Study Protocol & Statistical Analysis Plan

Improving Depression Management in Primary Care

NCT05050227

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1. Introduction/Background

VA's Primary Care–Mental Health Integration (PC-MHI) is rooted in evidence-based collaborative care models, where care managers, mental health specialists, and primary care providers jointly treat depression in primary care. While PC-MHI enabled specialists to support medication treatment in primary care, timely and sufficient access to psychotherapy is unattainable[1-3]. Alternative therapy modalities are needed.

Depression is disabling and affects one in five Veterans[4]. Psychotherapy is preferred by Veterans[5], but fraught with multilevel barriers (e.g., staff availability, patient travel to clinic, limited clinic hours)[6]. Without enhancing existing PC-MHI models to enable better primary care patient access to effective psychotherapies, Veteran engagement in depression treatment is unlikely to improve.

This intervention proposal aims to close the gap in psychotherapy access for VA primary care patients with depression by adapting PC-MHI collaborative care models to improve uptake of computerized cognitive behavioral therapy (cCBT). cCBT is accessible 24/7 via the internet and has effectively treated depression in more than 30 trials[7-9]. With modest specialist support, it is non-inferior to face-to-face psychotherapy[10,11]. PC-MHI can facilitate Veteran uptake of cCBT, using an evidence-based collaborative care model to provide the follow- up care management and mental health specialist back-up that characterizes the most effective cCBT trials.

2. Aims and Purpose

This protocol is for "Pilot RCT", a pilot randomized control trial to examine feasibility, acceptability, and potential effects of cCBT-enhanced collaborative care on Veterans' depression outcomes in one primary care clinic, in preparation for a larger hybrid effectiveness-implementation trial. Overall, 74 eligible primary care patients with clinically significant depression will be 1:1 randomized to (1) cCBT-enhanced collaborative care; or (2) only VA usual care (UC), which typically includes medication prescription. Since a substantial proportion (25-60%) of patients with depression treated with just placebo have significant reductions in symptoms, the control group offers a more robustly designed pilot study to prepare for a larger RCT.

Our primary hypothesis is that cCBT-enhanced collaborative care will be feasible and acceptable among Veterans in primary care. We also hypothesize that patients receiving cCBT-enhanced collaborative care may report moderate improvements in depression symptoms, compared to patients receiving UC at 3-months follow-up. Finally, we hypothesize that the cCBT-enhanced group will have improvements in behavioral/patient activation, health-related quality of life, and other mental health symptoms, compared to UC patients.

3. Activities Overview

Study participants will be randomized to either Usual Care (UC), typically medication, under their own PCP or the Intervention. Those in the intervention arm will receive cCBT-enhanced collaborative care supported by a depression care manager. The depression care manager (a licensed social worker) will facilitate access to cCBT, promote and monitor cCBT use, reinforce CBT concepts (during outside CBT session "homework"), and monitor mental health symptoms for each participant. Participants will be contacted weekly via 15-30-minute phone calls or by other means (e.g., email, Vets Prevail platform). Additionally, a Primary Care and a Psychiatry Consultant will meet weekly with the depression care manager in order to oversee study patient progress and the cCBT-enhanced collaborative care model broadly.

Computer-based CBT (cCBT) will be provided via the VA-sponsered Vet's Prevail[SM] program. This program is free for all Veterans, provides self-paced CBT lessons tailored to patients based on sociodemographics, and engage

users with modest financial incentives (e.g., gift cards). It also features a community message board, a peer support specialist chat support, and safety monitoring that includes warm-handoffs to the VA Crisis Chat Line.

4. Study Design

This is a 2-year pilot randomized control trial to assess the feasibility, acceptability, and potential effects of a cCBT-enhanced collaborative care model on depression symptoms and related outcomes.

Eligible and consenting patient subjects will be randomly assigned to one of two treatment conditions: 1) cCBT-enhanced collaborative care (n=37), or 2) usual care (n=37). Randomization to condition will be stratified by gender, to account for differences in care delivery structure and for in treatment outcomes.

4.1. Data collection methods

A study team member will perform baseline (0-month) assessments immediately following informed consent during a 45-60-minute telephone (or in-person interview should it be necessary). A research assistant (RA) will perform the post-intervention (3-month) assessments during another 45-60-minute telephone interview. Post-intervention assessments will only differ between intervention and control arms by inclusion of feasibility and acceptability questions (e.g., CSQ-8) for intervention participants only. As in prior studies, the GLA Veteran Engagement Team members provided feedback on assessment content and timing. See Table 1, for a list of measures.

Measure	**Pre- (# of items)**	**Post- (# of items)**
PROMIS Global Health	10	10
Patient Activation Measure (PAM-13)	13	13
Behavioral Activation for Depression Scale (BADS-SF)	9	9
Patient Health Questionnaire (PHQ-9)	9	9
General Anxiety Disorder (GAD-7)	7	7
PTSD Checklist for DSM-5 (PCL-5)	20	20
Alcohol Use Disorders Identification Test (AUDIT-C)	3	
Screening Test for Drug Use	2	
Medication use	3/CR	3/CR
Health Services Use	11	11
Chronic conditions	CR	
Demographics (age, gender, race/ethnicity, marital status, education level, employment status, homelessness)	5 (+2 CR)	
MEASURES FOR INTERVENTION ARM ONLY		
Client Satisfaction Questionnaire (CSQ-8)		8
System Usability Scales (SUS)		10
Open-ended questions (liked, disliked, suggestions for improvement)		3
	92	103
Table 1: Data Collection Measures. CR=chart review		

4.2. Sample description, development and rationale

74 (37 male, 37 female) Veterans will be recruited from the Greater Los Angeles Healthcare System, using a mix of purposive and convenience sampling. Purposive sampling will entail using electronic medical records (e.g.,

services utilization, depression diagnostic codes and/or screening data from CDW or other database) for targeted mailing of recruitment letter and flyer. Convenience sampling will entail posting flyers on physical buildings and social media, accepting referrals from providers.

Sample Sizes and Power Analyses: The trial will have the power to detect an effect size (ES) of 0.78 or greater ITT on the PHQ-9 of cCBT-enhanced collaborative care versus UC patients at 3-month follow-up. Data are based on Richards et al's 2012 study,[10] which reported a d=0.78 ES for therapist-guided cCBT trials for improving depression outcomes. This is consistent with literature showing that therapist support yields greater effects for cCBT.[10] Assuming an 80% 3-month assessment completion rate (consistent with prior relevant studies)[12-14] and 2-tailed type I error of 0.05, if we then enroll 37 subjects to the intervention arm and 37 to the control arm (74 total) we will have 80% power to detect at least a 0.78 ES improvement of cCBT-enhanced collaborative care over usual care on the PHQ-9 (primary hypothesis). The pilot is not powered to detect changes in HRQoL or differences by gender.

4.3. Participant interactions and interventions

Participants in cCBT-enhanced collaborative care arm (i.e. intervention arm) will be enrolled in VA-sponsored computerized cognitive behavioral therapy (cCBT) program, Vets Prevail[SM]. This cCBT program delivers 5 sessions of CBT online via desktop or mobile app, features a community message board, and provides peer support specialist chat support and safety monitoring (e.g., warm handoffs to the Crisis Chat Line). A licensed social worker with a master's degree and knowledge/experience delivering CBT will serve as a care manager. The study care manager will facilitate access to cCBT, promote and monitor cCBT use, reinforce CBT concepts (during outside CBT session "homework"), and monitor mental health symptoms for each participant. She will contact them weekly via 15-30 minute phone calls or other means (e.g., email, Vets Prevail platform) for 3 hours total. The goal is to encourage patients to complete the online CBT modules over a total of 3 months. As such, the caseload is approximately 6 Veterans per 8 weeks, totaling 37 intervention arm participants over 12 months. A psychiatrist consultant and Primary Care consultant will meet weekly with the study care manager to oversee study patient progress and the cCBT-enhanced collaborative care model broadly. Brief electronic health record (EHR) template notes will be completed at study enrollment and conclusion and additional notes as needed, if patient safety monitoring protocols are activated

Patients in the control condition will receive care that is consistent with recommended VA practice – usually PCP-prescribed antidepressant medications and/or referral to see a mental health specialist (who usually offers a brief assessment and a few short visits). The VA also has a wide suite of veteran-centric digital mental health tools for depression, posttraumatic stress, insomnia, etc., which are publicly available and free.

Participants will be assessed in both conditions at baseline and 3 months (post-intervention) via 45-60 minute telephone interviews. The baseline assessment will measure depression and other mental health symptoms; health-related quality of life; patient activation; demographics; physical and mental health comorbidities; substance use history; and treatment utilization. The 3-month assessment will re-measure depression and other mental health symptomatology; health-related quality of life; patient activation, plus assess intervention group participants' satisfaction with treatment; cCBT program usage; and interactions with care management. Intervention entails the cCBT-enhanced collaborative care, using VA-sponsored Vets Prevail.

Compensation: Participants will be compensated with $30 VCS vouchers for completing the baseline assessment and a $45 VCS voucher for completing the 3-month assessment ($75 total). Vouchers will be distributed at the time assessments are completed.

5. Recruitment and Consent

5.1. Recruitment Methods

Veterans will be recruited from VA Greater Los Angeles (GLA) Healthcare System primary care clinics (e.g., Primary & Ambulatory Care Clinic, Women's health Clinic), except for individuals empaneled to the study PI to avoid the possibility of coercion. Patients with clinically significant depression (as detected on mandated annual screening or other means) will be referred by their primary care or mental health teams. Additionally, local case finding activities will be conducted for targeted mailing of recruitment letters and flyers.

Direct Referrals: The study team will advertise the study through clinical staff meetings and emails to providers. The study team will be available online (via MS Teams, email, telephone).

Mailers: The study team will identify Veterans based on screening data (e.g., Patient Health Questionnaire – 2), diagnostic codes, encounter data, antidepressant medications, and suicide flags from the Corporate Data Warehouse and other VA databases.

A recruitment letter and study flyer will be mailed (via USPS) to the potential participant from their provider, clinic, or program representative (e.g., primary care providers), only if the provider agrees to the study team reaching out to the Veteran on their behalf. Mailings will describe the purpose of the study and request that the potential participant initiate contact with the study team (via phone or email) to indicate his/her agreement to participate. If no response is made within a 2-week period, the potential participant may then be contacted by phone. We will not conduct any "cold calls", that is use prior knowledge of private information to initiate contact with the potential participant, who would otherwise not know the study team.

Flyers and Social Media: The research team will advertise the study directly to Veterans via flyers developed for both male and female Veterans. The flyers contain the study phone number and email contact information and provide the Project Coordinator's contact information to answer any questions. As in prior studies, the GLA Veteran Engagement Team was consulted regarding design and content of recruitment flyers. Local primary care and mental health clinic teams will be consulted regarding flyer placement and distribution. In addition to physical posting of recruitment flyers, the study team will contact VA media for assistance with electronic distribution of the flyer (e.g., display on campus TVs or on social media).

5.2. Informed Consent Procedures

All study procedures for this component will be conducted via telephone and the internet. For this reason, we will request a HIPAA waiver and a Waiver of Documentation of Informed Consent from the IRB.

We will obtain verbal consent and study team members will be trained to recognize signs of cognitive and hearing impairment. Veterans who self-report that they are unable to hear the project coordinator will be asked to paraphrase the first sentence of the study procedures. Veterans who cannot accomplish this task will be excluded from participation. Veterans who do not initially self-identify as hearing impaired will also be excluded from participation if they indicate not being able to hear or understand the consent items after they are repeated 3 times.

The study PI will ensure that all study team members are up to date with VA trainings on human subjects protection, government ethics, privacy and HIPPA, and information security, as well as project-specific training.

5.3. Inclusion/Exclusion Criteria

Inclusion:

- Have access to computer (mobile or desktop), internet, telephone, and email

- Able to read English text on a computer screen
- Score 10 or higher on the PHQ-9

Exclusion:

- Have moderate-high suicide risk (e.g., suicide flag) or active suicidality
- Have other serious mental illness (e.g. bipolar disorder, psychosis) or medical disorder that would prevent/interfere with participation (e.g. dementia/cognitive impairment, terminal illness).

6. Data Sources and variables

Study team members will perform baseline (0-month) and 3-month (post-intervention) assessments. Deidentified data (containing study participant ID) will be entered into VA REDCap or a comparable database which supports trial data and will then be exported securely for analyses after study conclusion. See Table 3 for a list of primary and secondary outcomes and covariates.

	Constructs	Measures	Data Source
Primary Outcomes	**Acceptability**	Client Satisfaction Questionnaire (CSQ-8),	Patient
		Open-ended questions (likes, disliked, suggestions for improvement)	Patient
	Feasibility	Number, proportion, and representativeness of participants	Study Data
	Recruitment	Reasons for declined participation and/or study termination	Study Data
		Number, proportion, and representativeness of referring providers	Study Data
	Intervention	Number, duration, and type of care manager contacts	Vets Prevail
		cCBT usage activity (registration, enrollment, completion, messaging)	Vets Prevail
	Depression	Patient Health Questionnaire (PHQ-9)	Patient
Secondary	**Quality of life**	Promis-10 Global Health	Patient
	Activation	Behavioral Activation for Depression Scale (BADS-SF)	Patient
		Patient Activation Measure (PAM-13)	Patient
	Anxiety	Generalized Anxiety Disorder (GAD-7)	Patient
	PTSD	PTSD Checklist for DSM-5 (PCL-5)	Patient
Covariates	**Demographics**	Age, gender, race/ethnicity, marital status, education level, employment status, and housing status	Patient
	Other patient information	Distance from home to clinic, combat status, service connection, medical & psychiatric diagnosis, empaneled PCP	Chart Review
	Alcohol use	Alcohol Use Disorders Identification Test (AUDIT-C)	Patient
	Substance use	Single Item Drug Screen	Patient
		Single Item Cannabis Use	Patient
	Antidepressant use	Per medication list (6 months before & after intervention)	Chart review
	Health services use	Mental health, PC0MHI, primary care, etc. (6 months before)	Patient

Legend: Implementation outcomes shaded in gray

Table 3: Data Sources.

7. Data Analysis

An electronic database for data entry and management (using VA REDCap or other comparable software) will be built. We will perform all data analyses using STATA15 other available statistical package. A statistician will be available for consultation in statistical design and analyses but will not have access to identifiable patient data. The full analysis set will be based on an intention-to-treat (ITT) analysis, which will comprise all participants who have been randomized to either study arm, regardless of length of follow-up or actual intervention received. As

a preventive measure, every attempt will be made to document all reasons for missing data and will compare the rates of lost-to-follow-up between study arms. In addition, baseline characteristics will be compared between participants who do and do not withdraw from the study, to assess the impact of missing information and attrition.

Demographic and baseline characteristics (e.g., demographics, combat status, alcohol and substance use disorders, medication use, health services use) will be presented as mean and standard deviations for continuous variables and sample proportions for categorical variables. All descriptive statistics will be accompanied by 95% confidence intervals. Baseline comparisons between study arms (for each hypothesis) will be performed using t-tests for continuous variables, chi-squared tests for categorical variables, or their nonparametric counterparts. Diagnostics (i.e., conditional studentized residuals, plots of outcomes over time) will be performed on each linear mixed model to assess whether necessary assumptions were met.

To assess feasibility, the number of participants approached each month, the proportion who enroll, the rate and timing of dropouts, the proportion of referring providers, and the number of study care manager contacts will be calculated. Additionally, Vets Prevail program usage data, including the proportion of participants in the intervention arm who become registered users, enroll in the cCBT program, and complete the entire cCBT program will be calculated; Vets Prevail data will be further aggregated to understand average/median duration of and number of completed cCBT sessions, community message board posts, and peer chats.

To quantify acceptability, summary statistics (e.g., median/mean) for CSQ-I items scores will be computed. Under an health anthropologist's guidance, responses to the open-ended survey questions will be categorized as positive, neutral, negative, or ambivalent. Responses will be independently coded by multiple people, resolving disagreements through discussion and examining positive and negative factors.[15]

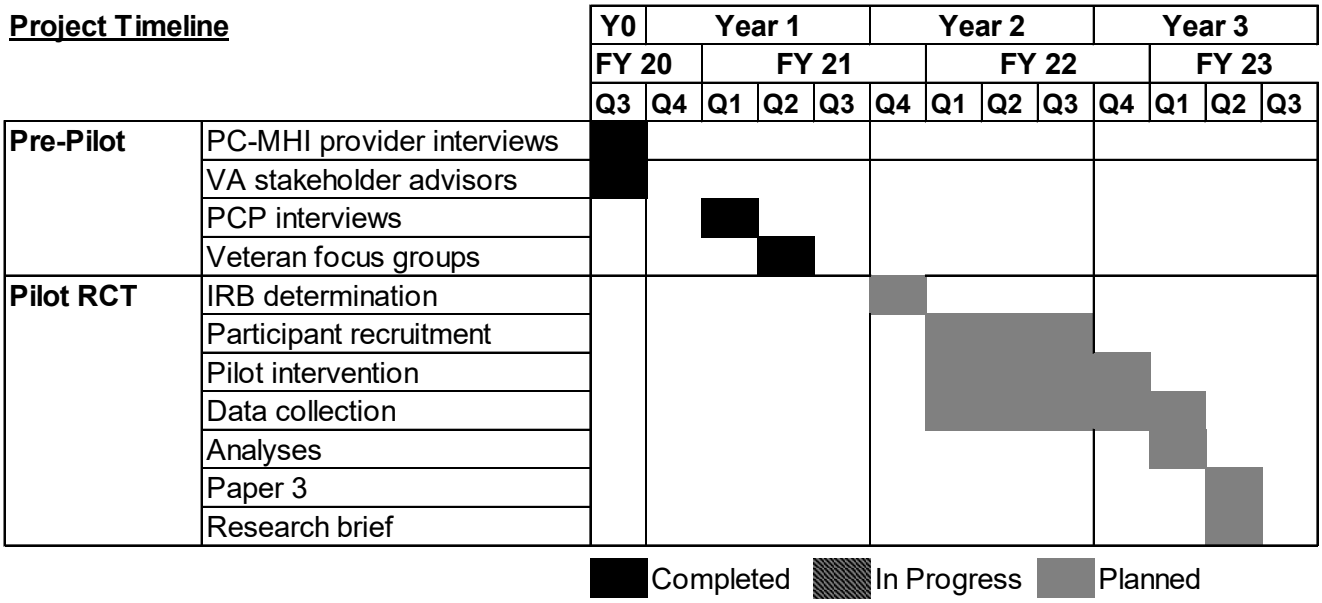
To assess feasibility, acceptability, and other depression related outcome measures, generalized linear mixed model (GLMM) will be used, which provides a unified framework for the analysis of outcome trajectories over time by allowing for the modeling of repeated measures for each participant. GLMM is robust to imbalanced designs and provides unbiased estimates even when data are missing at random. GLMM will be fit as a function of study arm, time, time-by-study arm, and gender. In addition, the intercept will be allowed to vary randomly to account for subject-level variability of the outcome at baseline. [standard errors will be adjusted to account for provider/clinic clustering.] Analyses will first be conducted on complete data only and will estimate the adjusted mean difference in 3-month improvement on PHQ-9 (depression symptoms), GAD-7 & PCL-5 (other mental health symptoms), PROMIS (HRQoL), and BADS-SF/PAM-13 (behavioral/patient activation) between cCBT-enhanced collaborative care and control arms. As an exploratory measure, we will conduct additional analyses on study outcomes using predefined numbers of completed cCBT sessions (e.g., >2 sessions, all 5 sessions).

Sample Sizes and Power Analyses: The primary purpose of this pilot is to assess feasibility of trial methods, including recruitment, intervention, and follow-up. Nevertheless, given the sample sizes we plan to enroll, the trial will have the power to detect an effect size (ES) of 0.78 or greater ITT on the PHQ-9 of cCBT-enhanced collaborative care versus UC patients at 3-month follow-up. Data are based on Richards et al's 2014 study,[10] which reported a d=0.78 ES for therapist-guided cCBT trials for improving depression outcomes, which is slightly higher than the reported ES (d=.56) for the Vets Prevail RCT. This is consistent with literature showing that therapist support yields greater effects for cCBT.[10] Assuming an 80% 3-month assessment completion rate (consistent with prior relevant studies)[12-14]and 2-tailed type I error of 0.05, if 37 subjects are enrolled to the intervention arm and 37 to the control arm (74 total) 80% power to detect at least a 0.78 ES improvement of cCBT-enhanced collaborative care over usual care on the PHQ-9 (primary hypothesis) will be achieved. The pilot

is not powered to detect changes in HRQoL. We lack pre-existing data to estimate effects on behavioral/patient activation. It is underpowered to detect differences by gender. Other analyses, e.g., access, is exploratory.

8. Timeline

Project Timeline



9. Relevant publications

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