

**Project Title:** Reducing Anxiety and Stress in Primary Care Patients: Pilot RCT of a Brief Intervention

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## **Study Protocol with Statistical Analysis Plan**

### **BACKGROUND**

Anxiety disorders and symptoms are common among Veteran primary care patients.<sup>1-3</sup> Anxiety has a significant impact on the lives of Veteran primary care patients,<sup>1-3</sup> including functional impairment,<sup>4-5</sup> decreased quality of life,<sup>6</sup> increased risk for suicidal ideation and attempts,<sup>7</sup> and increased health care utilization.<sup>1,8</sup> The impact of anxiety within the primary care setting is even greater given the high degree of comorbidity with depression.<sup>9</sup> Approximately 55% of primary care patients with anxiety disorders have current major depressive disorder,<sup>4,5</sup> and 52% reported depressive symptoms of at least moderate severity, among a sample of treatment seeking primary care Veterans with significant anxiety symptoms.

Anxiety is under-treated in primary care.<sup>10-12</sup> As few as 15% of VHA patients complete  $\geq 1$  session of behavioral treatment in the 12 months following a new anxiety diagnosis.<sup>13</sup> Reasons for under-treatment of anxiety in primary care are varied. PACT providers may be pressed for time, struggle with identification and treatment of complex subthreshold symptoms and comorbid presentations, and face competing demands for clinical attention that prohibit the use of full-length anxiety-treatment protocols.<sup>14</sup> Although a large percentage of patients prefer psychological treatments over pharmacotherapy,<sup>15-16</sup> pharmacological treatments are the most common intervention offered in primary care.

VHA developed the PC-MHI initiative to improve the identification and treatment of mental health problems in the primary care setting.<sup>18-19</sup> Most patients with anxiety who seek treatment do so in primary care.<sup>20,21</sup> VHA PC-MHI providers are most often psychologists or social workers,<sup>22</sup> who have expertise in psychological treatments. Offering anxiety treatment within PC-MHI improves the patient-centeredness of care by meeting patients where they are at (i.e., in primary care) and accommodating patient preference for psychological treatment over pharmacotherapy.<sup>15,16</sup> Facilitating patient-centered care for Veterans is one of the primary long-term goals of PACT<sup>23</sup> and VHA as a whole.<sup>24</sup> PC-MHI providers can fill a critical need within PACT by providing Veterans with patient-centered anxiety treatment.

Established treatments for anxiety disorders have garnered empirical support for delivery in specialty mental health settings.<sup>25</sup> However, these treatments are not readily translated to PC-MHI. Existing protocols were developed for a higher frequency and longer duration of treatment (e.g., 12-15 weekly 50-minute sessions) than that used in PC-MHI (e.g., 1-6 biweekly to monthly 30-minute sessions).<sup>26,27</sup> Most existing treatments are disorder-specific (e.g., CBT for panic disorder<sup>28</sup>). However, choosing treatments based on specific anxiety disorders is not practical in PC-MHI given that primary care patients often exhibit subthreshold anxiety symptoms, meet diagnostic criteria for multiple anxiety disorders<sup>29</sup>, or are given a diagnosis of anxiety not otherwise specified.<sup>13</sup> Furthermore, PC-MHI providers do not conduct comprehensive diagnostic assessments. In addition, 55% of primary care patients with an anxiety disorder also report current major depressive disorder.<sup>4,5</sup> In sum, a critical need remains for brief, evidence-based interventions that are feasible within the PC-MHI format and applicable across the spectrum of anxiety presentations, including comorbid depressive symptoms.<sup>17,30,78</sup>

To address this gap in care, my program of research has comprised several studies building toward the current study: identifying Veteran primary care patients' anxiety treatment preferences, examining usual care for anxiety in PC-MHI, examining perceived feasibility of various anxiety intervention techniques among PC-MHI providers, and adapting and refining the treatment manual for the brief PC-MHI intervention for anxiety. We developed the manual by adapting evidence-based techniques from extant anxiety treatment protocols to fit the unique scope and format of the PC-MHI setting. We also incorporated our prior findings on primary care Veterans' anxiety treatment preferences to ensure the intervention is Veteran-centered.<sup>76</sup> In the most recent study, we obtained preliminary feedback on the treatment manual from Veterans who received the intervention as well as PC-MHI providers who were asked to consider feasibility for real-world clinical practice. We used this stakeholder feedback to refine the treatment manual. Now we are ready to evaluate the intervention in a formal trial. Therefore, in the current study we will evaluate the effectiveness of the intervention (compared to PC-MHI usual care) in reducing symptoms of anxiety and depression. Secondary outcomes include functional impairment and quality of life as well as several potential mediating variables. We will include healthcare utilization (mental health, primary care, emergency department visits) as an exploratory outcome because individuals with anxiety disorders are known to have higher healthcare utilization,<sup>83</sup> which is costly to the

healthcare system.

### **Specific Aims**

The current study is a pilot hybrid effectiveness-implementation RCT. The primary aim is to evaluate feasibility, acceptability, and effectiveness of the brief anxiety intervention compared to PC-MHI usual care. As this is a pilot study, the emphasis is on evaluating feasibility and acceptability<sup>77</sup>, although we will also examine preliminary effectiveness by comparing the effects of the intervention to those of PC-MHI usual care on the primary outcome of anxiety symptom severity. The secondary aim is to identify potential barriers and facilitators to implementation in real-world clinical practice.

## **METHOD**

### **Study design**

We will evaluate the intervention through a RCT using a hybrid I effectiveness-implementation design<sup>79</sup> with PC-MHI usual care as the comparison condition. We elected to conduct an effectiveness trial (with less restrictive eligibility criteria), rather than an efficacy trial, because we are not creating a brand-new treatment, but rather adapting existing evidence-based techniques into a new intervention package in a format suitable for PC-MHI. We selected PC-MHI usual care as the comparison condition given our interest in determining whether the intervention is superior to current routine PC-MHI practices. The hybrid I design is appropriate<sup>79</sup> because the brief anxiety intervention has strong face validity and a base of indirect evidence (from brief CBT for anxiety used in specialty mental health and PC-MHI), although it still needs to be evaluated for effectiveness in its current format. Further, addressing implementation earlier in the process will help to reduce the lag in translating research to practice, which is highly valued in VHA.

### **Participants**

Participants will be adult Veteran primary care patients ( $N=35$ ) at the Syracuse VA Medical Center. Eligibility criteria are as follows:

#### Inclusion criteria:

- (1) age 18 years or older
- (2) Veteran seen in the Syracuse VAMC primary care clinic in the past year
- (3) screen positive for current (past 2 weeks) clinically significant anxiety symptoms ( $\geq 8$  on GAD-7)

#### Exclusion criteria:

- (1) inability to communicate in English (as assessed by study staff)
- (2) report or demonstrate hearing impairment that would preclude telephone screening (as assessed by study staff)
- (3) (a) inability to demonstrate informed consent (defined as not being able to comprehend the study description as assessed by study staff and/or not being able to answer the comprehension of consent questions),  
OR (b) have a diagnosis of dementia or severe cognitive impairment (defined by primary care provider or self-report, or having a diagnosis in Problem List),  
OR (c) screen positive for cognitive impairment ( $\geq 3$  errors on screener)
- (4) (a) have a diagnosis of obsessive-compulsive disorder (OCD), or serious mental illness (SMI, i.e., psychotic disorders, bipolar disorder) in Problem List,  
OR (b) have an encounter diagnosis of post-traumatic stress disorder (PTSD) within the past 2 years OR screen positive for PTSD ( $\geq 3$  on PC-PTSD-5)
- (5) currently in psychotherapy/counseling for anxiety and/or depression (defined as any of the following within the past 30 days: (a) attending  $\geq 1$  specialty mental health sessions [excluding intake sessions], (b) attending  $\geq 2$  PC-MHI sessions, or (c) being hospitalized for mental health treatment)
- (6) report severe depressive symptoms ( $\geq 20$  on PHQ-9)
- (7) at imminent risk of suicide (defined as being identified as imminent risk based on study staff's suicide risk assessment [verified by the PI] and in need of intensive treatment [e.g., hospitalization] to ensure safety)
- (8) started or had dosage change in psychotropic medication for anxiety or depression in the past 30 days

**Rationale for exclusions:** We will exclude Veterans with SMI and/or cognitive impairment given that their mental health and/or other treatment needs are likely to be greater than those of Veterans without such

conditions, and our focus is on the wider population of primary care patients. We will exclude those with PTSD and OCD because (a) our focus is anxiety disorders likely to respond to brief treatment, (b) these disorders are no longer considered anxiety disorders in DSM-5,<sup>31</sup> (c) they typically require a higher treatment dosage, and (d) the intervention will not cover trauma- or OCD-specific education. We will exclude those who were hospitalized for mental health reasons in the last 30 days or are currently in psychotherapy/counseling for anxiety and/or depression to eliminate confounding treatments. We will not exclude patients on the basis of receiving medication management from psychiatric prescribers. We will exclude those with severe depressive symptoms due to the focus of this intervention being primarily on anxiety, but we will not exclude those with mild, moderate, or moderately severe symptoms (based on PHQ-9) given that the intervention will have at least one module on depression and will attend to mood throughout. We will exclude those at imminent risk of suicide for safety reasons, but we will not exclude patients based on mild to moderate risk (ongoing risk assessment and safety plans will be used as needed). We will allow patients to be on medication for anxiety and/or depression, provided it was started or the dosage was stabilized at least 30 days prior.<sup>32</sup> We will ask those excluded for this reason if they would like to be contacted to be re-screened for eligibility once the dosage has been stable for 30 days.

### **Recruitment**

Recruitment will occur using four methods that we have used in previous work: (1) direct referrals from primary care or PC-MHI providers when patients report bothersome anxiety symptoms, (2) flyers in primary care clinic waiting rooms that briefly describe the study and invite interested Veterans with anxiety symptoms to contact us for more information, (3) referrals from other ongoing local behavioral health research studies, and (4) case-finding followed by letters (sent with primary care provider approval) describing the study sent to patients with anxiety diagnoses in their (a) Problem List or (b) primary care encounter diagnosis who were seen in the last month alerting them that research staff may call them in 7-14 days to explain the study (letters will include a telephone number to call to opt out of any future contact if the Veteran prefers not to be called). We expect the latter method to identify the most participants. We will also use case finding for patients referred from primary care to the outpatient mental health clinic for anxiety. There are several other local behavioral health research studies, and patients who are ineligible for other studies may be interested in a referral to this study if it seems appropriate. For the case finding recruitment method, potential participants will be identified via data pull from CPRS. Thus, we are seeking a waiver of HIPAA authorization for recruitment. We will pull data for all living Veterans who meet inclusion criteria 1 and 2 and have an anxiety diagnosis in (a) their Problem List or (b) recent primary care encounter, but do not meet exclusion criteria 3, 4, 5, or 8.

In addition to VISN2 data pull or study staff chart review of the VA electronic medical record, recruitment lists may be obtained through the VA Informatics and Computing Infrastructure (VINCI). Recruitment lists are generated through VINCI with an IRB-approved data request to the VA Corporate Data Warehouse, where data are prepared and placed into a secure database for use only by approved members of the study team.

### **Procedure**

*Overview:* Following an initial telephone screening, eligible Veterans who provide written informed consent to participate will complete a baseline assessment. They will be randomized to either the intervention condition or the control condition (PC-MHI usual care). Participants will then complete a brief telephone assessment every 4 weeks and a post-assessment at 16 weeks.

*Eligibility screening:* Research staff will call Veterans identified via any recruitment method to explain the study and screen for eligibility. Eligibility screening will be conducted over the telephone to reduce participant burden. (If Veterans specifically request in-person eligibility screening, we will accommodate their preference). We are requesting a waiver of documentation of written consent for the eligibility screening only. We will describe the study and obtain verbal consent to participate in the eligibility screening, which includes comprehension of consent questions to ensure Veterans understand the screening purpose and procedure. (Prior to the baseline assessment, we will obtain written informed consent for participation in the remainder of the study). The eligibility screening will take approximately 15 minutes. To reduce participant burden, screening will be discontinued once any of the exclusion criteria are met. RAs will exclude those who demonstrate inability to communicate in English, hearing impairment that would preclude telephone screening, or cognitive impairment that would preclude providing informed consent as appropriate during the eligibility screening process. The eligibility screening begins with basic demographic questions (age, gender, race, and ethnicity). RAs will then

administer a brief screener for cognitive impairment.<sup>57</sup> Veterans who make  $\geq 3$  errors on the screener are ineligible. RAs will screen Veterans for current anxiety symptoms using the GAD-7<sup>44</sup> self-report questionnaire, a validated measure that is widely used in VHA PC-MHI and is a good screening tool for Generalized Anxiety Disorder, Panic Disorder, and Social Anxiety Disorder.<sup>33</sup> RAs will next administer the PHQ-9<sup>46</sup> to assess current depressive symptoms. Veterans who are ineligible due to scoring  $\geq 20$  (severe) on the PHQ-9 will be asked if they want a referral to PC-MHI or specialty mental health for depression treatment. For any Veteran who reports suicidal ideation on PHQ-9 item 9, RAs will follow the detailed suicide risk assessment protocol as appropriate to evaluate and ensure safety (assessments will be reviewed with the PI for clinical supervision). RAs will next administer the PC-PTSD-5<sup>58</sup>; Veterans who score  $\geq 3$  on PC-PTSD-5 are ineligible and will be asked if they want a referral to PC-MHI for further assessment/treatment. RAs will then assess for receipt of psychotherapy/counseling for anxiety and/or depression in the last 30 days and mental health hospitalization in the past 30 days. RAs will then assess starting, or having a dosage change in, psychotropic medications for anxiety or depression in the last 30 days. Veterans who have started a new medication for anxiety or depression, or had a dosage change in the past 30 days will be ineligible; however, we will offer to rescreen them once the dosage has been stable for 30 days if they would like to be reconsidered.

If the Veteran is ineligible to participate in this study but may be eligible for other local behavioral health research studies (e.g., Veteran screens ineligible for this study due to PTSD symptoms and thus may be eligible for current PTSD studies), we will ask them if they are interested in hearing about other studies going on at the local VA. If they are interested in more information, we will help connect the Veteran participant with the research team.

Veterans who are interested and eligible based on the eligibility screening will be scheduled for a baseline assessment. At this time, RAs will further describe the study and obtain written informed consent to participate, along with a HIPAA Authorization. Participants will then complete the baseline assessment, consisting of a demographic questionnaire and self-report measures of anxiety, depression, and other relevant mental health constructs (see Measures section below and Table 1 for summary of measures), a medication and mental health treatment history interview. The RA assessor will be blinded to condition. This appointment will require approximately 75-90 minutes, and participants will be compensated \$40 for their time. Participants will be paid via either direct deposit (electronic fund transfer) or a Direct Express® prepaid debit card. At the baseline session, participants will be given an information sheet with relevant phone numbers for VA behavioral health services as well as crisis resources including the Veterans Crisis Line; this is simply for future reference for them. Given occasional difficulties contacting participants, if we are unable to reach someone by telephone, we will send a letter requesting a return call if still interested in learning about or continuing with the study.

For all participants, treatment initiation and completion (or dropout/withdrawal notes as applicable) notes will be entered into CPRS as required. For participants in the intervention condition, progress notes will be entered into CPRS for treatment sessions.

Modifications to the baseline process during the COVID-19 outbreak:

To address public health concerns during the outbreak of covid-19, the baseline assessment will be modified to prioritize the health and safety of Veteran patients. The modifications will include the completion of the baseline assessment using one of VA's current telehealth modalities (telephone or VA Video Connect). If using VA Video Connect, research staff will work with interested and eligible Veterans to establish the VA Video Connect option in preparation for the telehealth appointment. At any VA Video Connect appointments, study staff will follow standard VA Video Connect procedures to create a confidential medical virtual room. At the beginning of the appointment, we will verify the participant's current location and phone number to ensure if any disruptions occur, we can re-contact the Veteran and provide assistance.

Before the scheduled baseline assessment, a research assistant will mail two copies each of the Informed Consent Form and the HIPAA Authorization form to the participant before the scheduled assessment, along with a postage-paid, pre-addressed envelope so they can send the signed informed consent and HIPAA authorization forms back to study research staff at the Syracuse VAMC. The packet will also include copies of the response options for the questionnaires as well as an information sheet with relevant phone numbers for VA behavioral health services and crisis resources including the Veterans Crisis Line. The participant will be able to reference these materials during the informed consent process and will be asked to sign both forms during the telehealth appointment prior to completing any baseline questionnaires. Participants will be asked to

send back the signed informed consent and HIPAA authorization within the self-addressed envelope. No intervention sessions or follow-up assessments will occur until this documentation is received. All consent and authorization forms will be stored in the same locked file cabinets in the same offices as usual/ previously approved. All other assessments will occur via telephone, which is already an option in our standard protocol.

*Randomization:* Participants will be randomized to the intervention or usual care using a stratified random assignment based on anxiety severity (GAD-7 score of <15 vs ≥15 [≥15 indicates severe symptoms]<sup>44</sup>) as well as depression severity (PHQ-9 score of <15 vs 15-19 [15-19 indicates moderately severe symptoms]<sup>46</sup>). Patients with comorbid anxiety and depression symptoms are more functionally impaired than patients with either anxiety or depression alone, so it is important to balance out the proportion of patients with worse depressive symptoms across the two conditions.

*Usual care condition:* Usual care will involve the Veteran receiving an appointment with a PC-MHI provider at his/her primary care clinic. At this encounter, providers can choose to deliver whatever interventions they deem appropriate. In addition, providers and Veterans can collaboratively decide whether and when they would like to meet again during the 16-week period of the active portion of the study. These sessions will be audiotaped so we can determine what intervention techniques were used in usual care treatment. Independent raters (RAs with mental health background and intervention training), will review at least a subset of the usual care session recordings and complete a treatment session recording form to identify the interventions used and the overall quality of delivery. If the audio recorder should fail during the session, the usual care provider will be asked to complete the Content (interventions) portion of the recording form as a self-report measure as soon as possible after the session to try to capture the information, whereas the Delivery portion of the form would be omitted.

*Intervention condition:* The intervention will be conducted in up to six 30-minute in-person sessions. The first session will occur within two weeks of randomization to minimize potential for changes in health status. Sessions will ideally occur approximately biweekly, but to allow flexibility for Veteran scheduling preferences, may be scheduled anywhere from weekly to monthly. Because the intervention will be modular and Veteran-centered, it will be flexible in terms of number of sessions, and this will be determined by the patient and therapist, as in real-world PC-MHI clinical practice. (For the purposes of the research study timeline, if all six sessions are indicated, they will occur as close to biweekly as possible). Participants will be seen in primary care exam rooms to be consistent with routine PC-MHI practice. Requests for telephone sessions will be accommodated (if possible based on module content) after the initial session. During the covid-19 outbreak, telehealth modalities including telephone and VA Video Connect will be used for both initial and follow-up sessions per VA clinical guidance to minimize in-person appointments to reduce unnecessary exposure and risk. At the beginning of each session, participants will complete self-report measures of anxiety and depression for as part of measurement-based care.<sup>80</sup> Participants who endorse >0 on the PHQ-9 item 9 about morbid/suicidal ideation item will be assessed further according to our suicide risk assessment protocol. Therapists will keep track of which modules were completed and in what order on the post-session checklist.

*Therapists:* Usual care providers will be local PC-MHI providers. The intervention will be delivered by study therapists to reduce the risk of contamination of usual care with the intervention. Study therapists will be advanced doctoral students, predoctoral interns, or postdoctoral fellows in psychology or related mental health fields who have clinical experience in the PC-MHI setting. Study therapists will be trained by the PI on the intervention, including an initial training workshop followed by ongoing weekly/biweekly clinical supervision. All intervention sessions will be audio-taped for supervision and training purposes as well as fidelity assessment. Independent raters (RAs with mental health background and intervention training), will review the tapes and complete a treatment fidelity checklist. (If the audio recorder should fail during an intervention session, the study therapist will complete the Fidelity portion of the checklist as a self-report measure as soon as possible after the session to try to capture the information, whereas the Delivery portion of the checklist would be omitted.) Therapists will receive regular feedback to ensure adherence to essential protocol elements as well as competent delivery (e.g., empathy, collaborative spirit).

*Follow-up assessments:* Participants will complete brief follow-up assessments via telephone approximately every 4 weeks between the baseline and post-assessment. An RA who is blinded to condition (and is not the interventionist) will administer 3 self-report measures at 4 weeks, 8 weeks, and 12 weeks. Telephone

administration was chosen to improve feasibility and reduce burden on participants. (If a Veteran prefers to complete these assessments in-person, for example if they are coming in to the VA anyway for another appointment, we will accommodate their preference.) These assessments will be brief with only 3 measures (total of 31 items) and will allow us to capture symptoms of anxiety, stress, and depression as well as functional impairment regularly throughout the study period so we can examine how quickly changes occur with treatment. We are interested in the necessary dose to achieve improvement, and these follow-up assessments will permit evaluation of whether changes may occur prior to completing the full intervention (e.g., after only 1-2 vs. 3-4 vs. maximum dose of 6 sessions). In addition, having more regular contact with research staff to complete assessments should help to improve retention in the study over time. These assessments will take approximately 10-15 minutes, and participants will be compensated \$10 for each one they complete.

*Post-assessment:* At approximately 16 weeks, participants will return for an in-person post-assessment. An RA who is blinded to condition (and was not the interventionist) will administer the self-report measures (see Measures section below and Table 1 for summary). (If necessary or per patient preference, the post-assessment may be conducted via telephone.) After completion of all the aforementioned blinded measures, the RA will open a sealed envelope, which will reveal the participant's condition. The RA will then administer the treatment satisfaction, treatment credibility, and therapeutic alliance self-report measures for all participants who attended at least one treatment session (regardless of condition), and for those in the intervention condition only, the semi-structured acceptability interview. The session will take approximately 90-120 minutes, and participants will be compensated \$50. Participants will also be provided with a resource information sheet and appropriate referrals if interested in obtaining further treatment (e.g., specialty mental health care).

*Process evaluation:* As part of our hybrid I effectiveness-implementation trial approach, we will conduct a mixed methods process evaluation<sup>81</sup> of the implementation of the intervention. The goal is to inform future implementation rather than evaluate a specific implementation strategy.<sup>79</sup> Quantitative data will include acceptability including patient satisfaction and credibility, and feasibility including session attendance. We will also compare patient perception of therapeutic alliance across conditions. Qualitative data will include patient interviews at post-assessment and informal study therapist feedback throughout (e.g., aspects of the intervention or modules that may be challenging to deliver in brief sessions). At the end of the study or whenever a study therapist is leaving the study team, they will be asked to anonymously complete the Study Therapist Debriefing, which includes acceptability, appropriateness, and feasibility<sup>84</sup> for the VA PC-MHI setting as well as questions implementation barriers and facilitators and training needs.

### ***Intervention Content***

The treatment manual is grounded in evidence-base practice, employs a modular approach, and is applicable across a range of anxiety symptom presentations (i.e., type [e.g., generalized anxiety, social anxiety, panic symptoms] and severity [subthreshold, mild, moderate]). The treatment type (individual), format (face-to-face, for at least the initial session), setting (VHA primary care), and provider (PC-MHI) were selected based on Veterans' clear preferences for this type, format, location, and provider in our prior research.<sup>43</sup> To develop the treatment manual for this study, we adapted content from extant evidence-based anxiety treatment protocols to fit PC-MHI practice. We selected intervention techniques from cognitive-behavioral therapy (CBT) that have demonstrated efficacy in treating anxiety,<sup>25</sup> including psychoeducation,<sup>34</sup> relaxation training,<sup>35</sup> cognitive restructuring,<sup>25</sup> and exposure,<sup>25</sup> as well as behavioral activation<sup>36</sup> for depression. We also drew on techniques from Acceptance and Commitment Therapy (e.g., values, mindfulness) because it has strong empirical support for reducing anxiety,<sup>37</sup> and evidence-based CBT techniques to address insomnia<sup>38</sup> because our pilot data indicated Veterans place a high priority on sleep. All of the included intervention techniques have been used within modules in prior studies of primary care-based anxiety treatment with good results.<sup>32,39,40,41</sup> We adapted the scope of existing interventions to fit into the PACT population-based model of care and the brief format necessary for PC-MHI.<sup>42</sup> The manual emphasizes a psycho-educational approach, focusing on key concepts that can be easily taught to a wide audience, and teaching self-management skills<sup>26</sup> to empower patients using behavioral techniques that can be quickly demonstrated in session and assigned for at-home practice (e.g., 5-minute deep breathing exercise for relaxation). Consistent with prior research,<sup>32,39,40,41</sup> we employed a modular approach in the treatment manual to facilitate tailoring the content to individual patients, which will increase patient-centeredness. The choice and order of modules used within the intervention will be a collaborative decision between the therapist and patient based on patient preference in combination with therapist clinical recommendations. The content and format of the intervention were tailored to Veterans' anxiety treatment

preferences<sup>43</sup> as much as possible to enhance treatment engagement. We also incorporated findings from our prior research with PC-MHI providers regarding feasibility of implementing anxiety intervention techniques in real-world practice. Although the intervention focuses primarily on anxiety, it includes a module targeting comorbid depressive symptoms, given high comorbidity of major depression among primary care patients with anxiety.<sup>4,5</sup> This module is optional and will be used as clinically indicated. At the beginning of each session, participants will complete self-report measures of anxiety and depression symptoms as part of measurement-based care.<sup>80</sup> (Participants who endorse >0 on the PHQ-9 item 9 will be assessed further according to our suicide risk assessment protocol.)

## **Measures**

See Table 1 for a summary of all measures and time of administration.

Demographics collected during the telephone screen will include: sex, age, race, ethnicity. Additional demographic information collected at the baseline assessment will include: marital status, living situation, employment status, educational level, household income, distance from VAMC, smart phone status, internet access and comfort, non-VA primary care provider, and military service history.

Cognitive impairment will be assessed during eligibility screening using the six-item screener for cognitive impairment.<sup>57</sup> This measure was adapted from the widely used Mini Mental Status Examination to provide a brief screening tool for cognitive impairment for use in clinical research studies. Participants are given three objects to recall (apple, table, penny) after repeating them once and then asked three temporal orientation items (day of the week, month, year). The scale is unobtrusive and was designed for easy telephone or in-person administration. A cutoff score of  $\geq 3$  errors yields high sensitivity and specificity for cognitive impairment and dementia.<sup>57</sup>

The primary outcome of anxiety symptom severity will be measured by the GAD-7<sup>44</sup> self-report questionnaire, a validated measure that is widely used in VHA PC-MHI, in part due to its applicability across the anxiety disorders beyond GAD as well as its brevity. Participants rate how much they have been bothered by each problem over the last 2 weeks on a Likert scale from 0 (not at all) to 3 (nearly every day). Scores are summed to create a total score indicating severity of anxiety symptoms: minimal (0-4), mild (5-9), moderate (10-14), and severe (15-21).<sup>44</sup> The total score is sensitive to change from treatment across the anxiety disorders.<sup>45</sup> The GAD-7 ( $\alpha = .92$  in primary care sample) has demonstrated construct and criterion validity and is a good screening tool for GAD, SAD, and PD.<sup>33</sup>

Depressive symptom severity will be measured by the PHQ-9 self-report questionnaire,<sup>46</sup> a validated measure that is widely used in VHA primary care and PC-MHI as part of mandated annual depression screenings. Participants rate how often they have been bothered by each problem over the past two weeks on a Likert scale from 0 (not at all) to 3 (nearly every day). Scores are summed to create a total score indicating severity of depressive symptoms: minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27). A cut-point of 10 is recommended for identifying cases of depression. The total score of the PHQ-9 is sensitive to change from treatment.<sup>47</sup> The PHQ-9 ( $\alpha = .86$  in primary care samples) demonstrates construct and criterion validity.<sup>46</sup>

Presence of probable PTSD will be assessed during eligibility screening using the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5),<sup>58</sup> a six-item measure that was designed specifically for use in primary care. The first item assesses whether the individual has had any exposure to a Criterion A trauma. If not, the additional 5 items are not administered. If the individual indicates past trauma exposure, 5 items assess the presence or absence (yes/no) of 5 PTSD symptoms in the past month (nightmares/intrusive thoughts, avoidance of triggers, hypervigilance, detachment, trauma-specific blame/guilt). The PC-PTSD-5 has good diagnostic accuracy and was rated as very easy to understand and complete in primary care. A cutoff score of  $\geq 3$  was found to be the optimal score for balancing high sensitivity and specificity.<sup>58</sup> This measure is very similar to the Primary Care PTSD Screen (PC-PTSD) that is currently used for annual PTSD screening of all Veterans receiving VA primary care services.<sup>59</sup> However, there are 2 key differences.<sup>58</sup> First, the PC-PTSD-5 items were updated to reflect the latest understanding of PTSD symptoms, resulting in the addition of a fifth item. Second, the PC-PTSD-5 begins with an item assessing whether the individual has experienced a true traumatic event. In contrast, the PC-PTSD asks about “any experience that was so frightening, horrible, or upsetting,” which can



be interpreted widely; as a result, many individuals respond to the items with respect to an upsetting or stressful event, such as a divorce, which is stressful but does not meet the clinical definition of a trauma. With this change, the PC-PTSD-5 reduces the potential for false positive screens.

Readiness to change will be assessed with a 1-item readiness ruler (adapted<sup>61</sup>) that asks respondents to indicate how ready they are to make a change to improve their anxiety, that is, how ready they are to try out new skills learned in treatment for anxiety at home, outside of appointments. The scale ranges from 1 (not ready to change) to 10 (already trying to change). Scores of 1-2 suggest being not ready to change, 3-4 suggest being unsure if ready to change; 5 suggests being at least somewhat ready to change.

Medication and treatment history will be assessed at baseline using a brief interview covering lifetime use of mental health treatment.

Functional impairment from anxiety symptoms will be measured using the *Overall Anxiety Severity and Impairment Scale* (OASIS),<sup>48</sup> which measures symptom severity and functional impairment across anxiety disorders and subthreshold symptoms. The 5-item scale demonstrates reliability ( $\alpha = .84$  in primary care sample) and validity in primary care patients.<sup>49</sup> Participants indicate the frequency and intensity of anxiety, level of avoidance, and interference with activities and social functioning on a Likert scale from 0 to 4.<sup>48</sup>

Functional impairment from depressive symptoms will be measured using the *Overall Depression Severity and Impairment Scale* (ODSIS),<sup>51</sup> which measures symptom severity and functional impairment across depressive disorders and subthreshold symptoms. Adapted from the OASIS<sup>48</sup> to apply to depression, the 5-item scale demonstrates reliability ( $\alpha = .92$  in community sample of adults) and validity.<sup>51</sup> Participants indicate the frequency and intensity of depressive symptoms, difficulty engaging in activities, and interference with work/school/home activities and social functioning on a Likert scale from 0 to 4.

Stress symptoms, as well as anxiety and depressive symptoms, will be measured with the Depression Anxiety Stress Scale-21 (DASS-21),<sup>62</sup> which consists of three 7-item subscales: depression, anxiety, and stress. Participants indicate how much each of 21 items applies to them over the past week on a scale from 0 (did not apply to me at all) to 3 (applied to me very much, or most of the time). This measure has good psychometric properties in both clinical and non-clinical samples.<sup>63</sup> This measure reliably distinguishes between symptoms of anxiety (panic/worry), stress (tension/agitation), and depression (low mood/anhedonia) which are highly comorbid. This measure will be administered during the follow-up assessments rather than the GAD-7 and PHQ-9 because the GAD-7 and PHQ-9 will be administered at every session to participants in the intervention condition as part of measurement-based care and may therefore be subject to assessment reactivity if we also administer it during monthly follow-up assessments.

Quality of life will be measured using the Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF),<sup>52</sup> which measures overall enjoyment and satisfaction with various aspects of life. The 16-item scale is reliable ( $\alpha=.86$ ) and valid. Participants rate satisfaction with each domain on a Likert scale from 1 to 5.

### *Exploratory/tertiary outcomes*

Sleep will be measured using the Insomnia Severity Index (ISI),<sup>64</sup> which consists of 7 items evaluating perceived insomnia (e.g., severity, satisfaction with sleep pattern, interference with daily functioning) over the past week. Response options range from 0 (none/not at all) to 4 (very/very much). The ISI has good evidence of reliability and validity in clinical and community samples.<sup>65</sup> It is responsive to insomnia treatment<sup>65</sup> and performs well as screening tool for insomnia.<sup>64</sup>

Pain intensity and interference will be measured using the PEG,<sup>66</sup> which is an ultra-brief, 3-item measure. Participants indicate their pain intensity, pain interference with enjoyment of life, and pain interference with general activity in the past week on a scale from 0 (no pain/does not interfere) to 10 (pain as bad as you can imagine/interferes completely). The PEG has good reliability and validity and is sensitive to change.<sup>66</sup> This measure will be included because chronic pain is extremely prevalent in the VHA primary care population and is associated with greater psychological distress,<sup>67</sup> and it may impact treatment engagement or effectiveness.

Behavioral activation/engagement will be measured using the Behavioral Activation for Depression Scale-Short Form (BADSF),<sup>70</sup> which consists of 9 items assessing changes in activation. Participants rate how true each item was for them over the past week on a scale from 0 (not at all) to 6 (completely). The BADSF has good reliability and validity.<sup>70</sup>

Behavioral avoidance will be measured using the Behavioral Avoidance subscale of the Multidimensional Experiential Avoidance Questionnaire (MEAQ),<sup>71</sup> which consists of 11 items assessing overt situational avoidance of unpleasant emotions. Participants rate how much they agree with each item on a scale from 1 (strongly disagree) to 6 (strongly agree).

Healthcare utilization will be assessed using self-report items about non-VA appointments (primary care, emergency department, and mental health visits) at baseline (6 months prior to baseline) and post-assessment (4 months while in study). We will also conduct a chart review in CPRS to obtain objective data (e.g., patient's presenting complaint, diagnoses, GAD-7/PHQ-9 scores, and other indicators of whether appointments were related to anxiety symptoms) from progress notes of VA appointments (primary care, emergency department, and mental health visits) in the 6 months prior to study enrollment, the 4 months in the study, and the 6 months following study completion.

Addition to our assessments in response to the COVID-19 outbreak:

Given the relevance of the COVID-19 outbreak to the study's primary outcome of anxiety, we have included a few questions related to COVID-19 in the baseline, follow-up, and post assessments so that we can understand whether this public health situation had a systematic impact on the study results. The baseline questions assess from March 16, 2020 (when the first case was detected in Onondaga County) to the date of the baseline, and the post questions assess from the baseline to the date of the post. The single item added to the 4, 8, and 12 week assessments references the past week consistent with the other measures given in those assessments. Items added to the acceptability interview will help us understand whether delivery by telehealth modalities impacted treatment engagement (in either condition).

#### *Treatment related outcomes*

Treatment satisfaction will be measured by the Client Satisfaction Questionnaire (CSQ), an 8-item self-report questionnaire with evidence of reliability ( $\alpha = .93$ ) and validity.<sup>54</sup> Each item rating and the total CSQ score will be used to evaluate participants' satisfaction with the treatment they received.

Treatment credibility will be assessed at post-assessment using a 4-item adapted version<sup>55</sup> of the Expectancy Rating Scale (ERS),<sup>56</sup> which asks patients to rate, on a Likert scale from 0 (not at all) to 10 (extremely), how logical this type of anxiety treatment seems, how confident they are that the treatment would eliminate anxiety, how confident they would be in recommending the treatment to a friend with anxiety, and how much improvement they expect to result from it.

Therapeutic alliance will be assessed at post-assessment using the 12-item Working Alliance Inventory-Short Form Revised (WAI-SR),<sup>85</sup> which asks patients to rate, on a Likert scale from 1 (seldom) to 5 (always), their experience of the therapist in terms of quality of the relationship bond, agreement on the goals of treatment, and agreement on the tasks of treatment. This measure has good reliability and validity.<sup>85,86</sup>

Acceptability will be assessed by an acceptability interview, which we adapted from our prior work. The semi-structured interview is designed to assess Veterans' satisfaction with and perceived helpfulness of specific components of the intervention (including handouts), or for those who did not attend any intervention sessions, what prevented them from attending and how we could improve the way the treatment is described to appeal more to Veterans. It will be used to identify barriers and facilitators to engagement, adherence, and retention to guide future implementation efforts.

**Table 1: Summary of Measures and Time of Administration**

Measure	Construct	Telephone screening	Baseline	Each intervention session	Follow-up assessment (telephone)	Post-assessment
Demographics	Demographics	x	x			
6-item screener	Cognitive impairment	x				
GAD-7	Anxiety symptom severity	x	x	x		x
PHQ-9	Depressive symptom severity	x	x	x		x
PC-PTSD-5	Probable PTSD (screen)	x				
Treatment history	Counseling/therapy and medication use	x (past month)	x (lifetime)			
Readiness ruler	Readiness to change		x			
OASIS	Impairment due to anxiety		x		x	x
ODSIS	Impairment due to depression		x		x	x
DASS-21	Stress / Anxiety / Depression		x		x	x
Q-LES-Q-SF	Quality of life		x			x
ISI	Insomnia		x			x
BADS-SF	Behavioral activation		x			x
MEAQ-BA	Behavioral avoidance		x			x
PEG	Pain intensity/interference		x			x
Healthcare visits	Healthcare utilization		x			x
COVID-19	COVID-19 questions		x		x	x
CSQ	Treatment satisfaction					x
ERS	Treatment credibility					x
WAI-SR	Therapeutic alliance					x
Interview	Acceptability of intervention					x

## DATA SAFETY, MANAGEMENT, AND SECURITY

All research staff will be trained by the PI in the responsible conduct of research, including privacy, confidentiality, HIPAA and IRB regulations, as well as recruitment procedures, conduct of telephone screening, and data entry, management, and analysis. RAs participate in mandated IRB training as well as internal training on informed consent. Research staff are trained on maintaining confidentiality and the security of the data with supervision by the PI. All study staff are up-to-date with VA Privacy and Information Security and Rules of Behavior training. Only current, IRB-approved research staff will have access to the data; if study staff leave the research team at any point, their access to data will be terminated. All data will be kept strictly confidential and secure per American Psychological Association (APA) ethical standards and IRB requirements.

Research staff conducting eligibility screenings and research assessments will alert the PI to any safety concerns. All research staff are trained by the PI in data collection regarding mental health topics and suicide risk assessment. In addition to the PI, other licensed independent mental health providers will be available as back-up on call clinicians to ensure safety in the event of urgent clinical concerns. For patients receiving the anxiety intervention, session data (i.e. response to PHQ-9 item 9 suicidal ideation question) will be monitored regularly by the PI to ensure patient safety during the treatment. The PI will notify the IRB, in writing, immediately, of all serious and unexpected adverse events, regardless of whether or not the event was related to the study. The PI supervises periodic internal audits to ensure data integrity and management in accordance with VA guidelines and IRB regulations.

Data collection tools such as questionnaires will be labeled with a random identification number, rather than the name, so there will be no way to connect a participant to his/her specific responses without the key. The key with participant names and linked ID numbers will be stored separately from study data to maintain confidentiality and protect participants' privacy.

Data will be used for research purposes only. All data will be stored securely within the VA. No data will be removed from VA premises. Data will be stored in paper (e.g., field notes, questionnaires) and electronic (e.g., data from CPRS) form. Paper data will be stored in locked file cabinets located in locked offices in the Center for Integrated Healthcare's main offices. Electronic data will be stored on the VA secure server in password-protected files. Data obtained through VINCI is stored on secure VA VINCI servers, until it is downloaded by the study team to store on the local secure server. To ensure the protection of Veteran data, VINCI maintains compliance with the guidelines in VA Handbook 1200.12 and all other applicable VA and VHA policies and regulations. Data will not be transmitted outside VA at all. Identifiable data will not be transmitted within VA, with the possible exception of being uploaded to VINCI or sent via encrypted VA email to IRB-approved staff for data analysis. Excel, SAS, SPSS, and Atlas.ti (licenses owned by the Center for Integrated Healthcare and/or accessible through VINCI) may be used for data cleaning and analysis. After data analysis is complete, results from group or aggregate data may be reported in research publications; however, no identifiable data will be included. Data will be maintained as defined in the VHA Records Control Schedule and destroyed at the appropriate time in accordance with these regulations and IRB guidelines.

## **STATISTICAL ANALYSIS PLAN**

The data will be screened for missing cases, outlier scores, and non-normal response distributions. Assumptions underlying statistical models will be assessed by examining standardized residuals, influence diagnostics, and homogeneity of variance (e.g. among groups). Descriptive statistics will be calculated for all variables. Analyses will be conducted using the intention-to-treat approach; participants who are randomized will be analyzed according to their assigned group regardless of amount of treatment received. The a priori alpha level for all analyses is 0.05.

The primary outcome is anxiety symptom severity, measured by GAD-7 scores. The primary analysis will be an analysis of covariance (ANCOVA) controlling for baseline GAD-7 score. Secondary analyses will use the same approach to evaluate effects on other pre-post outcomes (PHQ-9 and Q-LES-Q-SF). We will adjust for baseline scores, thus reducing the residual variance, and theoretically giving us increased power.

Multilevel modeling (MLM) will be used for outcomes with multiple (>2) assessment points (OASIS, ODSIS, DASS-21 subscales). MLM will be used to test the primary null hypothesis that no differences exist in the rate of change in outcomes between the intervention group and PCMH usual care group against the two-sided alternative that differences do exist. A composite equation consisting of within- and between-person effects will be used to analyze our data. The within-person (level 1) equation estimates participants' unique intercept (time=0) and outcome trajectory. The between-person (level 2) equation estimates the average initial status at time 0 and rate of change in the outcome. Random effects include an intercept and slope. Both level-1 and 2 (subject) residuals are assumed to be normally distributed.

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