety data to identify potential safety concerns in the intervention and control groups, meeting approximately every six months during the study period and as needed when concerns arise. The DMC will communicate any necessary information to other study staff as needed. Any findings or issues that require reporting to the IRB, participants, or PCP will be disseminated by the overall PI and project coordinator. The issue in question will determine the mode of information transmission (e.g., letter, secure e-mail, phone call).

Integrity of study data

Accuracy and integrity of study data will be ensured in two ways. First, the Durham VHA COIN conducts computer operations in a secure Centralized Computing Facility managed by VHA network and server administrators. Within this computing facility, all research data are stored on VHA-Administered servers, which are physically secured in the Durham VAMC computer room. VHA network access to research data is controlled in accordance with the COIN's standard operating procedures and VHA policies. In addition, standard COIN procedures ensure that servers, workstations and portable computers are kept up-to-date with virus filters, security patches, software updates and firmware updates.

Data management

Study tracking data will be entered into an intervention database created by our COIN's software development team (Microsoft .NET). Because this study's recruitment, enrollment, and follow-up processes are similar to multiple previous studies that have used this database, we will be able to customize the database to meet our needs. This database will allow us to track: patient study status (i.e., eligible, enrolled, refused); the results of screening interviews; intervention tasks due for each participant; and encounter-specific data (e.g., attempted/completed phone calls, duration of phone encounters, modules delivered, medication changes). The randomization sequence and any necessary stratification variables can be imported and will allow our project coordinator to be able to randomize participants within the database. Screening and outcome measures will be entered directly into the study database using DatStat Illume™ or RedCAP, web-based survey tools. RedCAP will be hosted on the VINCI servers. Data will be stored in a restricted folder on a secure VHA server.

Future Use of Data

We may want to run secondary data analyses related to the original aims of the grant (for example moderator/mediator analyses, analyses of baseline data, etc.). It is also possible that data collection under this protocol might be used to inform future surveys, interviews, and/or intervention development among patients with diabetes. Data would only be used from patients who agreed that their data could be stored and used for future analysis on their complete Informed Consent and HIPAA Authorization forms. For these secondary analyses we would not use data from patients who provided written documentation of study withdrawal, as detailed in the section below. To facilitate participation of investigators outside of our core study team in these study-related secondary analyses, we will create a de-identified PRACTICE-DM data set (see 'De-identified dataset' below).

For any new projects unrelated to the original aims of the grant, a separate protocol, defining the new project(s) would be submitted to the Durham VA IRB. Such future studies would request either a waiver/ alteration to the ICF/HIPAA requirements or a consent form and updated HIPAA Authorization, as appropriate.

Withdrawal of Participants

Patients may be withdrawn from the research study without their consent under the following conditions (also previously listed as exclusion reasons):

1. Inability to communicate by telephone

2. New diagnosis of dementia or psychosis
3. Active alcohol or substance disorder
4. Current report of new pregnancy during study
5. New instance of hypoglycemic seizure or coma
6. Refusal to perform self-monitored blood glucose (SMBG)
7. Use of continuous subcutaneous insulin infusion pumps
8. HbA1c value < 8.5% at baseline study assessment

Patients who choose to withdraw from the study after enrolling will be asked to provide written documentation of the request to the study team. If a patient withdraws, no new data will be collected about him/her, other than a possible reason for withdrawal. All data collected prior to the date of withdrawal will remain with the study files and may be used for analysis.

Privacy and Confidentiality/Information Security

Our experienced team has a strong understanding of research-associated risks and will take all necessary measures to protect patients at both study sites. Dr. Crowley (overall study PI) sits on the Durham VAMC IRB, and Dr. David Edelman (co-investigator) is the Chair of the Durham VAMC IRB. Data security for this project will be overseen by the VA OIT via use of security user groups that limit data access. The Durham COIN has developed standard operating procedures for data acquisition and data management, which are designed to protect against data loss and maintain patient confidentiality. These procedures have been used in many studies and we will adhere to these procedures at both sites for the proposed study.

All participant information collected in the context of this research study, even the fact that an individual is participating in the study, will be considered confidential, and the study team will take steps to ensure the participant's confidentiality is protected at each step of the research process:

- Each participant will be assigned a study identification number (ID), which links all computerized research records; all research data files are organized by study ID, with no names or other identification attached.
- All PHI will be housed on a secure server behind the Durham VAMC firewall at both sites, and access will be restricted. Computerized study data will be maintained on VHA network servers which are secured behind a firewall (as well as through controlled physical access). Server access is controlled by OIT, and staff members will only be allowed access to data pertinent and authorized for their role. All study forms and paper records that contain participant information will be kept in secured, locked areas when not in use, accessible only to appropriate personnel; when in use, these materials will be kept from public view.
- All voice recordings will take place at Durham VAMC. Staff will use a VHA encrypted laptop in conjunction with VA approved software that has been installed and configured by VA OI&T personnel after sanctuary exemptions have been obtained. Originally a "Sparky" USB-attached audio recording device and then the VA network WebEX program to record interviews, which will then in both methods be saved on the encrypted computer, immediately uploaded to a restricted folder on the VHA server network, and then removed from the laptop. We will remove identifiers from the file names and interview notes.
- All study personnel will maintain IRB research certification, with special training in research ethics. This training includes detailed instruction on confidentiality.
- Participants will not be identified by name in any reports or publications, nor will data be presented in such a way that the identity of individual participants can be inferred. All information obtained in the course of the study that identifies an individual will be treated as confidential in accordance with section 903C of the Public Health Service Act (42 U.S.C.299a-1). We will strip all identifiers from analytic data sets after data merging, and keep all personal identifiers in a separate location from the analytic data. Database files needed to generate mailing labels will contain no research data.

Privacy, Confidentiality, and Information Security

1. *Lists of Data Reviewed and/or Collected for Screening/Recruitment and Conduction of Study:*
   The Personal Health Information that will be obtained, used, and/or shared for this study includes:

Identifier(s)	Source(s) of Health Information
☒ Names	☒ Medical history & physical exam information
☒ All geographic subdivisions smaller than a State, including street address, city, county, precinct, and zip code. Describe: Full mailing address to include street, city, state and zip code	☒ Photographs, videotapes, audiotapes, or digital or other images
☒ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, visit or treatment dates, etc.; and all ages over 89, Describe: DOB, Dx dates, Visit, treatment, hospitalization and outpatient dates	☒ Biologic specimens (e.g., blood, tissue, urine, saliva). Describe: blood samples to test HgA1c (applicable only when not using VA lab services for collection and testing)
☒ Telephone numbers	☒ Progress notes
☐ Fax numbers	☒ Diagnostic / Laboratory test results
☐ Electronic mail addresses	☐ Operative reports
☒ Social Security Numbers	☒ Imaging (x-ray, CT, MRI, etc.)
☒ Medical record numbers	☒ Discharge summaries
☐ Health plan beneficiary numbers	☒ Survey / Questionnaire responses
☐ Account numbers	☐ Billing records
☐ Certificate and/or license numbers	☐ HIV testing or infection records
☐ Vehicle identifiers and serial numbers, including license plate numbers	☐ Sickle cell anemia information
☐ Device identifiers and serial numbers	☒ Alcoholism or alcohol use information
☐ Web Universal Resource Locators (URLs)	☒ Drug abuse information
☐ Internet Protocol (IP) address numbers	☒ Mental health (not psychotherapy) notes
☐ Biometric identifiers, including finger & voice prints	☐ Psychological test results
☐ Full-face photographic images and any comparable images	☐ Genetic testing
☒ Any other unique identifying number, linked study ID, characteristic, or code, describe: Randomly assigned study ID number (for example: PRACTICE#####)	☒ Other, describe: Specialty consults related to DM care (such as Nephrology, Neurology/pain/anesthesia, Ophthalmology, Lipid clinic, Cardiology, and Hepatology/Gastroenterology)

Although we will enroll non-Veterans in this study, we will not be collecting any personal health information on the non-Veterans. Therefore, we will not provide the VA Notice of Privacy Practices (NOPP) for signature. Non-Veterans that will be enrolling in the study include the affiliated study staff members (HT nurses and administrators). We acknowledge that these staff members may be also be Veterans. We will obtain verbal consent from the study staff members so that we can gather their feedback in a qualitative interview related to the implementation of the study procedures and education provided to the patients.

2. *Data and/or Specimen Acquisition:*

Data for this study will be collected through (*check all that apply*):
☒ Prospective data and/or specimen collection obtained from participants. Provide description of processes:

Participants will be contacted by a mailed recruitment letter followed by a telephone call, if they have not previously opted out, to assess interest in study participation. If the patient is interested, an in-person appointment will be arranged in which the patient will be asked to provide informed consent. All data collection will occur during study contacts and visits in which we collect data using approved scripts and questionnaires. Patients will also be asked to provide blood samples to the lab for HbA1c testing throughout the study (baseline, 3m, 6m, 9m, 12m). We will also obtain biometric measures (height, weight, blood pressure) from the patients at each in-person study visit.

Employee stakeholders will be contacted via telephone. Those who are interested will be provided a verbal consent process and asked to respond to questions included in the corresponding semi-structured interview guide during a telephone interview.

☒ Retrospective data collection and/or specimens obtained from medical chart review/data access. Describe how data will be obtained (e.g., fileman, CDW, etc.):

Once IRB approval has been obtained, we will initiate a DART request to identify the eligible patient sample, identify upcoming appointments and to obtain necessary information from the CDW as well as perform a chart review of the patient's medical records as needed in either CPRS or VistaWeb/JLV. We may need to access the medical records throughout the study to monitor study progress, obtain lab values, pertinent health information, contact information changes, adverse events, etc.

☐ Retrospective data collection and/or specimens obtained from an IRB-approved data and/or specimen repository. Indicate the repository source including name, VA location, and IRB number: .
Note: for data and/or specimens obtained from a VA approved data repository, a Data Use Agreement (DUA) must be executed prior to obtaining data and/or specimens. See VHA Handbook 1200.12 for further information.

3. Level of Data:

The following level(s) of data will be acquired/maintained for this study (*check all that apply*):

☒ Identified (e.g., names, addresses or other identifiers included)
☒ Coded (direct and/or all identifiers removed, but study code/ID included)
☒ De-Identified (all HIPAA 18 and study ID/code removed):
- ☐ Verified Statistically
  OR
- ☒ Verified by Absence or Removal of HIPAA 18 and study ID

☐ Limited Data Set
☐ Other: Describe:

4. Location of Data and/or Specimens, and Data Retention Plan:

A. Data and/or Specimen Location:
   a. The Durham VAHCS OI&T staff has computer servers located at the Durham VAMC. This center houses database servers, web servers, file servers, and the like that provide the computing infrastructure used by HSR&D.

B. Data will be stored electronically in a secure folder located: R:\\[server name]Practice_DM
   a. Data that will be stored electronically include Data that will be stored on this server include: study sample identified from the CDW, study documents, reports, and all other electronic study files
   b. All study data will be backed up on a regular schedule.

C. Paper records of data including any Durham project source documents will be stored in a locked file cabinet located in the secured HSR&D research space in Legacy Tower in office 719 and/or 632G. Paper records from the Richmond, VA will be scanned and stored on the Durham VA server and kept in locked file cabinets in the care of the local site PI. Once all study related data collection activities have been completed, the Richmond paper forms may be returned to Durham for consolidated storage in accordance with VA record control requirements. This process will be submitted to IRB prior to any file transport.

D. Specimens include blood samples collected by the lab or certified study personnel to test HbA1c values and will be obtained and stored in accordance with local VA policy.

E. ☒ Data will be also be placed at the VA Informatics and Computing Interface (VINCI; http://vaww.vinci.med.va.gov/vincicentral/VINCIWorkspace.aspx). The VA Informatics and Computing Infrastructure is a partnership between the VA Office of Information Technology and the Veterans' Health Administration Office of Research and Development. Researchers and operations staff can use VINCI to access data and statistical analysis tools in a virtual working environment through a certified VHA network computer using the VA Intranet or Virtual Private Network (VPN).

B. Data Retention Plan
☒ Research records will be maintained and destroyed according to the National Archives and Records Administration, Records Schedule Number: DAA-0015-2015-0004. Records destruction, when authorized, will be accomplished using the then current requirements for the secure disposal of paper and electronic records. Currently, destruction of research records (see DAA-0015-2015-0004, section 7.6 "Research Investigator Files" for materials included in research records) is scheduled for 6 years after the cut-off (the cut-off is the completion of the research project) and may be retained longer if required by other federal agencies. Records will not be destroyed without pre-notification to the facility records manager.
☐ Other data retention plan, describe:

5. Data Access and Data Recipients:

a. Only those individuals listed on the project staff listing will be granted access to the data.
    i. Computerized study data and access to data will be user group protected, and staff members will be assigned individualized permissions that allow them access to only those elements of the data management system to which they are authorized.
    ii. The study tracking forms containing names and patient contact information will be protected using study user group policies and will only be accessible to study personnel who need access to patient identifiers.
b. All data will be maintained on a password protected secure VA server behind the VA firewall and no data will transfer outside of the VHA system.
c. All VA research personnel who have access to VHA records are instructed, in accordance with VA policy, on the requirements of Federal privacy and information laws and regulations, VA regulations and policies, and VHA policy. All study personnel who are VA employees working within the VA system have fulfilled all required HIPAA and other VA security and privacy policy training requirements and have agreed to follow guidelines pertaining to the protection of patient data. All research staff sign VA Rules of Behavior, and all study staff are up-to-date with VHA Privacy Policy Training and the VA Office of Cyber and Information Security Awareness Training Course. The data security and privacy procedures summarized in that course include logging off or locking the computer when walking away from it; no sharing of access codes, verify

codes or passwords; not allowing anyone else to use the computer under one's password; and disposing of sensitive information using VA-approved methods (e.g., shredder bins).

d. The deidentified data set that contains A1c lab values, arm assignment, and timepoint in study participation will be shared with Frank Neelon, MD at Duke University Medical Center.
e. Access to study data will be removed for all study personnel when they are no longer part of the research team.

6. Data and/or Specimen Transportation and/or Transmission for all data and/or specimens involved in the study:

I. ☐ Data and/or specimens will not be transported or transmitted outside of Durham VAMC environment.

II. ☒ Data and/or specimens will be transported BETWEEN sites that are under the auspices of the Durham VA Medical Center. To meet the needs of Durham VAHCS patients, the possibility exists that patients may be seen at one of the affiliated CBOCs . If patients are seen at one of the non DVAMC locations, all electronic data will be entered immediately using VA computers, paper source documents (signed consent forms, outcome measure forms, etc) will be immediately transported back to the HSR&D office space by the research staff that collected the information. Patients that enroll at the Richmond site will have information directly entered onto the Durham VA's network (access will be granted to the study folder and study tracking system) and paper copies (signed consent forms, outcome measurement forms, etc) will be kept by Richmond study personnel and stored in locked file cabinets in accordance with local policy.

III. ☒ Data and/or specimens will be transmitted to other VA sites using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted disk (encryption is optional).

☐ Data are coded or contain identifiers and thus will be sent

☒ Other, describe: All study related data will remain on the Durham VAHCS servers. Richmond and Salt Lake City study staff will be granted access to Durham's study folder and all electronic study files will remain behind Durham's firewall. Blood samples obtained in Durham will remain in Durham, blood samples obtained in Richmond will remain in Richmond and will be stored/maintained in accordance with local policy. Any paper records (source documents, consent forms, etc) will be stored/maintained in accordance with local VA policy. The HT interventionist will conduct intervention interviews using the HSRD created tracking application and other hard copy scripts. If the HT nurses create source documents to record the intervention survey answers, these will be identified using a study ID number and will not contain PHI. This method is being used to limit the burden on the home telehealth nurses and any hard copy responses will be transferred back to the patient's research file located in Legacy Towers. The home telehealth nurses will utilize the study tracking database to document all contact and patient PHI. Since the study utilizes the clinical services of HT, the EHR will also be utilized for data collection and all data will be maintained in accordance with VA policy.

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional).

☐ Specimens are coded or contain identifiers and thus will be sent via VA-authorized carrier with tracking.

☐ Other, describe:

IV. ☒ Data and/or specimens will be transported to non-VA/VHA sites (e.g., academic affiliates, laboratories, etc.) using the following method(s):

A. Data

☒ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted CD.

☐ Data are coded or contain identifiers and thus will be sent via <chose method of transfer such as FIPS 140-2 encrypted CD or FIPS 140-2 encrypted hard drive/flash drive> using VA—approved carrier with tracking.

☐ Data are coded or identified and will be uploaded to sponsor website using electronic case report form (eCRF)

☐ Other, describe:

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional) or will be hand-delivered by research study personnel. Specify method of delivery:

☐ Specimens are coded and thus will be sent via VA-approved carrier with tracking or will be hand-delivered by research study personnel. Specify method of delivery:

In accordance with the HIPAA and the Privacy Act, for any coded or identifiable data or specimens released from the Durham VAMC (with the exception of Limited Data Sets), an Accounting of Disclosure (AOD) will be maintained (e.g., in a database or spreadsheet) that includes the participant's name, date of the disclosure, description of the nature of the Individually Identifiable Information (III) disclosed, purpose of each disclosure, and the name and address of the person/agency to whom the disclosure was made.

C. ☒ Local DVAMC memorandum "Authorization to Use, Process, Store, or Transmit VA Sensitive Information Outside VA Owned or Managed Facilities" has been pre-filled out for each study team member who may transport the data and/or specimens off-site. This (these) forms are included with the IRB materials. *The memo referenced above is required to be fully signed for each study team member BEFORE any data can be transported by that individual.*

D. ☒ Containers (e.g., briefcase, bin) are labeled with the following notice (label placed on the outside of container) in accordance with VHA Directive 6609:

NOTICE!!!
Access to these records is limited to: AUTHORIZED PERSONS ONLY.
Information may not be disclosed from this file unless permitted by all applicable legal authorities, which may include the Privacy Act; 38 U.S.C. §§ 5701, 5705, 7332; the Health Insurance Portability and Accountability Act; and regulations implementing those provisions, at 38 C.F.R. §§ 1.460 – 1.599 and 45 C.F.R. Parts 160 and 164. Anyone who discloses information in violation of the above provisions may subject to civil and criminal penalties.

7. Risk Mitigation Strategies:

a. All study records that contain participant information will be kept in secured, locked areas located in the HSR&D research space in Legacy Tower, office 719 and/or 632G when not in use. In addition, such materials, when in use, will be kept away from public scrutiny.
b. Computerized study data and access to data will be user group protected, and staff members will be assigned individualized permissions that allow them access to only those elements of the data management system to which they are authorized.
c. All electronic study materials will remain behind the VA firewall on the VA server in the project specific folder.

d. Direct identifiers (patient name, address, etc) will be maintained separately in the study's tracking forms from data by using a study ID number to identify subjects. The separate tracking forms will be linked to identifying subject information and will be limited to only those who need access to patient identifiers.
e. All research files are in the care of the PI, Dr Matthew Crowley.
f. All study personnel listed on the staff listing will maintain certification with the Durham VA IRB to ensure that they have completed training in research ethics and confidentiality.
g. Study participants will not be identified by name in any reports or publications, nor will data be presented in such a way that the identity of individual participants can be inferred.

☒ Data are fully de-identified (stripped of HIPAA 18 and study ID/code) before being shared outside of Durham VAMC.
☐ Specimens are fully de-identified (stripped of HIPAA 18 and study ID/code before being shared outside of Durham VAMC.
☒ Direct identifiers will be maintained separately from data and or specimens by using a code to "identify" subjects. In a separate database (i.e., a "linking" or "cross-walk" database) this code will be linked to identifying subject information.
☐ Other, specify:

8. Suspected Loss of VA Information:

Should any incident such as theft or loss of data, unauthorized access of sensitive data or non-compliance with security controls occur it will be immediately reported according to VA policy. All incidents regarding information security/privacy incidents will be reported to the ISO and PO within 1 hour of acknowledgement of issue and done so using the VHADUR Research Events Report e-mail group (VHADURResearchEventReport@va.gov).

9. Reporting of Results:

☒ Reporting of results, such as in scientific papers and presentations, will never identify individual subjects. Data will be presented in aggregate and individual-level data will not be published.
☐ Other results reporting plan, describe:

10. Future Use of Data:

☒ Data will be retained for future use. This is described elsewhere in the protocol and is noted in the HIPAA authorization.
☒ Future Use of data is optional (i.e., not required by the research subject).
☐ Future Use of data is required for participation in the study.
☐ No future use of data is currently planned.

11. Use of Mail Merge Technology

☒ Mail merge programs will be used to generate letters and/or address labels for mailings to potential or already enrolled research subjects. The study team is aware that to reduce risk of mail merge related privacy incidents, use of mail merge programs requires a 25% accuracy check to verify that (potential) research subject name and mailing address are properly "matched". If discrepancies are found, a 100% accuracy check is required before letters may be mailed.

12. Use of Non-Standard Software

☒ I do NOT intend to use any new specialized software (i.e. Software that's not already approved OR installed) in this study.

We will be using DatStat Illume or RedCAP for survey data collection, USB 'Sparky' audio recording pass through devices and or VA approved and installed audio recording programs (for example, WebEX), and HSR&D developed tracking databases during this study. All have previously been used in other past and ongoing Durham studies.

☐ I intend to use specialized software that has not already been installed and it has been approved for use by the VA Technical Reference Model (TRM) Group.
(Note: All new software must be approved by TRM before it can be installed on VA systems.)

☐ I intend to use previously installed software on my VA computer.

13. Use of Cloud Computing Services
☒ Cloud computing services will NOT be used in this study.

☐ Cloud computing services WILL be used in this study as described below and have been approved nationally by the VA Chief Information Officer (CIO). (Note: ONLY cloud computing services that have been approved nationally may be used.)

Data Analysis and Statistical Considerations
Primary analysis

HbA1c will be collected at 0, 3, 6, 9 and 12 months. Because HbA1c is a continuous outcome, we will use linear mixed-effects models (LMM) to examine between-arm differences over time.(68) LMM will allow implicit accounting for the correlation between a patient's repeated measures over time. The general mean structure of the LMM we will use to examine this hypothesis will be:

$$Y_{ij} = \beta_0 + \beta_1 * I(month = 3) + \beta_2 * I(month = 6) + \beta_3 * I(month = 9) + \beta_4 * I(month = 12) + \beta_5 * arm * I(month = 3) + \beta_6 * arm * I(month = 6) + \beta_7 * arm * I(month = 9) + \beta_8 * arm * I(month = 12)$$

Here, Yij represents HbA1c for patient i at time j. We will fit a common intercept, and arm reflects PRACTICE-DM vs. active control). Time is also classified; for example, I(month=12) is a dummy variable equal to 1 for the 12 month time point (baseline is the referent). Random intercepts will be included for each individual to account for correlation among repeated measures over time. The primary analytic model will adjust for stratification variables (study site, prior HT, prior Endocrinology). Mixed effects model parameters will be estimated and tested using SAS PROC MIXED (SAS Institute, Cary, NC). The hypothesis of between-arm differences over time will be tested using estimate statements within PROC MIXED. The estimated difference in HbA1c between HT and ST arms at 12 months (8) will be the primary effectiveness outcome.

Secondary analyses

Diabetes-related distress, diabetes self-care, self-efficacy, *BMI,* and depression will be fit using the same model structure as for the primary outcome, but with the 3- and 9-month terms removed (as they are only collected at 0, 6, and 12 months). We will evaluate intervention engagement (SMBG transmission) and adverse events descriptively, examining mean occurrence in each group during the study. Additional secondary analyses of data relating to diabetes and complications and comorbidities will be conducted using standard statistical approaches, similar to above.

Missing data

Clinical outcome values may be missing due to dropout, incomplete follow-up, or item non-response. Mechanisms for missing data will be investigated by describing missingness by intervention group, identifying missing data patterns, and understanding which observed covariates predict missingness. Our main analysis technique, LMM, implicitly accommodates missingness when the response is Missing At Random (i.e., due either to treatment, to prior outcome, or to other baseline covariates in the LMM).(68) In our study, we will also address missing data explicitly using multiple imputation procedures,(69) which are useful when covariates have missing data, when time-varying covariates

are predictive of future missingness, or when there is no scientific interest in conditioning on baseline covariates that are predictive of missingness in the final LMM. Once missing values have been multiply imputed, each dataset can be analyzed using standard complete-data methods, such as LMM. Final parameter estimates and standard errors will be calculated using Rubin's formula for combining results from multiply imputed data sets.(70) We will analyze our data and report final study results with and without multiple imputation, and carefully examine discrepancies.

Intention-to-treat analysis

Per the intention-to-treat principle, all participants must be included in the final data analysis once randomized, and all should be analyzed in the group to which they were randomized. Because HbA1c will be measured pre-randomization, we do not expect missing baseline HbA1c or study arm indicator variables in the randomized sample, so our primary analytic technique fulfills both requirements.

Power calculation

We derived power estimates empirically via simulation (SAS 9.4). Based on our pilot work,(19) we assumed a baseline HbA1c of 10.3% for both arms. We assumed a reduction in the control arm of 0.5% by 12 months; given uncertainty about the quality of existing telemedicine studies, this is a conservative estimate. For the PRACTICE-DM arm, we assumed a reduction of 1.1% at 12 months; this reflects a conservative hypothesis that PRACTICE-DM will reduce our primary outcome (HbA1c) by 0.6% relative to control by 12 months.(1) Based on prior work,(1) we conservatively assumed a 20% dropout by 12 months, a standard deviation (SD) of 1.6 and a within-individual correlation of 0.55 for repeated HbA1c measurements. After generating 1,000 simulated datasets with these assumptions, we fit the LMM to each and assessed the effect of interest using two-sided tests with α=0.05. With 100 patients in each arm and our conservative variance estimates, the power estimate is 80.5% for our primary outcome. We will also be able to detect meaningful between-group differences in our secondary outcomes.

Qualitative analysis

All interviews will be recorded and transcribed verbatim. Approved staff from the VA Salt Lake City (VASLC) will transcribe the PRACTICE-DM audio files. The VASLC has a Professional Transcription Service available to VA sites and monitored by their own IRB. The PRACTICE-DM audio recordings to be transcribed by VASLC staff will be labeled by the subject's unique alphanumeric code and saved behind the VA Firewall PRACTICE-DM's secure shared project folder on the Durham HSR&D's Project R drive ([server name]\PRACTICE_DM). The VASLC Transcriptionist staff will be given access to a sub-folder within PRACTICE-DM's secure project folder ([server name]\PRACTICE_DM\Audio Recordings and Transcriptions). Approved Durham study staff will place a copy of the audio files in this folder for an approved VASLC transcriptionist to access for the purposes of transcription.

The VASLC transcriptionist will transcribe each interview verbatim and save the completed transcript in the sub-folder using the same alphanumeric code. No data (audio files, in-process transcripts, or completed transcripts) will leave the Durham VA's secure research server. As completed transcripts become available, approved Durham study staff will move these files from the transcription sub-folder into another sub-folder that is only accessible to Durham study staff, where they will be stored and accessed for qualitative analyses. Transcription of the qualitative interviews will be conducted by the VASLC staff using the Express Scribe or Start-Stop Universal Transcription System.

Transcripts will be analyzed with directed content analysis,(71) in which existing knowledge is used to identify concepts. These concepts, along with any newly emergent themes from the transcripts, are used to develop descriptive 'codes' to categorize text. All team members will review and agree upon the coding scheme, including labels and their definitions, by consensus. Content analysis involves reading and rereading transcripts to compare codes and develop higher-order themes by integrating related codes or retaining conceptually distinct codes. Higher-order themes are summarized with short phrases and example quotations. A qualitative codebook that includes code definitions, categorizations, and all coding decision rules will be developed as part of a qualitative audit trail. Qualitative data will be managed in Atlas.ti, which facilitates coding management and analysis of patterns.

Cost analysis

Since PRACTICE-DM is a 12-month intervention, between-arm differences in VHA health care costs will be analyzed by person-year units. Outpatient and total VHA costs will be estimated using generalized linear models with the distribution and link functions that best fit the data. VHA inpatient costs will be estimated using the cross-sectional marginalized two-part (MTP) model to account for the expected high proportion of zeros associated with lack of admission.(72) The MTP model allows for inference to the entire study sample, not just the subset who have positive inpatient costs due to being admitted as in traditional two-part models. All stratification variables and the treatment indicator will be included as covariates in the model.

De-identified dataset

A deidentified dataset containing intervention arm and A1c data values during the course of the study will be created after all data collection has been completed. A de-identified study ID will be created for the dataset, as well as a variable counting the number of days from randomization to be used instead of dates. This dataset may be used for further study-related analysis and comparison of PRACTICE-DM to non-VA programs. Patients who refused future use of data will not be included in this dataset, nor will patients who formally withdrew consent.

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