17-087, Diabetes Disparities: Texting to Extend Treatment (DD-TXT)

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Abstract

Background: Type 2 Diabetes, a common, complex condition with high comorbidity, affects 24% of Veterans. Vulnerable Veterans (e.g., African American, rural, comorbid mental health diagnosis, low-income) are less likely to have controlled diabetes, and have higher mortality and morbidity compared to other Veterans.

Significance/Impact: Health Care Informatics interventions to support chronic disease self-management through technology can improve access, health equity, and health outcomes for vulnerable Veterans. Customizable, interactive self-management support through Annie addresses the VA's priority of improving access, including via virtual modalities, and providing a tailored experience that incorporates Veteran needs and preferences (VA Strategic Imperative 2). Research priority areas of access to care, women's health, mental health, primary care practice, informatics, virtual care, health equity, and patient-centered care are all addressed.

Innovation: By incorporating the needs and preferences of vulnerable Veterans with diabetes in a self-management texting intervention and testing its effectiveness against a more traditional education-only intervention**,** lessons learned can improve the development of text-based support for other complex chronic conditions. It can also improve future implementation of Annie-based self-management support throughout VA.

Specific Aims: AIM 1: Refine and beta test components of an interactive, tailored self-management texting protocol (DD-TXT) using a participatory design process incorporating vulnerable Veterans' preferences, VA clinician input, and evidence on effective texting-enabled self-management programs. The DD-TXT protocol will consist of: *Core Messaging:* Customizable core modules on medication management, blood sugar and blood pressure monitoring, preventive care, problem solving, appointment reminders, administrative messages; and *Optional Messaging:* A library of patient-selected modules (e.g. nutrition, physical activity, weight management, emotional coping, goal setting) designed to motivate and educate.

AIM 2: Conduct a randomized controlled comparative effectiveness trial with 400 Veterans whose diabetes was uncontrolled (defined as HbA1c over 8.0% for at least 50% of the most recent 6 months) in 2018 in Gainesville, FL or Chicago, IL. The primary aim will be to assess the comparative effectiveness of DD-TXT compared to DSE, a diabetes skills education-only texting protocol based on a skills workbook that is currently given to VA patients with diabetes. The primary outcome will be HbA1c percent time in control. Secondary outcomes include self-reported adherence to diabetes self-care recommendations (SCI-R), diabetes self-efficacy, diabetes distress, LDL, and blood pressure control. We hypothesize that DD-TXT will result in better proximal health outcomes and diabetes self-management behaviors vs an education-only protocol (DSE).

AIM 3: Obtain information to guide future implementation of diabetes self-management support through texting by (a) gathering and analyzing qualitative feedback from patients engaged in the comparative effectiveness trial, overall and by subgroup (b) collecting qualitative feedback from providers and key stakeholders on the barriers/facilitators of future RCT evaluation and implementation of DD-TXT vs DSE, (c) conducting a cost-identification analysis and safety analysis to identify resources required for larger-scale implementation.

Methodology: We will refine the DD-TXT protocol through a participatory design process, conduct a randomized controlled comparative effectiveness trial with 400 Veterans with uncontrolled diabetes, and collect qualitative feedback from patients, providers, and other stakeholders and conduct a cost-identification analysis to guide future implementation.

Next Steps/Implementation: This project will inform future processes for incorporating Veteran input into Annie protocol development and lead to a future Type 2 hybrid implementation trial of DD-TXT or DSE (based on our findings) to determine best implementation strategies for Annie-based self-management support.

List of Abbreviations

%TIC	% Time in Control
A1c%TIC	Hemoglobin A1c % Time in Control
ARMS-D	Adherence to Refills and Medication Schedule for Diabetes
BP	Blood Pressure
BP%TIC	Blood Pressure % Time in Control
CDA	Career Development Award
CDW	Corporate Data Warehouse
CHOIR	Center for Healthcare Organization and Implementation Research
CIA	Cost-Identification Analysis
CPRS	Computerized Patient Record System
DBP	Diastolic Blood Pressure
DDS	Diabetes Distress Scale
DD-TXT	Diabetes Disparities: Texting to Extend Treatment
DoD	Department of Defense
DSE	Diabetes Skills Education
DSME	Diabetes Self-Management Education
DSMS	Diabetes Self-Management Support
DSS	Decision Support System
FY	Fiscal Year
HBA1c	Hemoglobin A1c
HSR&D	Health Services Research & Development
ICD	International Statistical Classification of Diseases and Related Health Problems

ID	Identification number
IIR	Investigator Initiated Research
IRB	Institutional Review Board
IV	Independent Variable
LDL	Low-density Lipoprotein
LDL%TIC	Low-density Lipoprotein % Time in Control
MCA	VHA Managerial Cost Accounting
MHV	My Health*e*Vet
NHS	National Health Service
OCC	Office of Connected Care
PBRN	Practice-Based Research Network
PCP	Primary Care Provider
PI	Principal Investigator
RA	Research Assistant
REDCap	Research Electronic Data Capture
RCT	Randomized Controlled Trial
SBP	Systolic Blood Pressure
SCI-R	Self-Care Inventory – Revised
SD	Standard Deviation
SES	Socioeconomic Status
SM	Secure Messaging
SMS	Short Messaging Service
VA	Veteran's Affairs
VAMC	Veteran's Affairs Medical Center

VHA	Veterans Health Administration
VINCI	VA Informatics and Computing Infrastructure
VR-12	The Veterans RAND 12-Item Health Survey
VSSC	VHA Support Service Center

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1.0 Study Personnel

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VA Participating Sites

- VA Bedford Healthcare System, Bedford, MA – Lead Site and Aim 1 participatory design surveys and interviews, beta testing, and data collection and analysis for all Aims

- Malcolm Randall, Gainesville, FL – Aim 1 participatory design interviews, Aim 2 recruitment site, Aim 3 interviews

- Jesse Brown, Chicago, IL – Aim 1 participatory design interviews, Aim 2 recruitment site, Aim 3 interviews

- Hines, Hines, IL – data analysis for all Aims

Note: We will monitor Aim 2 recruitment numbers closely over the first three months; if unexpectedly high refusal rates prevent adequate progress, we may expand recruitment to Hines (Chicago), Bedford, or via the VA Women's Health Practice Based Research Network. The participatory design interviews for Aim 1 will be led out of Bedford and take place virtually.

2.0 Introduction

VA Cares for Veterans with Complex, Chronic, Multimorbid Conditions Such As Diabetes:

The Veterans managed by the VA Healthcare System are complex, often with chronic conditions and multiple physical and mental health comorbidities. In particular, diabetes results in many complications and negative outcomes, leads to high medical costs,[1] requires intense self-management, and is complicated by changing recommendations for care. Nearly 24% of VA patients struggle with type 2 diabetes.[2] Effective management is even more complicated for those living in rural areas.[3, 4]

Veterans Struggle with Diabetes Management:

Nationwide, rates of diabetes are high among vulnerable populations,[5] and diabetes management is particularly complex within the VA patient population. Social determinants of health are a major barrier to diabetes management among Veterans, who tend to be socioeconomically vulnerable. 89% of Veterans reside in census tracts with poor access to health food alternatives and opportunities for physical activity.[6] Multimorbidity also complicates management; in FY13, 25.6% of Veterans with a serious mental illness had diabetes,[2] and 25% of Veterans living in rural areas had diabetes.[2] African-American, Hispanic, and rural Veterans with diabetes also have higher odds of having multiple comorbidities than white Veterans.[4] Veterans with diabetes and a comorbid mental health diagnosis are less likely to have diabetes-related exams compared to those with diabetes without a mental health diagnosis.[7] Low-income Veterans have worse diabetes outcomes compared to Veterans with higher incomes[8] and rural Veterans exhibit less desirable self-management behaviors.[9]

Veterans with Complex Needs Require Tailored, Continuous Care:

Patients with complex chronic conditions like diabetes are not well managed by episodic clinic visits.[10] They need frequent communication with their healthcare providers for medication titration, management of side effects, and monitoring of disease progression and complications. Chronic conditions also require considerable patient engagement to manage health information, interact with the healthcare system, and pursue healthy daily behaviors. Recognizing these points, VA has a mandate to emphasize tailored, continuous care -- supporting patient autonomy, understanding patient preferences, and motivating patient engagement. Virtual care technologies can help achieve this mandate by enhancing communication, supporting care management, and improving self-management. Advantages of technology-assisted interventions for self-management include portability, timeliness, efficiency,[11] scalability,[12] and fewer barriers based on geography or mobility.[13] Patient-accessible health information technology can be tailored,[14] deliver support as needed,[11] prevent relapse,[15] increase access to healthcare professionals, and may lower healthcare costs.[12]

Text Messaging Can Improve Self-Management and Patient Outcomes in Diabetes:

Virtual care technologies have the potential to improve diabetes outcomes,[16-20] and research shows that diabetes self-management plans are more likely to work when they are designed to fit patients' priorities, resources, and lifestyles, and are supported by technology.[21] Automated text messaging systems have been shown to be effective in supporting behavior change, including smoking cessation rates,[22] diet and exercise,[23] and receipt of preventive medical services.[24] Some of this work has focused specifically on diabetes.[25, 26] A 2015 systematic review of evidence for texting[27] supports the use of texting interventions, concluding that the majority of published text-messaging interventions are effective when addressing diabetes self-management,[28] weight loss,[29] and physical activity.[30, 31] Benefits have been found with both one-way [32-35] and two-way[36, 37] texting interventions for diabetes. This is also true in vulnerable populations, such as minority[25] and low-income[38-40] populations, those with low health literacy,[41] and those living in rural areas.[42]

The Rollout of Automated Text Messaging in VA – The Annie Automated SMS Texting System:

Increasingly, text messaging is used to interact with and provide automated, personalized, and timely information to patients.[43, 44] VA has developed its own automated text messaging system and called it "Annie" after Annie G. Fox, the first woman in the military awarded the Purple Heart. The **Annie automated short message service (SMS) text messaging system** (or simply "**Annie**") is currently being implemented at select VA facilities with more widespread rollout underway. Any Veteran with an SMS text-enabled cellular telephone or smartphone can enroll in Annie. Annie is designed as a multi-component, automated web-based text messaging application that can also be accessed online. The system contains (1) an authoring component, (2) an enrollment component, and (3) a monitoring component. The **Annie 4.2 authoring tool** consists of templates designed to support two-way messages that can collect vitals and respond to patterns (increases, decreases, repeated in-range or out-of-range values) in vitals; elicit categorical, yes/no, and scaled responses to preset queries; send one-way educational content or appointment reminders, and send announcements to panels of patients. These templates can be chained together to design more complex protocols. To date, the protocols that exist in the system have been designed with clinical input only and most have a relatively narrow focus. **The Annie monitoring dashboard** can be used to view logs of messaging activity history between Annie and a specific patient, and view reports about a patient (e.g., graphs of their blood glucose values submitted over time). Patients can obtain access to the monitoring

dashboard component if desired. The **enrollment portal** allows staff or providers to consent and enroll patients, assign specific protocols, and tailor protocols to patients as needed. Annie is not designed to support the exchange of lengthy, open-ended text messages. Rather, it uses expert-written protocols to tailor messages to individual Veterans. Protocols can remind patients to contact their health care teams based on patient response. For example, after submitting 3 critically high blood pressure readings in a row, a patient might receive a response such as "Your blood pressure has been at a critical high more than 3 times in 2 days. Please contact your physician." Such timely feedback helps ensure safety and promote Veteran engagement. At enrollment, Veterans must voice their understanding that the Annie system is for self-care, not regularly monitored by clinicians, and that they are responsible for contacting their clinicians as needed.

Access to Technology: The Pew Research Center reported in 2018 that 95% of American adults owned a cell phone, 77% owned a smartphone;[45] 97% of smartphone owners text message, and 62% search for health information.[46] Rural, low-income, and less educated adults remain less likely to own cell phones, but ownership is increasing and is over 90% in these groups.[47] Smartphones are helping to close the digital divide for some minority groups, such as African-American and Latinos, who rely on them for their access to the internet and health information.[48] Low-income or minority adults were more likely to be smartphone dependent for their online access.[45] Rural Americans lag in their access to digital technologies, but the gap is closing;[49] 91% of rural residents own cell phones.[45] In 2017, 89.5% of 2,700+ Veterans we surveyed owned a smartphone, and another 9.6% owned a cell phone with texting capabilities; 55% used smartphones to look up health information on the internet; texting use was much higher among minority Veterans than white Veterans.

Veteran Engagement, Culturally-Appropriate Care, and Participatory Design: The rapid uptake of cell phone and smartphone use among low-income, rural, and minority Veterans provides an ideal opportunity to refine a texting intervention aimed at improving diabetes care and outcomes for vulnerable Veterans. In accordance with National Standards for Diabetes Self-Management Education (DSME) and Support (DSMS),[50] our goal is to design an effective, culturally relevant, Veteran-centered DSME/DSMS protocol that is responsive to the needs of vulnerable Veterans with diabetes. To do so, it is important to not rely solely on a medically-oriented research framework, but to have input from key stakeholders. A participatory research approach can bridge community or Veteran perspectives with the research process, and thus can contribute to intervention success.[51, 52] In particular, the partnering emphasized in participatory research[52, 53] is essential to the development of a research plan and intervention and to maintain the Veteran perspective throughout the research process.[53]

3.0 Objectives

Purpose

Diabetes type 2 is a common, complex condition with high comorbidity that affects 24% of US Veterans. Diabetic Veterans suffer from medical complications, mental health comorbidities, and high medical expenditures. **Vulnerable Veterans, such as low-income, rural, or minority Veterans, and Veterans with comorbid mental health diagnoses, are disproportionately affected by type 2 diabetes**. Vulnerable Veterans are less likely to have controlled physiological outcomes, leading to higher morbidity and mortality.

Control of type 2 diabetes requires ongoing self-management efforts. Veterans with diabetes need to understand their disease and treatment, be motivated and empowered to control risk factors, remember to take their medications, and participate in treatment and monitoring. VA/DoD Diabetes Guidelines require self-management education.[54] However, intense diabetes interventions, while successful at improving outcomes, are difficult to disseminate. Consequently, many do not receive needed self-management education or support.

Automated short messaging service (SMS) texting interventions are particularly effective for addressing these challenges.[29, 33, 55-57] Reasons for their success include: (a) brief text messages can be timed to deliver at important moments ("time to take your medicines") and thus integrated into patient's daily lives, (b) text-enabled cell phone ownership is now over 95% in Veterans and the general population, thus helping to bridge the 'digital divide' in technology access, and (c) compared to other technologies, texting is lower cost.

Specific Aims

AIM 1: Refine and beta test components of an interactive, customizable texting self-management protocol (DD-TXT) using a participatory design process incorporating vulnerable Veterans' preferences, VA clinician input, and evidence on effective texting-enabled self-management programs. The DD-TXT protocol will consist of core messaging and optional messaging modules:

- *Core Messaging:* Customizable core modules on medication management, blood sugar and blood pressure monitoring, preventive care, problem solving, appointment reminders, administrative messages.

- *Optional Messaging:* A library of patient-selected modules (e.g., , nutrition, physical activity weight management, emotional coping, goal setting) designed to motivate and educate.

AIM 2: Conduct a **randomized controlled comparative effectiveness trial** with 400 Veterans (no greater than 440) whose diabetes was uncontrolled (defined as HbA1c over 8.0% for at least 50% of the most recent 6 months) in 2018 in Gainesville, FL or Chicago, IL. The primary aim will be to assess the comparative effectiveness of a customizable, interactive diabetes self-management support texting protocol **DD-TXT** developed through a participatory design process compared to **DSE, a diabetes skills education-only** texting protocol based on a skills workbook that is currently given to VA patients with diabetes. The primary outcome will be **HbA1c percent time in control**. Secondary outcomes include self-reported adherence to diabetes self-care recommendations (SCI-R), medication adherence, missed appointments, diabetes self-efficacy, diabetes distress, LDL, and blood pressure control. We hypothesize that a customizable, interactive texting protocol developed with patient input (DD-TXT) will result in better proximal health outcomes and diabetes self-management behaviors vs an education-only protocol (DSE).

- **Moderation by Subgroups:** To investigate whether certain texting intervention components are more effective in vulnerable subgroups (e.g., African-American, rural, comorbid mental health diagnosis, low-income, low literacy, women), we will gather data on sociodemographic risk factors and social determinants of health from all participants and examine heterogeneity of treatment effects by groups.

AIM 3: Obtain information to guide future implementation of diabetes self-management support through texting by (a) gathering and analyzing **qualitative feedback from patients** engaged in the comparative effectiveness trial, (b) gathering and summarizing **qualitative feedback from providers and key stakeholders** who are likely to be "prescribing" DD-TXT or DSE to Veterans to gather information on the barriers/facilitators of future RCT evaluation and implementation of DD-TXT vs DSE, (c) conducting a **cost-identification analysis** to identify the resources required for larger-scale implementation.

Hypotheses

Physiologic Measures Associated with Health Outcomes (HbA1c, blood pressure, cholesterol).

H1: Veterans in the DD-TXT arm will have better control of their diabetes-related intermediate outcome measures (such as HbA1c (H1a), blood pressure (BP) (H1b), or low-density lipoprotein (LDL) cholesterol (H1c)) at follow-up than those in the DSE arm. **A1c%TIC at follow-up is considered the primary outcome variable** because glycemic control is an important, objective, and readily interpretable clinical goal of diabetes self-management. Patients will be selected based on their A1c%TIC<50; not all patients will be uncontrolled on other measures. Cutoffs for control defined as HbA1c<8.0%, LDL<100mg/dL for LDL, SBP<130mmHg and DBP<80mmHg for BP, respectively, based on VA guidelines.[54]

Behavioral Responses include self-care behaviors and adherence to medication and follow-up visits.

H2: Veterans in the DD-TXT group will report more positive behavioral responses (as measured by higher SCI-R score (H2a), and higher ARMS-D medication adherence score (H2b)) than those in the DSE group, and Veterans in the DD-TXT group will show evidence of greater changes in health care utilization (fewer missed primary care appointments) than the DSE group (H2c). SCI-R will be the main outcome for H2 since it is the best available measure of self-care behaviors across all relevant diabetes self-care domains.

Affective Responses include self-efficacy and diabetes distress

H3: Veterans in the DD-TXT group will show more positive affective responses (as measured by higher diabetes self-efficacy (H3a), lower diabetes distress (H3b) than those in the DSE group.

Relevance to Veterans and VA

This project addresses VA research priorities around access / rural health, health equity / disparities, patient-centered care, and informatics, and for increased Veteran engagement in research. Our team has worked with patient-facing technologies in VA for over ten years, and **has strong support from the Office of Connected Care and Office of Health Equity.** This project will (a) inform future processes for incorporating Veteran input into Annie protocol development and (b) lead to a future Type 2 hybrid implementation trial of either DD-TXT or DSE (based on our findings) to determine best implementation strategies for Annie-based self-management support.

4.0 Resources and Personnel

Dr. Stephanie Shimada, investigator at CHOIR Bedford will serve as PI. The team is organized into working groups to coordinate efforts across study years. Ms. Linda Am, Project Manager, will be in charge of day-to-day operations, and report directly to Dr. Shimada and coordinate the research coordinators at the recruiting sites.

The DD-TXT Development Working Group (Aim 1) will consist of a Veteran Stakeholder Group and a Clinical Stakeholder Group. The Veteran Stakeholder Group will be co-led by Dr. Shimada and a Veteran, who will work closely with Dr. Hogan and the Veteran Co-Is throughout the study on desired content for DD-TXT, lead the participatory design surveys and interviews, and work on alpha testing.

Dr. Cutrona will lead the **Clinical Stakeholder Group** and work with Dr. Vimalananda and site PIs Drs. Howard Gordon and Connie Uphold to incorporate clinical stakeholder input, new literature, and guidelines into DD-TXT in clinically appropriate ways, and beta test DD-TXT.

We will also form a **Panel of Clinical Experts** to review the content of the modules developed in Aim 1. In addition to the Clinical Stakeholder Group (4 study clinicians, 2 of whom treat patients in the local diabetes clinic) who will be reviewing the modules, we will include at least 4 outside clinical experts who are not engaged in the study's human subjects research. The outside clinical experts will include those who treat and/or conduct research on women Veterans with diabetes or pregnant Veterans, including the following: VA OB/GYN, VA endocrinologist, clinician who treats vulnerable patients, and VA clinician with mental health expertise.

The **RCT Working Group** (Aim 2) will consist of Drs. Cutrona, Shimada, Gordon (site PI), and Uphold (site PI) as well as Ms. Am, Bedford project coordinator, and the site project coordinators. They will work with Veteran Co-Investigators to design trial materials, including recruitment, enrollment, data collection, and safety monitoring instructions for the site RAs, and meet regularly during the trial to ensure recruitment is progressing. This group will also work to oversee safety monitoring.

The **Evaluation Working Group** will consist of all investigators, the data analyst, and the Veteran Co-Investigators. Dr. Zocchi will guide the overall data analysis. This group will review data collection and management, and plan data analysis. Veteran Co-Investigators will weigh in on data collection materials, suggest possible additional research questions of interest, and help with data interpretation. Dr. Stroupe will advise on the cost-identification analysis.

Dr. Robinson will work closely with Dr. Shimada, Dr. Hogan, and other team members to analyze the data as part of **the Qualitative Data Analysis Group.** This group will lead the qualitative interviews with key stakeholders and providers **.**

The **Dissemination / Implementation Workgroup** will be led by Dr. Hogan, who will work with all investigators and Veteran Co-Investigators to engage in dissemination of study findings and analyze lessons learned for future implementations of Annie or participatory design work. Veteran Co-Investigators will help identify Veteran partner organizations for dissemination and be invited to participate in those efforts.

5.0 Study Procedures

5.1 Study Design

Overview: We will conduct a randomized comparative effectiveness trial of two diabetes self-management support texting interventions: DD-TXT, with customizable, interactive core components and optional modules to provide patients autonomy in choosing which support is most important to them (to be refined in Aim 1), and DSE, which will provide education-only based on skills workbook content. Aim 2 focuses on the primary aim of assessing the comparative effectiveness of the texting interventions, Aim 3 on the secondary aim of improving our understanding of the context for future implementation of Annie-based diabetes self-management support.

Inclusion of Vulnerable Populations: We are specifically including women and vulnerable Veterans in development of the self-management support protocol because they face a number of social determinants of health that increase risk of diabetes, make them especially vulnerable to poor chronic disease management due to challenges such as poor healthcare access or treatment adherence, and greater burden of comorbid disease. Their input into the texting protocol will likely make it more patient-centered and relevant to their life contexts and responsive to their needs.

Aim 1. Refine and Expand Existing Diabetes Protocols through a Participatory Design Process

Experimental design: We will first develop a set of self-management protocols, using our conceptual framework and current VA/DoD guidelines for diabetes self-management. As part of the refinement, with input from Veteran Co-Is and Veteran participatory design workshops, we seek to address barriers in all five areas. We will combine input from stakeholders to refine the DD-TXT intervention.

The clinicians on the team (two primary care clinicians, one endocrinologist, and one nurse practitioner) will ensure that the information in the Annie modules reflects current standards of care, is consistent with VA/DoD Clinical Practice Guidelines for Diabetes[54] and other VA-approved educational materials.[58] The team will also seek input from local diabetes educators and behavioral health staff.

Participatory Design with Patient Stakeholders: We will recruit **3-6 "Veteran Co-Investigators"** (1-4 men, 1-4 women, 1 from each of the 2 sites with a history of uncontrolled diabetes who represent different vulnerable subgroups) to work alongside the team for the duration of the study. These Veterans will help review and provide input into content for the core and optional modules, including evaluation of links to educational sites and selection of motivational statements from previously developed materials (e.g., VA Clinical Practice Guidelines). The Veteran Co-Investigators will not participate in the Participatory Design interviews because they do not have access to PHI. Site PIs will reach out to clinical colleagues at primary care and/or diabetes clinics at their station to help identify and recruit appropriate

Veteran Co-Investigators. They will ideally be Veterans who have struggled with diabetes management in the past, but who are doing relatively well at present.

Participatory Design Process (see COVID-19 related changes below): We had planned to seek input from a broader **group of 50-60 Veterans** via a series of **participatory design workshops[59] with Veterans with diabetes from vulnerable subgroups**. Due to **COVID-19** making it impossible to conduct workshops with groups of Veterans, the team decided to obtain Veteran input for the participatory design process in a different manner. While converting the workshops to online workshops using video conferencing technology would have been simplest, requiring it ran the risk of excluding the voices of members of vulnerable groups if they did not have equal access to these technologies or the computer literacy to participate. Based on recommendations from experts who regularly engage patients in the design process, it was recommended that old fashioned surveys and telephone would be most inclusive. We have therefore **converted the Participatory Design Workshops into a Participatory Design Survey (mailed paper survey or option to complete via telephone) and a series of Virtual Participatory Design Interviews (conducted one-on-one via telephone or video conferencing, according to patient preference).** We plan to initially mail surveys to approximately 400 Veterans living with diabetes sampled around the country who represent the vulnerable groups of interest and who have cell phones in order to receive **at least 100 survey responses**, and to conduct follow up interviews with **50-60 Veterans** selected from among survey respondents. If we obtain fewer than 100 responses or fewer than 50 Veterans indicate a willingness to be called for an interview, we plan to resend a second wave of surveys to nonrespondents and/or send out copies of the survey to an additional sample of Veterans who meet our inclusion criteria with the goal of reaching 100 survey responses and 50 interviews. The total sample we will send the survey to will not exceed 1000 Veterans. If the study team notices survey responses are not meeting the intended goal (N=100) and/or are not representative of the Veteran population, for example, low number of respondents from racial/ethnic minority backgrounds or living in rural areas, program coordinators will reach out by phone to Veterans who received a survey by mail to invite them to participate in the survey by phone and/or participate in the interview only. If the Veteran selects interview only, we will ask for some demographic information and information about technology use/preferences that would have been collected on the survey during the interview so that we can ensure we are reaching adequate representation of vulnerable Veterans. Program coordinators will gauge the Veteran's interest in participating over the phone, answer any questions about mailing back survey, offer to complete the survey over the phone, or offer to schedule an interview via phone or video conferencing based on the Veteran's preferences.

The mailed **Participatory Design Surveys** would ask participants to rate, rewrite, or suggest alternatives to a set of text messages (because the survey would be prohibitively long if all texts were included, surveys will cover different texting modules so that we receive feedback on each module from at least 5 Veterans); include general questions on self-management challenges and the likelihood of wanting to receive messages from the different modules; and collect demographics. The survey will also ask about access to and comfort with technology and interest in participating in a follow-up interview to take place either by telephone or by video conferencing technology, or in-person if the patient is coming into the VA for a clinical visit and the facility is allowing in-person data collection at the time. The **Virtual Participatory Design Interviews** will be one-on-one semi-structured interviews with Veterans about the content and timing of the modules. The Virtual Participatory Design Interviews will take place over a VA approved video conferencing platform such as Microsoft Teams, Zoom, or WebEX or by

telephone if the Veteran participant prefers and will be audio recorded to help team members review discussions that occurred in the interviews.

Limited Testing of Actual Annie System with Veteran Co-Investigators, Staff, and Patients:

***Alpha testing*:** After initial programming of the protocols by the Project Manager, the study's Veteran Co-Investigators and project staff will be enrolled through Annie as protocol testers, to test portions of the DD-TXT protocol as they are developed or modified. Testers will provide ongoing feedback on the functioning of the modules, reporting back on any programming failures or "bugs" encountered in how the templates are chained together to guide iterative improvements to DD-TXT. During this testing phase, some testers will also receive the education-only DSE protocol.

Clinical Expert Panel Review: The clinical expert panel will review the modules. A minimum of two clinicians will be assigned to carefully review each module that contains clinical content and to bring concerns to the group for discussion. We would have the clinical expert team review the specifics of the modules (i.e., screenshots or *s*preadsheets/word documents of all the programmed content that specify message wording, triggers, and thresholds) and make a determination about whether certain modules (or certain module content) had the potential to pose a safety risk. They would determine if they felt a protocol was likely suitable for all, suitable with modifications (e.g., change of threshold levels that trigger certain responses (e.g., a critical high/low) or eliminate certain messages), or inappropriate for pregnant women. This will have the added benefit of providing more guidance for users in case the modules are adopted for clinical practice in the future.

Beta testing: After the alpha testing and making the changes suggested based on Veterans' participatory design survey and interviews feedback, we will ask approximately **8-12 patients with uncontrolled diabetes in Bedford** to test DD-TXT over a two-month period. Participants will customize the core modules according to preference but be assigned to one or more optional modules so that we obtain feedback on all modules. The local project coordinator will check with the patients at one week, two weeks, and one month to see what they like/dislike about DD-TXT and will update their module settings. At the end of two months, beta testers will complete follow-up data collection and provide feedback on their experience with DD-TXT. Drs. Cutrona and Vimalananda and local Bedford study staff will pilot all the enrollment and data collection procedures for the Aim 2 trial, so that beta testing can inform improvements to (a) DD-TXT protocol and customization process, (b) patient materials, (c) project coordinator instruction manual, (d) recruitment processes, (e) data collection processes, (f) patient support processes, and (g) new safety monitoring process.

Aim 2. Conduct a Randomized Comparative Effectiveness Trial of Annie DD-TXT Compared to DSE, a Diabetes Skills Education-Only Annie Protocol

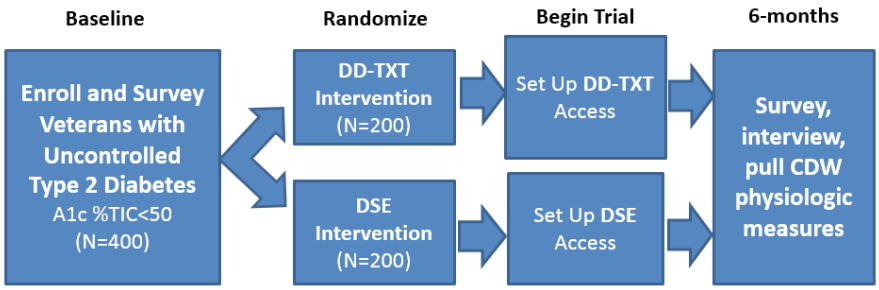
We will conduct a trial to assess the comparative effectiveness of DD-TXT vs DSE.

Setting and Sample: The two main sites for the trial are Jesse Brown VAMC in Chicago, IL and Malcom Randall VAMC in Gainesville, FL. These two sites were selected because Dr. Shimada's CDA analyses showed that they both had large numbers of vulnerable Veterans with uncontrolled diabetes who were minority (African American or Latino), low-SES, and/or had comorbid mental health diagnoses and disparities in diabetes outcomes. The two facilities

represent different regions of the United States, the first a highly urban population and the second a mixed population with high numbers of rural patients with diabetes. In 2016, there were 5,054 patients at the two sites who meet A1c criteria for inclusion in our study. As shown in Figure 1, **we will aim to recruit 200 to 220 patients at each site (for a goal of 400 total but not to exceed 440) and randomize them to DD-TXT or DSE protocol**.

We will monitor Aim 2 recruitment numbers closely over the first three months; if unexpectedly high refusal rates prevent adequate progress, we may expand recruitment to Hines (Chicago), Bedford, or via the VA Women's Health Practice Based Research Network.

Figure 1: Aim 2 Randomized Comparative-Effectiveness Trial Design



DD-TXT Intervention vs DSE Intervention: Effectiveness of DD-TXT will be compared with a limited Diabetes Skills Education-only (DSE) texting protocol consisting of content from the VA educational materials entitled "Self-Care Skills for the Person with Diabetes",[58] which was created in alignment with VA/DoD diabetes guidelines[54] and is recommended for patients as part of usual care. Everyone in the DSE arm will receive the same daily text messages taken verbatim or almost verbatim from workbook content but shortened to fit the 160-character limit of a text message. There will be no customizable or interactive content for the DSE arm with the exception of a monthly message to assess continued engagement with the texting protocol. DSE is a viable competing texting protocol for diabetes self-management education as it is less resource intensive to implement widely.

Randomization: Once verbally consented by project coordinators, patients will be asked to complete the baseline survey instruments either online or over the telephone with project staff. Participants will then be randomized with stratification by gender, using a separate randomization table per site. We will first recruit women, with the goal of achieving 10-20% of the sample at each site. We will then recruit male Veterans until we obtain 200 to 220 per site (100 to 110 to DD-TXT, 100 to 110 to DSE), for a total of 400 enrolled across sites (no greater than 440 total).

Annie Training, Project Coordinator Support and DD-TXT Customization: Project coordinators will educate and consent patients in both arms on Annie use, emphasizing that the Annie portal is not monitored by their providers. They will train patients on use of Annie via a teaching protocol that allows the patient to practice receiving and responding to different messages. All patients will receive written instructions on how Annie works and how to contact the project coordinators for guidance if problems arise. Project coordinators will emphasize that

it is extremely important for the patient to let the study team AND their doctors know right away if they have a major change to their health status (e.g., pregnancy).

Participants will receive text messages on their cell phones or smart phones via the Annie text messing system. If the study participant is using a cell phone or smart phone of a cohabiting family member, the participant could use the Annie app on the cohabiting family member's phone if they choose to do so to ensure extra privacy by having the app password protected. Participants randomized to DD-TXT will prioritize diabetes self-management topics, select optional modules of interest, and customize when they wish to receive texts. Our previous work has shown that patients are willing to receive messages at least three times a day and prefer consistency in timing. We will therefore recommend 3-4 texts over the course of the day, although patients will be allowed to select more frequent texts if desired (e.g., multiple medication reminders) on a Module Customization Form (see attachment). Patients on DD-TXT will be instructed that project coordinators will be available throughout the trial to update customization settings. The project coordinator will check with participants at one and two weeks to see whether they need help or would like to modify their settings. DD-TXT will also send monthly administrative messages inquiring whether patients would like to receive a call from the project coordinator for support or to modify their settings. Project coordinators will monitor the dashboard for requests for contact and respond; they will also proactively reach out to patients on a limited basis to see whether support is needed if there is evidence that patients are not responding to assessment items (e.g., no response to any two-way assessment texts two weeks within enrollment, lapse of over ten days after initial engagement). The project coordinator will document support needed to improve initial training and support materials for future implementation.

Follow-up Survey and Patient Interview: At the **6-month follow-up**, patients in both arms will be asked to complete another survey (online or by telephone). We will conduct brief (20-30 minute) qualitative interviews via telephone or video conferencing with all patients engaged in the Aim 2 Trial about their experiences receiving texts for diabetes self-management support, including impacts on their diabetes self-management and clinical care, any potential downsides, and suggestions for improvement and implementation. (See attachment). These interviews will be recorded and summarized to describe patients' experiences with DD-TXT and DSE, compare experiences across groups (i.e., are there similar or varied experiences with DD-TXT across different groups of vulnerable Veterans), and provide recommendations for how the interventions or their implementation might be improved overall or for particular groups.

Optional continuation of texts: For most patients, the 6 months of text messages will automatically end at around the time of the 6-month follow-up interview. However, in some instances patients request for certain text messages to continue beyond the study because they have come to rely on them as part of their diabetes self-management. If a patient requests that certain messages (e.g., medication reminders, blood sugar reminders, blood pressure reminders) continue, the study coordinators will make the requested changes in Annie so that the patients can receive the desired messages up to 12 months beyond the end of the trial. Patients will only be allowed to receive message types allowed for their trial randomization group. Participants will be reminded that messages are not monitored and that they can text STOP to end their subscription at any time if they later change their minds.

Aim 3 Evaluation to Guide Future Implementation of Texting for Diabetes Self-Management Support

Physician and Key Informant Perspectives: We will conduct a small number (15-20) of semi-structured interviews to gather important perspectives on DD-TXT and DSE. (1) At each study site, we will identify the primary care teams with the most patients enrolled in DD-TXT and DSE and interview the primary care provider (PCP) by telephone (N=5 teams per site, see attachment). Providers will be asked about their involvement with Annie, perceived fit of Annie texting with their workflow, overall impressions of DD-TXT vs DSE, and concerns with Annie diabetes self-management. They will also be asked for suggestions for improving the texting protocols, and about barriers and facilitators of future implementation of text-based diabetes self-management support. (2) We will also conduct telephone interviews with 5-10 other key informants at each facility such as Diabetes Educators, Health Promotion Disease Prevention Program Managers, and Health Behavior Coordinators to gather feasibility and contextual data to inform implementation strategy for a future Type 2 hybrid implementation trial. Recommendations will be summarized as lists of barriers and facilitators to future implementation, suggestions for appropriate workflows for texting implementation, and suggested improvements to DD-TXT or DSE.

Cost-Identification Analysis/Safety Analysis: We will conduct a cost-identification analysis (CIA) to assess the cost of implementing DD-TXT or DSE. To estimate costs, we will obtain cost data from VHA Managerial Cost Accounting (MCA) datasets (formerly known as Decision Support System (DSS) National Data Extracts), consultation with the Health Economics Resource Center, and consultation with the two study sites. We will track the cost of supplies (e.g., instructional materials on Annie use). In addition, we will also estimate the staff time associated with DD-TXT and DSE. To obtain estimates of staff time, we will have project coordinators keep track of the amount of time needed to enroll patients in Annie, associate them with the texting protocols (both DD-TXT and DSE), and customize those protocols to patient preferences (DD-TXT only). Project coordinators will also keep a log of how often patients contacted them with questions or requests to modify their assigned protocols during the trial, and the amount of time required to address those issues. In addition, we will have them track time spent on safety monitoring and confirmation of patients' continued engagement with Annie through the dashboard. We will then estimate per-patient costs based on facility staff wages. To address uncertainty in the CIA, we will use scenario analysis to construct multiple scenarios by varying input values and structural assumptions. These findings will be shared with OCC so they can use it to help facilities anticipate costs associated with both simple texting protocols (like DSE) or more complex, interactive protocols (like DD-TXT). Knowledge gained by monitoring the dashboard will be used to generate a safety analysis. We will track the frequency of text responses not recognized by Annie, potentially problematic responses (extreme blood pressure or sugar readings), or instances when the clinical team needed to be consulted due to ensure safety. These findings will be provided to OCC to inform safety monitoring for Annie in general. In addition, we will suggest Annie dashboard features to facilitate patient panel management and shape future Annie system updates.

Durations and Phases of Study

Table 8: GANTT Chart	Year 1				Year 2				Year 3				Year 4			
	Months				Months				Months				Months			
	1-3	4-6	7-9	10-12	1-3	4-6	7-9	10-12	1-3	4-6	7-9	10-12	1-3	4-6	7-9	10-12
Aim 1: DD-TXT Development																
Refine DD-TXT with Veteran Co-Investigators																
Incorporate evidence on diabetes self-management																
Obtain clinical stakeholder input																
Obtain expert panel review of modules																
Conduct participatory design workshops with Veterans																
Alpha and Beta testing																
Aim 2: Trial of DD-TXT vs DSE																
Pull CDW data for trial recruitment and randomization																
Trial enrollment and baseline assessment survey																
Track Annie use behavior; facilitate and monitor use																
Conduct follow-up assessments																
Pull follow-up physiologic, utilization data from CDW																
Conduct Aim 2 analyses																
Aim 3: Evaluation for Implementation																
Conduct /analyze patient interviews																
Conduct / analyze provider/ key stakeholder interviews																
Cost identification analysis / Safety analysis																
Summarize Veteran and clinical stakeholder feedback																
Dissemination of findings																

Risks

The risks of Aim 1 are minimal. Patients may share personal health information during the participatory design interviews. Recordings will be made on an encrypted digital audio recorder or via video conferencing software and stored on a secure VA server; they will be transcribed without using patient names, which will be replaced by a unique identifier. The list of identifiers will be stored separately from data to protect participant confidentiality.

Audio recordings will be used to double check interviewer notes and potentially transcribed. Transcriptions will be done in-house by approved study staff or by a VA privacy approved transcription vendor. In recent years our facility has had a VA-approved transcription contract with Alpha Transcription. However, the contract ended in FY21 and contracting is working on a new one for FY22 which may or may not be for the same vendor. We will do in-house transcription in the short term since there is no current approved contract. Once a new contract is approved, transcription may be done by Alpha Transcription (vendor for last few years) or whatever VA-facility-approved vendor our facility is contracting with for transcription services at the time of transcription. To protect patient identities, audio files will be saved only with the participant ID in the filename. We will remove any files from the audio-recorder as soon as they have been uploaded to the VA-secured servers.

For the beta testing in Aim 1, and for the trial and patient interview in Aim 2, patients may also experience some psychological discomfort in answering questions about their diabetes, or their health and healthcare in general. Participants may also become anxious or upset during discussions, or as a result of the survey questions, if they are reminded of negative experiences with their diabetes management. Study staff will be trained to respond to this emotional distress and to refer participants to appropriate resources as necessary. All participants will be free to terminate participation in the data collection or the trial at any time or refuse to respond to any questions. There is also risk of accidental disclosure of information, which exists with any data collection. Every precaution will be taken to prevent this from occurring. Our study team has had extensive experience with prevention of data loss; we have

developed a strong culture of secure, detailed operating procedures, and are hyper-vigilant about protection of confidential data. Most notably, there is risk inherent with the Annie web-based application, that the technology (if they are not very familiar with texting on their phones) or the texting program (based on the modules and content selected) might cause the patient distress or confusion. Participants may become frustrated with their phones or the intervention, or they may get confused that their doctors are monitoring their responses to the Annie system and/or fail to contact their providers when they should. There is also a risk that patients will incur additional texting costs, if they do not have an unlimited texting plan with their cellphone service. However, we have budgeted funds to cover texting costs to remove this barrier.

We recognize that there is potential for risks and unintended consequences when sending and receiving text messages in the DD-TXT intervention. First, when a patient is enrolled in the study, they will receive careful instruction on the functionality of the system (verbally and in writing). Second, any assessment text messages included in our protocols that ask patients questions about their health status or health behaviors will include immediate, system-generated tailored responses, the appropriateness of which will be determined with clinical input. A defining feature of this automated feedback will be encouragement, when warranted, to get in touch with one's care team and to share information with them. Third, project coordinators will monitor the Annie dashboard system, and have a clinical stakeholder-approved plan for action if patients report abnormal or potentially concerning values. The clinical stakeholder-approved plan will be developed early in the study during Year 1 so that it is finalized before Beta testing commences (Beta testing is planned to start at the start of Year 2). The site PIs and clinician co-investigators at Bedford will contribute to and review the safety plan. The safety plan will include the plan for action if patients report abnormal or potentially concerning values as outlined in Sections 5.7 and 6.0 below. Our team will continue to reflect on potential sources of safety risks and adverse consequences as we refine our texting protocols, incorporating them into our safety plan as appropriate.

We are taking special care to mitigate risks for participating women who may become pregnant after enrollment. We will not enroll pregnant women in the trial. During enrollment we will also highlight some of the risks of uncontrolled diabetes during pregnancy and emphasize that it will be extremely important for the patient to let the study team AND their doctors know right away if she were to become pregnant (or if there were another major change to her health status). The information sheet will specify that their choice of modules might be more limited if they become pregnant during the trial, and that they could choose to disenroll from the study if they wanted.

For the provider/key-stakeholder interviews in Aim 3, providers and staff will experience minimal risk. They may feel anxious if they feel they do not know enough about Annie, or if they are asked to recall a stressful interaction with a patient around Annie.

5.2 Recruitment Methods

Aims 1 and 2

We will be requesting a HIPAA Waiver to obtain the participant list from which to recruit for Aims 1 and 2. Eligible patients will be identified through the VA Corporate Data Warehouse (CDW) and VHA Support Service Center (VSSC) data. Patients with diabetes will be identified based on two or more outpatient diagnosis codes (ICD-9 or ICD-10) for diabetes or one or more inpatient codes for a diabetes-related hospitalization. For those patients, we will also save other ICD codes to identify

comorbid diagnoses (e.g., depression, hypertension, hyperlipidemia). We will also pull CDW data on race, ethnicity, gender, priority group (to identify low-income patients), rural residence, lab data on HbA1c within the previous 2 years, anti-hyperglycemic medication (oral or insulin), and contact information (mailing address, telephone number, email address). We will calculate %TIC (for HbA1c, LDL, and BP) for the 6 months immediately prior to recruitment. VSSC data will be consulted to identify which patients have upcoming appointments scheduled.

Aim 1

- Participatory design survey and interviews: Up to 1000 survey recipients, 50-60 interviews

    - Participants for the participatory design surveys and interviews will be recruited by identifying Veterans living with diabetes via CDW or VSSC data. Participants will be selected to represent a variety of vulnerable and diverse subgroups of Veterans living with diabetes such as rural, minority, rural Veterans, and those with comorbid mental health diagnoses. Potential participants will be mailed an Information Sheet and a survey booklet. Returning the survey will constitute consent to participate in the survey and for those that wish to complete the survey over the phone we will review the information sheet with them and ask for verbal consent. Their verbal consent and willingness/unwillingness to be contacted for a virtual participatory design interview will be documented in REDCap If the participants check off on the survey that they are willing to be contacted for a virtual participatory design interview, this will constitute consent for the interview as well. There will be different versions of the text message portions of each survey to allow the flexibility to reach out to a broader array of population subgroups including women, or ethnic minorities, or low income Veterans. The research staff will invite up to 60 participants who indicate on their survey that they are interested in being interviewed to a one-on-one virtual participatory design interview. Those who agree to participate in the interview will have the option to choose whether the one-on-one virtual participatory design interview be conducted either through a VA-approved video conferencing platform or by telephone. The survey will initially be mailed to 400 participants. If we do not get at least 100 surveys returned or 50 indicating an interest in being interviewed, we will attempt to increase the sample size by one or more of the following methods: (1) Follow up with the initial sample by sending a second copy of the survey accompanied by a letter outlining flexible options for participation; (2) Mail out survey invitations to up to 600 other Veterans who meet the selection criteria who were not sampled in the first round; or (3) call Veterans who were mailed a survey to gauge interest and/or offer to administer the survey over the phone or to move directly to participating in an interview. Recruitment calls will occur at least 14 days after initial mailing of survey to allow Veterans time to complete the survey and mail it back or contact the study team to opt out (by phone or opt out card).

    - Veterans who meet certain criteria (e.g., low-income, rural, minority, female) may be identified through the VA Corporate Data Warehouse (CDW) and VHA Support Service Center (VSSC) data.

- Veterans will receive a $25 gift card within 4 weeks of the research team receiving their completed mailed survey or within 4 weeks of completing the survey by phone. Veterans taking part in the one-on-one virtual participatory design interviews will be mailed a $30 gift card after completion.

- Beta testing: Approximately 8 to 12 patients with uncontrolled diabetes from the diabetes clinic in Bedford

  - Patients with diabetes will be recruited from the diabetes clinic at the Bedford VAMC to beta-test the DD-TXT intervention. Two investigators who see patients in Bedford (Drs. Cutrona and Vimalananda) will identify and ask potential participants if they are interested in participating. Approximately 8 to 12 patients who agree to participate will be referred to the Bedford project coordinator for enrollment. Once these numbers are reached, recruitment will stop.

  - Other recruitment methods may be used, such as (a) posting flyers at Bedford VAMC (such as in the clinic waiting area) indicating who to contact if one is interested in participating in the beta testing research study, (b) advertising at campus informational events where Veterans can learn about opportunities to participate in research studies, (c) allowing Veteran co-investigators to invite their peers by word of mouth, (d) sending mailed invitations to Veterans who meet certain criteria. Flyers will indicate eligibility for beta testing (i.e., Veterans, ages 18 years or older, diagnosed with diabetes, own a smartphone.) Interested participants will contact study staff utilizing the telephone number on the flyer to express their interest. If patients are contacted via mailed invitation, the mailed invitation will provide call information to opt-out. Those who receive the mailed invitation and do not opt out may be called after 10 business days to follow-up.

  - Veterans who agree to beta test the DD-TXT intervention will receive $50 each for their time to test and complete the intervention and provide detailed feedback to the team about any problems encountered.

  - Veterans will be given the option to choose either a cash voucher or direct deposit payment after completion of the beta testing. Veterans will be asked to provide their Social Security number and fill out a 10091 form if they are requesting direct deposit for the first time.

<u>Aim 2</u>

- We will recruit Veterans until we obtain 200 to 220 patients at each site (for a goal of 400 total but not to exceed 440).

- Eligible patients at each of the two sites will be identified through the VA Corporate Data Warehouse (CDW) and VHA Support Service Center (VSSC) data. Patients with diabetes will be identified based on two or more outpatient diagnosis codes (ICD-9 or ICD-10) for diabetes or one or more inpatient codes for a diabetes-related hospitalization. For those patients, we will also save other ICD codes to identify comorbid diagnoses (e.g., depression, hypertension, hyperlipidemia). We will also pull CDW data on race, ethnicity, gender, priority group (to identify low-income patients),

rural residence, lab data on HbA1c within the previous 2 years, anti-hyperglycemic medication (oral or insulin), and contact information (mailing address, telephone number, email address). We will calculate %TIC (for HbA1c, LDL, and BP) for the 6 months immediately prior to recruitment. VSSC data will be consulted to identify which patients have upcoming appointments scheduled. An invitation letter will initially be mailed out to women Veterans in the eligible cohort of women with A1c %TIC<50 at each site. Because women represent only 3-4% of eligible participants at each site, we seek to oversample them to the extent possible to ensure adequate representation (not to test for differences in effectiveness). Then we will mail letters to 300 eligible male Veterans per site, followed by additional mailings of 50-100 until a total of 200 to 220 participants are enrolled at each site (no greater than 440 total). A1c%TIC will be recalculated immediately prior to every mailing with the most recent 6 months of data to ensure A1c %TIC<50 at recruitment. Eligible Veterans will be mailed an invitation to participate in a study to use texting for diabetes self-management, with an opt-out card to mail back if they are not interested. Those who do not opt out will be contacted by telephone and screened to confirm eligibility and ascertain interest in participation (See attachment, screening telephone call script). Prior to calling, the project coordinator will prescreen patients in the electronic health record (National CAPRI Access) to make sure the patient hasn't had any health event (current hospitalization, terminal diagnosis, death) or recent controlled HbA1c lab value (<8.0%), which would make them ineligible. The project coordinator will track how many were not eligible (and why) and invite those eligible and interested to enroll in the study after the screening interview to set up a time for an in-person or virtual baseline assessment and Annie training either at their next scheduled visit or at their earliest convenience. Patients will have the option of completing the baseline assessment survey online, by phone, or in person (if COVID restrictions are lifted).

- Payment: Participants will be given $30 after completing the baseline assessment. This payment will be paid by gift card or by direct deposit. Veterans will be asked to provide their Social Security number and bank information and fill out a vendorization 10091 form if they are requesting direct deposit for the first time.

- Aim 2 Texting Fee Reimbursements: We will reimburse participants who do not have unlimited texting plans who require financial assistance. Participants will be reimbursed for the amount they are charged per text message by their cell phone provider, for the amount of text messages associated with their participation in this study. Based on these estimated costs, we will reimburse up to $20 per month for the DD-TXT arm and $5 per month for the DSE arm by direct deposit. While enrolling the participant, the project coordinator will ask what cell phone provider they use and how much is charged per text message and ask if they require financial assistance Typically, Veterans will be paid by direct deposit for texting reimbursements after completion of the follow up assessment and interview, but reimbursements can be pro-rated on a monthly basis if the Veteran continues to participate by responding to messages.

- Qualitative Interviews with Aim 2 Participants:

    - We will conduct a follow-up assessment and a brief qualitative interview (in-person or over the phone) with all patients engaged in the Aim 2 Trial at the 6-month follow-up about their experiences. Before that, we will send an email and mail confirmation confirming their follow-up interview. Research coordinators may

review VHA Support Service Center (VSSC) data to schedule a follow-up interview with enrolled patients that aligns with their medical appointment schedule.We will follow the structure of Appendix 13 Patient Interview Guide (from grant proposal approval), “Semi Structed Patient Interview Guide for Follow Up”.

- Participants will also be remunerated with $50 for completion of the follow up assessment and interview. They will be given the $50 after completion of the follow up assessment and interview. However, if they only complete the follow-up assessment survey, they will only receive $30. This payment will be paid by gift card or direct deposit. Veterans will be asked to provide their Social Security number and fill out a 10091 form if they are requesting direct deposit for the first time.

Aim 3 - No additional patient recruitment will take place as part of Aim 3. We will identify primary care team members whose patients participated in the Aim 2 trial, as well as key stakeholders at each site, for semi-structured interviews by video conferencing or telephone.

- We will identify primary care teams with mutiple patients enrolled in DD-TXT and DSE and interview the primary care provider (N=5 teams per site). We will also interview some key stakeholders involved in diabetes self-management education such as Diabetes Educators, Health Promotion Disease Prevention Program Managers, and Health Behavior Coordinators. We will use a Semi-Structured Provider Key Informant Interview Guide to help guide the interviews.

- In order to ensure that providers and key stakeholders do not feel coerced into participation, potential participants will be contacted by email and then study staff will follow up by email and/or telephone for interview scheduling if they do not reply to opt out.

- There will be no compensation to VA employees.

5.3 Informed Consent Procedures

We are requesting a waiver of documentation of informed consent from the VA Central Institutional Review Board (CIRB) for the entire study to make it possible and safer to conduct the study during the COVID pandemic. Those interested in participating in different study aims will be provided with the relevant Information Sheet which will cover the general nature of the study, what their particular involvement entails, the risk/benefits, and a description of confidentiality. Participants will be told that participation is voluntary, that they can withdraw at any time, and that this will not impact their treatment. Prior to participation, the Veteran will be given a chance to ask questions

about the Information Sheet and will verbally consent prior to partaking in any study related activities. Aim 1 (participatory design surveys and interviews): Participants will be mailed an Information Sheet describing the Participatory Design Survey and the optional virtual Participatory Design Interview. The Participatory Design Survey and Virtual Interview Information Sheet will include that participatory design interviews may be recorded. Returning the completed survey by mail will constitute consent to participate in the survey and if participant requests to complete Aim 1 survey or interview over the phone, the mailed information sheet will be reviewed with the participant and verbal consent will be obtained and documented in REDCap. If patients indicate on their survey that they are willing to be contacted for an interview, this will be their consent for the interview. At the start of the interview, the participant will have a chance to review the Information Sheet with the interviewer and will only be recorded if they provide verbal consent to do so.

- Aim 1 (beta testing): Patients receiving treatment for diabetes at the VA Bedford Healthcare System will be mailed a Beta Testing Information Sheet detailing the Beta Testing process. Patients who agree to participate during the Screening Call will have a chance to verbally review the Information Sheet with study staff. Participants will only be recorded at the Post Beta Testing Interview if they provide verbal consent to do so.

- Aim 2 (randomized comparative effectiveness trial): Participants will be mailed an Aim 2 Trial Information Sheet with their letter inviting them to participate in the trial. They will have a chance to discuss and verbally review the Aim 2 Trial Information Sheet content during their screening call if they agree to participate. The discussion will cover participation in the trial, as well as the baseline and follow-up assessments and follow-up interview. Once consented, participants will be randomized to either DD-TXT or DSE with stratification by gender. At the discretion of the site PI, a note may be entered into CPRS to indicate that they are participating in the trial. Participants will have the chance to decide at the follow-up interview whether they wish to verbally consent to being audio recorded via Microsoft Teams. See Aim 2 Trial Information Sheet

- Aim 3 (provider/key stakeholder interviews): We are requesting a waiver of documentation of informed consent for the provider/key stakeholder interviews. Participants will be given an information sheet to review at the time of interview, or prior to the interview. Verbal consent will be obtained by study staff prior to recording interviews. See Information Sheet for Key Stakeholder Interviews.

We will train site project coordinators in informed consent procedures. When enrolling women of childbearing age for the Aim 1 beta testing or Aim 2 trial, we will also emphasize some of the risks of uncontrolled diabetes during pregnancy and that it will be extremely important for the patient to let the study team AND their doctors know right away if they were to become pregnant (or if there were another major change to their health status). The Aim 2 Trial Information Sheet will specify that their choice of modules might be more limited if they become pregnant during the trial, and that they could choose to disenroll from the study if they wanted.

The Bedford project manager will hold training sessions including using video conferencing technologies to review and train project coordinators at local sites in obtaining informed consent.

5.4 Inclusion/Exclusion Criteria

For inclusion in the Aim 2 trial, Veterans must be active VHA patients with type 2 diabetes, have had VA outpatient encounters in the previous year, have a future appointment scheduled, and not be hospitalized or institutionalized at the time of enrollment or have participated in Aim 1 DD-TXT development. In addition, they must have access to their own or a cohabiting family member's cell phone or smartphone for participation. They must be willing and able to text, not have any visual impairment that would prevent them from reading or replying to text messages, and must be cognitively capable of consent to participate. They must also have HbA1c lab data for the 12 months prior to RCT recruitment. Eligible patients must have inadequate glycemic control for at least 50% of the 6 months before enrollment.

Women cannot enroll in the trial if they are currently pregnant. A participant who enrolls but later becomes pregnant would still be eligible to participate in the data collection and receive participant incentives. Any reimbursement for text messages received/sent (for those who pay per text) would be pro-rated based on months texts were received.

5.5 Study Evaluations

Aim 1

Participatory design survey and interviews: Veterans with diabetes from vulnerable subgroups will be asked to complete a mailed survey and respond to general questions on self-management challenges and demographics and the likelihood of wanting to receive messages from the different modules. The survey will also ask about access to and comfort with technology and interest in participating in a follow-up interview to take place either by telephone or by video conferencing technology, or in-person if the patient is coming into the VA for a clinical visit and the facility is allowing in-person data collection at the time. Each patient will also be asked to rate, rewrite, or suggest alternatives to a set of text messages (because the survey would be prohibitively long if all texts were included, surveys will cover different texting modules so that we receive feedback on each module from at least 5 Veterans). The **Virtual Participatory Design Interviews** will be one-on-one semi-structured interviews with Veterans about the content and timing of the modules and what else they would find helpful for text-based diabetes self-management support.

Alpha testing: The study's Veteran Co-Investigators and project staff will be enrolled through Annie as protocol testers, to test portions of the DD-TXT protocol as they are developed or modified. Testers will provide ongoing feedback on the functioning of the modules, reporting back on any programming failures or "bugs" encountered in how the templates are chained together to guide iterative improvements to DD-TXT. During this testing phase, some testers will also receive the education-only DSE protocol.

Beta testing: We will ask 8 to 12 patients with uncontrolled diabetes from Bedford to test DD-TXT over a two-month period. The local project coordinators will check with the patients at one week, two weeks, and one month to see what they like/dislike about DD-TXT and will update their module settings. At the end of two months, beta testers will complete follow-up data collection and provide feedback on their experience with DD-TXT (see attachment, Post beta testing Interview Guide). Drs. Cutrona and Vimalananda and local Bedford study staff will pilot all the enrollment and data collection procedures for the Aim 2 trial, so that beta testing can

inform improvements to (a) DD-TXT protocol and customization process, (b) patient materials, (c) project coordinator instruction manual, (d) recruitment processes, (e) data collection processes, (f) patient support processes, and (g) new safety monitoring process.

Table 1: Data Elements for Aims 2 and 3 **Variable Type and Source** (Timing of Data Collection B=Baseline, F=Follow-up, P=Post-Trial)	CDW	Patient Survey	RA & Annie	Interviews
Race/Ethnicity, Age, Gender	B	B		
Home Zip Code, Rural Location	B			
Diabetes Intermediate Outcomes (BMI, BP, HbA1c, LDL)	B,F			
Predictors of Diabetes Outcomes (comorbidities, duration of diabetes)	B, F			
Medication (Diabetes, hypertension, hyperlipidemia medications)	B	B, F		
Self-Care Inventory- Revised (SCI-R)[60]		B, F		
Diabetes Self-Efficacy Scale [61]		B, F		
Diabetes Distress Scale[62]		B, F		
Adherence to Refills and Medications Scale – Diabetes (ARMS-D)[63]		B, F		
Patient-Reported Health (VR-12)[64]		B, F		
Virtual Care Activity		B		
Virtual Care Predictors (Tech Access, eHealth Literacy (eHEALS)[65]		B		
Health Literacy (Chew 3-item Health Literacy Screen)[66]		B		
Perceived Benefits of Virtual Care		B		
Income, Education, Employment, Housing		B		
Marital Status, Family/Informal Caregiver, Social Support		B		
Housing stability; Food security; Neighborhood Characteristics (safety from crime, exercise environment, healthy food access)		B		
Use of Non-VA Healthcare		B, F		
Healthcare utilization (missed visits, urgent care visits, ED visits, hospitalizations)	F			
Costs associated with Annie utilization	F		F	F
Diabetes-related Process Measures (HbA1c frequency, foot care, retinal exams)	B,F	B, F		
Pros and Cons of Annie Diabetes Protocols and Suggested Improvements		F		F,P
Use of / Engagement with Modules			F	F
Project coordinator support required for Annie			F	
Implementation Barriers/Facilitators				P

Aim 2 - Trial

Module Customization form (see attachment): Participants randomized to DD-TXT will prioritize diabetes self-management topics, select optional modules of interest, and customize when they wish to receive texts. Our previous work has shown that patients are willing to receive messages at least three times a day, and prefer consistency in timing.

Baseline survey instruments & 6 month follow-up: At the time of the baseline assessment, patients will be consented verbally and then asked to complete a baseline survey (See attachment for draft Data Collection Instrument), either online or by telephone, including questions about their current use of technology, their current self-care behaviors, their diabetes self-efficacy and diabetes distress. (See Table 1 for a complete list of data elements).

- The Self-Care Inventory – Revised (SCI-R)[60, 67] is a 15-item self-report questionnaire assessing patients' perceptions of their diabetes self-care behaviors such as diet, glucose monitoring, medication management, exercise, hypoglycemia prevention, and preventive care. Self-report is the only feasible way to assess these diabetes self-care behaviors, which we are hoping DD-TXT will support. SCI-R will be our measure of diabetes self-management behavior. Range: 0-100.

- The Diabetes Self-Efficacy Scale[61] is an 8-item scale assessing patients' level of confidence in managing their diabetes through diet, physical exercise, and blood sugar, and has a reported internal consistency of α=0.83. Range: 1-10.

- The Diabetes Distress Scale (DDS) has established itself as a valuable measure of diabetes-related emotional distress for use in clinical practice.[62] The DDS has demonstrated consistent, internal reliability and validity across a variety of clinical environments and diverse patient populations.[68] Range: 1-6 (continuous) or can be scored dichotomous as high (>=3) or low (<3) distress.

- The 11-item Adherence to Refills and Medication Schedule for Diabetes (ARMS-D) scale includes 7 questions about medication taking and 4 items about refilling medications. It is reliable (Cronbach's alpha=0.86), has good convergent validity with other diabetes self-care activities scales, and is significantly associated with HbA1c. [63] Each item is measured on a Likert-type scale (1=none of the time, 2=some of the time, 3=most of the time, 4=all of the time). Range: 11-44.

Six-Month Follow-Up Assessment: The follow-up assessment will take place 6 months after their baseline assessment. Patients will be contacted by telephone, mail, or email to schedule a follow-up and complete a follow-up survey online or by phone to repeat key baseline measures. They will also be asked to participate in a brief (20-30 minute), semi-structured interview (to be analyzed as part of Aim 3) to provide feedback on the DD-TXT or DSE intervention and information on the personal relevance of the intervention and how it supported their autonomy in diabetes self-management. In addition to what they liked and disliked about the Annie protocol they were enrolled in, those in the DD-TXT group will be asked specific questions about the different modules, whether they used them, what they found most and least helpful about each module, and any suggestions for improvement. All participants will be paid $50 for completing follow-up (including both the survey and interview), but if they only complete the follow-up assessment survey, they will receive only $30. Annie dashboard data will show how many

weeks out of the 26 weeks (6 months) patients continued their engagement with Annie, their level of engagement (% of time they responded to Annie requests for a response), their Annie settings (e.g., medication reminders once a day vs. three times a day), and the actual modules and optional modules they selected. Project coordinator records will be used to document the number of contacts from each patient during the 6-month intervention period, the types of requests for assistance received (e.g., change modules), the amount of time the request required, and whether others' assistance was required (e.g., HelpDesk).

Aim 3

Analysis of Patient Perspectives from Aim 2: We will conduct brief (20-30 minute) qualitative interviews with all patients engaged in the Aim 2 Trial at the 6-month follow-up about their experiences receiving texts for diabetes self-management support, including impacts on their diabetes self-management and clinical care, any potential downsides, and suggestions for improvement and implementation. (See Patient Interview Guide). These interviews will be recorded, and coding will be applied to describe patients' experiences with DD-TXT and DSE, compare experiences across groups (i.e., are there similar or varied experiences with DD-TXT across different groups of vulnerable Veterans), and provide recommendations for how the interventions or their implementation might be improved overall or for particular groups.

Physician and Key Informant Perspectives: We will conduct a small number (15-25) of semi-structured interviews to gather important perspectives on DD-TXT and DSE. (1) At each study site, we will identify the primary care teams with the most patients enrolled in DD-TXT and DSE and interview the primary care provider (PCP) by telephone or video conferencing (N=5-10 teams per site, see Key Informant Interview Guide). Providers will be asked about their involvement with Annie, perceived fit of Annie texting with their workflow, overall impressions of DD-TXT vs DSE, and concerns with Annie diabetes self-management. They will also be asked for suggestions for improving the texting protocols, and about barriers and facilitators of future implementation of text-based diabetes self-management support. (2) We will also conduct telephone or video conferencing interviews with 5-10 other key informants at each facility such as Diabetes Educators, Health Promotion Disease Prevention Program Managers, and Health Behavior Coordinators to gather feasibility and contextual data to inform implementation strategy for a future Type 2 hybrid implementation trial. Recommendations will be summarized as lists of barriers and facilitators to future implementation, suggestions for appropriate workflows for texting implementation, and suggested improvements to DD-TXT or DSE.

5.6 Data Analysis

Aim 1

- In Aim 1 we will collect information in order to improve the implementation process for Aim 2 through Participatory Design surveys and interviews to inform the development of core and optional modules, and Alpha and Beta testing to test out the use of Annie text messaging with the modules.

Aim 2

- Setting and Sample: The two sites for the trial are Jesse Brown VAMC in Chicago, IL and Malcom Randall VAMC in Gainesville, FL. Data will be collected at these two study sites and analyzed there and at Hines VA and Bedford VA.

- Note: We will monitor recruitment numbers closely over the first three months; if unexpectedly high refusal rates prevent adequate progress, we may expand recruitment to Hines (Chicago), Bedford, or via the VA Women's Health Practice Based Research Network.

- In analyzing data for the trial, we will begin by assessing baseline characteristic balance by group, then describe engagement in the DD-TXT intervention. Then, we will evaluate our effectiveness outcomes for H1, H2, and H3.

- Comparing Baseline Characteristics: We will begin our analyses by examining univariate statistics (means, medians, standard deviations and 95% confidence intervals) and distributions. We will examine the balance of participant characteristics by study arms and account for any imbalances in our multivariable analysis. Key characteristics (covariates) to examine include gender, age, urban/rural, education, income, housing stability. Randomization arm differences will be tested using chi-square tests of independence (categorical variables), t-test (continuous variables) or the equivalent non-parametric tests depending on the distribution of the variables. In accordance with best practices, baseline imbalance of DD-TXT and DSE arms will be established using standardized differences, rather than significance tests.[69, 70]

- Measuring intervention engagement: Further, we will report **use** (# of weeks until patient stopped using system altogether) for DD-TXT and DSE and **engagement** (# of weeks when patient sent in a reply in response to an Annie text, % of messages requesting a reply that the patient responded to) for DD-TXT group. In addition, we will report DD-TXT modules used (indicators for each core and optional module).

- Independent variable (IV): For all intent-to-treat analyses, the independent variable is randomization arm.

- Dependent variables (DV): Dependent variables will be measured at both baseline and follow-up. For BP%TIC, LDL%TIC, and **our primary DV, A1c%TIC**, we will compare 6 months before and after enrollment for each physiological measure, using 24+ months of longitudinal data from 12 months prior to enrollment to 6 months after trial completion to calculate **baseline %TIC** (%TIC over 6 months prior to enrollment, will be recalculated at the time of enrollment if there is a lag of more than a month between recruitment and enrollment) and **follow-up %TIC** (%TIC during the 6-month intervention). Figure 5 illustrates how this will be done. Data from our current IIR shows that for those with A1c %TIC<50 in 2015, nearly 96% had at least one HbA1c test in 2016 (range, 1-15), and 78.3% had 2+, with 88% having 1-4 HbA1c tests. For survey measures, DV will be the score (e.g., SCI-R score, self-efficacy score, medication adherence score) obtained from baseline and follow-up surveys. For missed appointments, the number missed during the 6-month trial period (vs. the 6 months before enrollment).

- Outcome Analyses: To preserve the power of randomization, all primary analyses will be on an intent-to-treat basis. However, secondary analyses will explore dose-response

effects among those with variable levels of adherence to the intervention. All analyses will be two-sided and α=0.05. We will use a similar approach to test all of the hypotheses. First, we will describe the dependent variables (DV) at baseline and at follow-up using frequencies, means, medians, range, and standard deviations; the distribution will be used to determine the appropriate modeling technique. We will compare the two arms to determine if the mean scores (%TIC, SCI-R score, self-efficacy score) are significantly different at follow-up for DD-TXT versus DSE. To address this question, we will use a random-effects model of the form:

- $g(\mu_{ijt}) = \alpha + X_{ij}^{\gamma} + \beta_i + \delta_t + (\beta\delta)_{it} + G_{ij}\,(\beta_i^G + \delta_t^G + (\beta\delta)_{it}^G) + u_{ij}$

where, $g(\mu_{ijt})$ is a link function (e.g., log link) of the mean response at time *t* for the *j*-th subject in the *i*-th group, α is the intercept, X_{ij}^{γ} is the vector of main effects associated with other covariates (such as age, gender, marital status) and key moderators, β_i is the main effect for the intervention group, δ_t is the main effect for time, $(\beta\delta)_{it}$ is the effect for the interaction between intervention group and time, and u_{ij} is the random effect corresponding to the *j*-th subject in the *i*-th group,. The coefficient $(\beta\delta)_{it}$ is the estimate of the interaction term which, if significant, indicates that the treatment effect. To explore potential moderating effects, we will expand the model to include G_{ij} as a vector of binary moderating variables for the *j*-th subject in the *i*-th group and $(\beta\delta)_{it}^G$ is the marginal treatment effect attributable to each particular moderating variable.

- Separate models with appropriate link and family (e.g. linear regression for continuous, logistic for binary outcomes, negative binomial or Poisson models for number of missed appointments) will include the following dependent variables: H1: A1c%TIC, BP%TIC, LDL%TIC, H2: SCI-R, medication adherence, missed appointments, H3: diabetes self-efficacy, diabetes distress, with the main DV for each hypothesis listed in Table 6. For the appointment models, we will include an offset to account for the number of appointments made. To address the oversampling of women, analyses will also be weighted to reflect the proportion of women Veterans in the eligible sample. It is expected that if randomization is successful, there will be few significant differences between the arms on patient characteristics. Our primary models will include group assignment (DD-TXT vs DSE) as the independent variable adjusting for baseline value of the dependent variable. Per guidelines for clinical trials, we will include variables known a priori to be strongly or at least moderately associated with the primary outcome as covariates and will only conduct sensitivity analyses in the case of strong imbalance in covariates.[71] Based on our current work, we have seen that age, gender, and marital status are significantly associated with A1c%TIC. Exploratory analyses will analyze moderation by social determinants such as minority race, rural residence, low-income, education, neighborhood safety, exercise environment, food access. False discovery rate adjustments will be applied.

Table 6: Main Dependent Variable by Hypothesis

	Measure	Source
H1	A1c%TIC (time in control) ***Primary Outcome Measure***	CDW
H2	Self-Care Inventory-Revised	Survey
H3	Self-Efficacy	Survey

- Intervention Fidelity (Mediation Analyses): As noted in our conceptual model, affective responses and changes in behaviors are in the causal pathway leading to changes in health outcomes. Thus, as secondary analyses, we will evaluate the degree to which self-management behavior change leads to change in A1c%TIC. Mediation occurs when the effect of an intervention is transmitted through an intermediate process (such as behavior measured by SCI-R, ARMS-D) to produce an observed outcome (improved A1c%TIC).[72] Mediation analyses will draw upon classic principles modified from Barron and Kenny.[73] Mediation ratios may be calculated, which provide the proportion of the intervention effect that is transmitted through a given pathway, with precision quantified by 95% bias-corrected confidence intervals from bootstrapped re-sampling with replacement.[74, 75]

- Heterogeneity of Treatment Effect: We will also conduct exploratory secondary analyses for heterogeneity of treatment effect (effect modification) by looking at interactions between the randomization arm and Veteran gender, age, computer literacy, urban/rural and facility (recruitment site). If we determine that there are significant interactions, we will stratify analyses by gender, age category, or site.

- Dealing with missing data: We will make every effort to maximize participant retention in the study. We approximate that there will be about 20% attrition (See Section H). We will estimate potential bias due to drop-outs in our study. Participants with missing data will be compared to those without. We will explore predictors of engagement to examine differences between those who do and don't complete the intervention or the follow-up assessment. Based on analyses of A1c%TIC from our current study data, we expect very little missing data for our physiologic outcomes; the rate of missing 2016 CDW data for those with A1c%TIC<50 in 2015 was low (HbA1c: 4.4%, BP: 1.9%, LDL: 11.9%). Our power calculations below assume 20% attrition and 320 Veterans completing follow-up.

- Power: **H1**: The primary outcome for H1 and for the study is glycemic control (HbA1c). The primary measure for glycemic control will be A1c%TIC. For mean HbA1c, a value <7.0% is considered clinically tightly controlled, a value<8.0% loosely controlled, and an improvement as small as 0.5% (e.g., from 9.2 to 8.7%) is considered a clinically significant change.[76] Based on our current IIR 15-307, among those with A1c%TIC<50, the mean(SD) of A1c%TIC was 26.3(14.1) and in the subsequent year was 47.9(40.3). Based on regression coefficients, an improvement of mean HbA1c from 9.2 to 8.7% (change of 0.5%) corresponds to an increase in A1c%TIC of roughly 13.8%; thus, 13.8% represents the minimal clinically important difference in A1c%TIC. We have 80% power to detect a clinically meaningful difference in A1c%TIC for DD-TXT vs DSE arms as small as 13.8% (e.g., 47.9 vs 61.7%TIC) with a sample size of only 134 per arm. **H2:** In prior studies, a 4 point difference in SCI-R represented a minimally clinically important difference.[60] Based on data that a previous educational intervention improved the SCI-R score from 57.9±10.6 at baseline to 64.4±10.8 post-intervention,[67] for H2a we would only need 111 participants in each arm to detect a 4 point difference between arms in SCI-R with 80% power at the .05 significance level. **H3**: For diabetes self-efficacy, assuming a baseline mean(SD) of 6.93(1.77),[61] 320 subjects (assuming 20% loss to follow-up) will allow us to detect a mean difference between arms as small as 0.55 at 80% power with a .05 significance level. For missed appointments, based on FY13 VA data showing an average of 1.84 missed visits (SD 2.09), our sample size will give us 80% power at the 0.05% significance level) to detect a change as small as 0.6 missed visits.

Aim 3

- **Patient Perspectives:** Evaluation Coding methods[77] will be applied to the Aim 2 participant interviews to describe patients' experiences with DD-TXT and DSE, compare experiences across groups, and provide recommendations for how the interventions or their implementation might be improved overall or for particular groups.

- **Physician and Key Informant Perspectives:** We will conduct a small number (15-20) of semi-structured interviews to gather important perspectives on DD-TXT and DSE. Recommendations will be summarized as lists of barriers and facilitators to future implementation, suggestions for appropriate workflows for texting implementation, and suggested improvements to DD-TXT or DSE.

- **Cost-Identification Analysis/Safety Analysis:** We will conduct a cost-identification analysis (CIA) to assess the cost of implementing DD-TXT or DSE. To estimate costs, we will obtain cost data from VHA Managerial Cost Accounting (MCA) datasets (formerly known as Decision Support System (DSS) National Data Extracts), consultation with the Health Economics Resource Center, and consultation with the two study sites. We will track the cost of supplies (e.g., instructional materials on Annie use). In addition, we will also estimate the staff time associated with DD-TXT and DSE. To address uncertainty in the CIA, we will use scenario analysis to construct multiple scenarios by varying input values and structural assumptions. These findings will be shared with OCC so they can use it to help facilities anticipate costs associated with both simple texting protocols (like DSE) or more complex, interactive protocols (like DD-TXT). Knowledge gained by monitoring the dashboard will be used to generate a safety analysis. These findings will be provided to OCC to inform safety monitoring for Annie in general.

Sample Size Determination and Analysis

Main hypotheses to be tested:

H1: Veterans in the DD-TXT arm will have better control of their diabetes-related intermediate outcome measures (such as HbA1c (H1a), blood pressure (BP) (H1b), or low-density lipoprotein (LDL) cholesterol (H1c)) at follow-up than those in the DSE arm. **A1c%TIC at follow-up is considered the primary outcome variable** because glycemic control is an important, objective, and readily interpretable clinical goal of diabetes self-management. Patients will be selected based on their A1c%TIC<50; not all patients will be uncontrolled on other measures. Cutoffs for control defined as HbA1c<8.0%, LDL<100mg/dL for LDL, SBP<130mmHg and DBP<80mmHg for BP, respectively, based on VA guidelines.[54]

H2: Veterans in the DD-TXT group will report more positive behavioral responses (as measured by higher SCI-R score (H2a), and higher ARMS-D medication adherence score (H2b)) than those in the DSE group, and Veterans in the DD-TXT group will show evidence of greater changes in health care utilization (fewer missed primary care appointments) than the DSE group (H2c). SCI-R will be the main outcome for H2 since it is the best available measure of self-care behaviors across all relevant diabetes self-care domains.

H3: Veterans in the DD-TXT group will show more positive affective responses (as measured by higher diabetes self-efficacy (H3a), lower diabetes distress (H3b)) than those in the DSE group.

Power calculations:

Our power calculations below assume 20% attrition and 320 Veterans completing follow-up.

Power: **H1**: The primary outcome for H1 and for the study is glycemic control (HbA1c). The primary measure for glycemic control will be A1c%TIC. For mean HbA1c, a value <7.0% is considered clinically tightly controlled, a value<8.0% loosely controlled, and an improvement as small as 0.5% (e.g., from 9.2 to 8.7%) is considered a clinically significant change.[76] Based on our current IIR 15-307, among those with A1c%TIC<50, the mean(SD) of A1c%TIC was 26.3(14.1) and in the subsequent year was 47.9 (40.3). Based on regression coefficients, an improvement of mean HbA1c from 9.2 to 8.7% (change of 0.5%) corresponds to an increase in A1c%TIC of roughly 13.8%; thus, 13.8% represents the minimal clinically important difference in A1c%TIC. We have 80% power to detect a clinically meaningful difference in A1c%TIC for DD-TXT vs DSE arms as small as 13.8% (e.g., 47.9 vs 61.7%TIC) **with a sample size of only 134 per arm**. **H2:** In prior studies, a 4 point difference in SCI-R represented a minimally clinically important difference. Based on data that a previous educational intervention improved the SCI-R score from 57.9±10.6 at baseline to 64.4±10.8 post-intervention,[67] for H2a **we would only need 111 participants in each arm to detect a 4 point difference between arms** in SCI-R with 80% power at the .05 significance level. **H3**: For diabetes self-efficacy, assuming a baseline mean(SD) of 6.93(1.77),[61] **320 subjects (assuming 20% loss to follow-up) will allow us to detect a mean difference between arms as small as 0.55 at 80% power with a .05 significance level**. For missed appointments, based on FY13 VA data showing an average of 1.84 missed visits (SD 2.09), our sample size will give us 80% power at the 0.05% significance level) to detect a change as small as 0.6 missed visits.

5.7 Withdrawal of Subjects

If at any time the local site PI feels the study is inappropriate for a participant or due to medical reasons, the PI reserves the right to discontinue/withdrawal the subject from the study.

If a woman becomes pregnant during the trial, we will modify her module selection. If the only modules she has signed up for are those deemed inappropriate, we will stop sending her those modules and proceed to the interview early if the patient is willing so that we can still record her input/feedback to inform future use of Annie for diabetes self-management support. If she chooses to discontinue participation, she may do so with no repercussion to their care or future opportunities in research or other at the VA.

If at any time a participant chooses to discontinue participation, they may do so with no repercussion to their care or future opportunities in research or other at the VA.

Because there is a small risk that participants may experience some distress or psychological discomfort during the assessments or while answering interview

questions, participants will be made aware of their right to refuse to answer any questions that make them uncomfortable or that they do not wish to answer, and they will be informed of their right to withdraw from the study at any time without penalty. Participants may also be informed that they can take breaks. Additionally, study staff will be trained extensively to respond to emotional distress and to discuss concerns and issues should they arise. More specifically, study staff will be trained to perform attentive and empathic listening as well as exhibit calmness during the assessments. To minimize this risk, research staff will be available during and following study activities, such as the participatory design interviews, assessments, and post-trial interview to manage (i.e., discuss and refer as needed) any unexpected issues that may arise.

Risk Reduction

During the 6-month trial, participants in both the DD-TXT intervention and DSE comparison groups will be enrolled into Annie and receive text messages from Annie on their phones. As part of the mandatory Annie consent and enrollment process built into the system to mitigate risk (this is separate from and in addition to any IRB-related consent process), both groups will receive careful instruction on the functionality of the Annie texting system. As part of this process, patients must verbally acknowledge and sign off that they understand that (a) although their physicians or other VA staff with permission can view their Annie dashboard and history, the healthcare team will NOT be monitoring it regularly**,** (b) Annie is designed as a patient self-care program where they get feedback from a computer, and that they are responsible for their own health, (c) that SMS texts are not secure, and (d) that there may be costs associated with receiving texts depending on their cellular plan (but that the study will reimburse them if these costs are incurred). Patients who do not understand or agree to these terms cannot be enrolled into Annie.

The project coordinator will instruct patients at enrollment that the texting system is not in fact a person and can only understand the answers to specific, simple questions, that VA clinical team members do not regularly monitor messages sent and received through Annie, and that ultimately, they are responsible for their own health. Patients will also be instructed at enrollment that clinical advice from their doctors, nurses, and diabetes educators should always come before Annie's recommendations and that any concerns about discrepancies should be addressed with their clinicians. Following a best practice used when enrolling patients in the UK NHS system, we will ask patients to explicitly acknowledge their understanding of these points prior to completing the enrollment process. Although the DSE group will only receive one-way educational messages, participants randomized to DD-TXT will be asked to report their blood sugars (and for some also their blood pressures) and provide responses to other two-way assessment items, and Annie will provide pre-programmed feedback determined appropriate based on clinical input.

Because it is known that patients may potentially misunderstand that their providers are monitoring the data they send in, there are several additional precautions built into place for the purposes of this study:

a. Any assessment questions that ask patients to report back to Annie on their health will be programmed to generate immediate responses to the patient. If patients report values that are out-of-range (e.g., dangerously high or low blood sugar or blood pressure readings), Annie will instruct the patient on how to proceed, and provide encouragement to get in touch with their clinical team if needed (e.g., "Your blood sugar is over 300, check your sugar before meals and at bedtime until less than 200. If it does not go down, you should call your healthcare team").

   In addition, as a second precaution, project coordinators will monitor the web-based "Annie dashboard" during the intervention period to check on patients' responses to Annie. Annie is designed with a VA intranet-accessible dashboard that supports viewing of responses from all patients engaged in the system. In the British National Health Service (NHS)'s experience with Annie-like texting, to alleviate safety and risk concerns among clinicians, once weekly patient "check-ins" are used for particular diagnoses whereby staff monitor incoming patient messages and respond to the patient via telephone with specific instructions. We propose to also follow this approach, checking the dashboard for patients on our Annie protocols using the following monitoring plan:

- The Annie dashboard will be checked by project coordinators 1 to 3 times per week throughout the study.
- If a Project Coordinator discovers potentially suicidal message content, then the Project Coordinator will immediately call the suicide hotline and report the patient's name and telephone number, and afterwards follow up with the site PI. Our clinical stakeholder group will have determined ahead of time what the appropriate guidance should be for the project coordinators for determining whether a value that patients report is abnormal or potentially concerning. If project coordinators discover potentially concerning responses to text messages, they will reach out to the site PI to determine whether outreach to the patient or their primary care team is warranted.
- *Problematic texting* includes if patient types in free text (that is not a typo for an acceptable response) more than twice OR if there is potentially clinically concerning content, OR if the patient is requesting help from the project coordinator.
- Weeks 1 and 2 of enrollment for each patient: Monitor 3 days a week unless the patient sends a problematic text. If problematic text reviewed, call patient to review proper texting procedures and extend monitoring to 3 days a week for 2 weeks after day of call.
- Weeks 3 and 4 of enrollment for each patient: Monitor 2 days a week unless patient sends a problematic text. If problematic text reviewed, call patient to review proper texting procedures and extend monitoring to 3 days a week for 2 weeks following that call,
- Weeks 5 through end of enrollment for each patient: Monitor once a week unless the patient has sent a problematic text in previous 2 weeks, in which case call to review proper texting procedures and increase monitoring to 3 days a week for 2 weeks following that call.

- All problematic texts and calls will be documented. The project coordinators will document how frequently they observe any potentially concerning behavior via the dashboard, including patients responding inappropriately with free text, reporting extreme blood pressure or blood sugar values, or any other potentially concerning behavior that the site PIs have deemed potentially unsafe and worthy of follow-up action.

In order to prevent participants from forgetting expectations around use for Annie, we will make sure warnings are included in study-related Annie reference materials handed out to participants. Periodic text reminders about these agreements will be sent out to participants via the Administrative core module. We will include a **periodic text reminder** to the texting protocol for all participants that they should always follow their healthcare team's advice over Annie's advice. We will also periodically remind them of the Research Assistant contact information in case of questions, if they need to update us on their change in health status (e.g., pregnancy) or if they need to modify their modules.

6.0 Reporting

Serious adverse events: During the Aim 2 trial, project coordinators will monitor the Annie dashboard system, and have a clinical stakeholder-approved plan for action if patients report abnormal or potentially concerning values. If a project coordinator discovers potentially suicidal message content, then the project coordinator will immediately call the suicide hotline and report the patient's name and telephone number, and afterwards follow up with the site PI. Any suicide-related content will be considered a serious adverse event and reported immediately to the ACOS for Research at Bedford and to CIRB.

Because some patients with diabetes are very ill, it is possible that a patient may pass away while being enrolled in the diabetes texting intervention. We may not realize this until we attempt to reach out for the follow up assessment. We will report any known deaths at the annual continuing review, unless there is reason to believe that deaths were caused by or related to participation in the trial.

Other reporting: The project coordinator will document how frequently they observe any potentially concerning behavior via the dashboard, including patients responding inappropriately with free text, reporting extreme blood pressure or blood sugar values, or any other potentially concerning behavior that the site PIs have deemed potentially unsafe and worthy of follow-up action. All instances will be reported to the team in Bedford and included in annual reporting/continuing review.

Unanticipated problems and protocol deviations: Dr. Shimada and the Site-PIs will ensure that all relevant IRB policies, procedures and stipulations are being followed. Any noted unanticipated problems or protocol deviations will be reported to the site-PI and subsequently the PI, and IRB will be notified.

The PI and Site PIs will provide a summary of recruitment and any reports of adverse events or confidentiality breaches to the CIRB on an annual basis as part of the progress report. The report will include participants' socio-demographic characteristics, expected versus actual

recruitment rates, any quality assurance or regulatory issues that occurred during the past year, summary of adverse events, and any actions or changes with respect to the protocol.

Psychological safety plan: Safeguards we have included for the protection of psychologically vulnerable subjects include: (1) All enrolled participants will be given the Veterans Crisis Line information at the time of consent signing and during the intervention as necessary, (2) clinicians at the local sites will provide clinical oversight for the study and provide referrals as needed, (3) If a Veteran expresses suicidal ideation either via text message or to a study team member, a VA provider will speak with the participant and the Veterans Crisis Line will be contacted as needed.

In the case of imminent risk and if the Veteran is present at the VA facility, the Veteran will be escorted to the Mental Health Walk-in Clinic. In the case of imminent risk and the veteran is present only by phone or videoconferencing, the local VA mental health crisis team will be contacted to intervene.

7.0 Privacy and Confidentiality

This study will obtain and keep confidential subjects' Protected Health Information (PHI).

The team will create a limited dataset that include all variables used in the publication. Some loss of information might occur given the need to remove most PHI. The PI will replace social security and medical station numbers with study-specific numbers. The team will drop date of birth and replace age with age categories for people 85 years of age and older. The DUA will clarify that users may not attempt to re-identify patients based on other VA data.

A Limited Dataset (LDS) will be created and shared pursuant to a Data Use Agreement (DUA) appropriately limiting use of the dataset and prohibiting the recipient from identifying or re-identifying (or taking steps to identify or re-identify) any individual whose data are included in the dataset.

All study personnel with access to PHI will be required to maintain current required trainings and follow protocol for maintaining records according to best practices (i.e. locked file cabinet, only study personnel access to drives or other e-locations of data). Study personnel's access to research study data will be removed when they are no longer part of the research team.

Several steps will be taken to minimize the risk of breaches of confidentiality. Throughout the study, IRB and HIPAA guidelines will be followed to ensure privacy of participant data. Every effort will be made to ensure that study data are confidential. Training of staff will include information about the importance of confidentiality and techniques to maintain confidentiality of all information reported by research participants. Although names and contact information will be kept during the trial so we can reach and schedule participants for follow-up, individual identifier information will be removed from study data files, as soon as possible, after database linkage. Unique study-specific identifiers will be assigned to support accurate linkage of data on the same individuals across multiple data files. The participant code will appear on data forms, including baseline and follow-up surveys, abstracted Annie dashboard data. The participatory

design interviews and patient perspective and provider/key informant interviews will be audio-recorded using a VA-approved digital recorder or VA-approved video conferencing software and transferred to the server for transcription and review. Participatory design interviews and patient perspective transcripts will only contain participant codes.

VA CDW data will be stored within the VA Informatics and Computing Infrastructure (VINCI), a secure analytical workspace with regulated data access for research, and access to data analysis software features and high-performance servers for data analysis. All VHA data files from CDW will be assembled within our project folder on VINCI, using approved secure methods. Once in VINCI, we will employ standard security protocols and data will not be moved outside the system (except for limited purposes such as printing mailing labels or tracking mailings to eligible trial participants) and will be accessed only by programmers and investigators who are IRB-approved to work on this study. Survey data (from mailed surveys) will be entered onto a secure VA server via VA REDCap and then merged in with the CDW data within our VINCI folder. For online surveys, participants will be provided with a unique code so that no identifying information is collected from the participant with their data. A random study identification number (ID) will be generated to identify patients who participate in the beta test or randomized trial data collection. The data manager will keep the crosswalk between the VHA identifier number and the study ID secure within VINCI so that the CDW data can be merged with data from other sources. Electronic audio files and any paper forms of data scanned into electronic form will be stored on a VA secure server with limited access. All paper records (e.g., signed consents) will be stored in locked file cabinets in locked offices, with access limited to those with appropriate training and IRB approval only.

All staff are trained in HIPAA compliance and will complete all required human subjects training. Research staff, with oversight by the PI, will be responsible for obtaining written consents. We also have established protocols for conducting calls to protect confidentiality including not leaving detailed messages containing health information on answering machines.

Special care will be taken to ensure confidentiality is maintained if the study participant is using a cell phone or smart phone of a cohabiting family member. On smart phones, Annie messages can be delivered via the Annie app instead of via text message (SMS). The participant could use the Annie app on the cohabiting family member's phone to ensure extra privacy by having the app password protected. For all participants using smart phone or cell phone, the text messages from the DD-TXT or DSE protocols will not be personal in nature. The DSE protocol will send education only messages, and the DD-TXT protocol will only ask for a patient's response with information such as blood pressure or diet.

8.0 Communication Plan

The coordinating site (Bedford) will be in charge of all CIRB communications and will assure submission of required documents. The project manager will meet regularly with all sites to ensure local notification and R&D approvals are obtained and remain current.

Dr. Shimada and the Site-PIs will ensure that all relevant IRB policies, procedures and stipulations (including informed consent procedures) are being followed. Drs. Shimada, Gordon, Uphold and Stroupe are responsible for ensuring that activities are approved by

the local R&D. Any changes to the protocol or HIPAA documentation will be discussed with participating sites and submissions/approvals will be communicated to each site as they are completed an obtained.

Refer to section 6.0 on Reporting for details on reporting unanticipated problems, serious adverse events, and protocol deviations.

Each participating site will be provided with a copy of the approved protocol and will receive updates as they occur.

Bedford PI will communicate with the LSI's regarding timing of site closures.

The PI and Site PIs will provide a summary of recruitment and any reports of adverse events or confidentiality breaches to the CIRB on an annual basis as part of the progress report. The report will include participants' socio-demographic characteristics, expected versus actual recruitment rates, any quality assurance or regulatory issues that occurred during the past year, summary of adverse events, and any actions or changes with respect to the protocol. We will also report how many times (if any) reports had to be made to the suicide hotline regarding abnormal or potentially concerning text message content.

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