Improving Mood in Veterans in Primary Care

Health Sciences Research & Development Title: RCT of Behavioral Activation for Depression and Suicidality in Primary Care – IIR 14-047-1

PI: Jennifer S. Funderburk, Ph.D.
VA Center for Integrated Healthcare

Co-PI: Wilfred Pigeon, Ph.D.
VA Center for Excellence for Suicide Prevention

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RESEARCH PROTOCOL

Background

Depressive symptoms are associated with considerable morbidity, mortality, and quality of life decrements[5-6, 10-11], as well as significant economic impact due to lost work days[12], disability[10], and increased healthcare utilization[13]. For instance, 14.3% of total healthcare costs within the Veterans Health Administration (VHA) are accounted for by depression[14].

Indirectly, depressive symptoms are related to a number of negative health behaviors, such as poor sleep[15-16], weight gain[17], smoking[17], substance use[18], and lack of compliance with medical regimens[19]. Depressive symptoms are also related to a loss of quantity and quality of social support[20], which is linked with increased risk for death[21].

Directly, the association between depression and medical morbidities is likely due to alterations in hypothalamic-pituitary-adrenal axis activity[23] and elevated inflammatory cytokine levels[24-25].which are intimately tied to morbidities including, for instance, risk for cardiovascular disease[26-27]. Taken together, the direct and indirect health consequences associated with depression make it the leading cause of disability in the United States[28].

Finally, there is a strong etiological link between behavioral disorders and suicide[29] with depressive symptoms being one of the most common and important risk factors among Veterans for suicidal thoughts and behaviors, including completed suicides[22]. Approximately half of Veteran suicide decedents in a national cohort study had a history of one or more behavioral health disorders[30]. In psychological autopsy studies approximately 90% of suicide victims had one or more behavioral health disorders during their last weeks of life[31].

Accordingly, sound delivery of evidence-based care for depression is a cornerstone of behavioral health care and an important element of comprehensive suicide prevention efforts[32]. The need to integrate clinical services to treat behavioral disorders such as depression in primary care settings is an ongoing focus within the VHA[42]. **Whether brief interventions for depression are effective and can also serve to reduce suicide risk remains to be fully established**.

Experience of Depressive Symptoms and Suicidality in VA Primary Care Settings

Within the VHA, Patient Aligned Care Teams (PACTs) have been identified as the frontline providers responsible for implementing strategies to identify/treat depressive symptoms and screen for suicidal ideation (SI). Targeting PACT teams would seem to be critical, as depression prevalence rates of 29%[3] have been found in primary care and a large percentage of Veterans report depressive symptoms are managed within primary care[33]. Similarly, the prevalence of SI in primary care settings is between 2.4-3.3%[34] with a majority of patients who commit suicide experiencing depressive symptoms[34-35] as well as being seen by a PACT provider within a month prior to completing suicide[36]. In fact, treating depressive symptoms in primary care is one of the few evidence-based practices for suicide prevention[32].

Recognizing the value of targeting the primary care setting and depression for Veterans' overall health, the VHA has supported several mental health initiatives over the past 10 years. In 1998, the VHA mandated annual screening for depressed mood using the Patient Health Questionnaire-2[37-38] and Patient Health Questionnaire-9[39]. This allows PACTs to easily identify patients with depressive symptoms and SI and follows recommendations to screen for depression among all adults aged 18 years and older[40]. Unfortunately, it is now evident that laudable strategies that succeed in improving identification of severe depressive symptomatology in primary care are not nearly as successful resolving depressive symptoms[41].

The Role of Integrated Primary Care and Mental Health Services

In an effort to fully address this problem, the VHA mandated a national initiative in 2008 to integrate mental health services within all PACTs to improve communication and collaboration between primary care and mental health providers (MHPs), otherwise known as the Primary Care-Mental Health Initiative (PC-MHI[42]). Each VAMC primary care setting is mandated to integrate one or more MHPs to serve each PACT, who can provide assessment and brief treatment for a variety of mental health problems[44]. Currently, 82% (*N*=124) of VA primary care clinics have at least one integrated MHP[43]. In addition, each VAMC is also mandated to blend these services with a care management program, which are typically protocol-driven and diagnosis-specific interventions often serving to support the PACT's interventions[42]. The integrated MHPs and care management

programs are intended to result in a blended model of integrative care, which is collaborative and establishes a foundation for communication among providers about mental health issues.

The Behavioral Health Laboratory (BHL[44]) and Translating Initiatives for Depression into Effective Solutions (TIDES[45]) are the two currently acceptable care management models within the VA, with approximately 56% of primary care clinics providing some form of care management services[43]. **Both the BHL and TIDES target depressive symptoms; however, their efforts are usually complemented with services provided by the integrated MHP**. For instance, the TIDES program involves the use of a depression care manager to help assess and monitor Veterans reporting symptoms of a Depressive Disorder (i.e., MDD or Dysthymia) for 6 months to make sure the Veterans are receiving appropriate care from the PACT. This may include a referral to specialty care, a prescribed anti-depressant, and/or meeting with the integrated MHP[45]. The BHL is a care management system typically telephone-based that provides structured comprehensive assessments for psychiatric disorders, including depression, and the option of ongoing assessment (i.e., "Watchful Waiting") for patients reporting subthreshold symptoms of depression. The BHL and TIDES programs assess SI; however, neither care management program offers any specific treatment management program for SI within primary care[44-45]. Instead, they recommend immediate crisis intervention, if needed, and referral to more intensive mental health services than typically provided in care management protocols as clinically appropriate. For patients recently started on an antidepressant, the BHL provides a "Depression Monitoring" protocol that includes the elements of "Watchful Waiting," with additional questions targeted at the Veterans' experiences with the antidepressant medication[44]. Depending on the Veteran's preference and/or symptomatology, the BHL may also recommend that a Veteran receive services from the integrated MHP.

Therefore, it is not surprising that depression is the most commonly referred problem seen by integrated VA MHPs in primary care and 3.5% of these patients also report SI[4, 46] (see Relevant Empirical Studies). **Thus, integrated MHPs fill a critical gap in health care. They help PACTs in collaboration with care management programs to effectively provide brief treatments to Veterans reporting a range of depressive symptoms, including those reporting subthreshold symptoms and those who may not be willing to seek mental health care services. Therefore, the goals within treatment are different than traditional specialty care settings. Ultimately, the goals are to decrease symptomatology and increase functioning. When necessary, it is also hoped Veterans who likely would be treated more effectively in specialty care will become more comfortable with a referral to specialty care after receiving a brief intervention, allowing the integrated MHP to serve as the bridge[47].**

Challenges to Delivering Empirically Supported Treatments in Primary Care

Pharmacotherapy and psychotherapy are the two treatment strategies recommended by the VHA for depression[48]. Although pharmacotherapy is a common treatment strategy used within the primary care setting[49], alternative strategies are necessary because medication is not recommended for patients reporting lower levels of depressive symptoms[50] and is not always the preferred choice depending on patient preference and/or side effects[49, 51-52]. For instance, van Geffen et al.[53] reported that one in four patients prescribed an antidepressant never initiate treatment (i.e., take medication longer than 2 weeks). In addition, many antidepressants carry a U.S. Food and Drug suicide risk warning complicating their use in patients reporting SI[54], although they do remain an important tool in the management of depression.

On the other hand, long-term psychotherapy is not conducive to delivery in primary care. Several empirically-based brief psychotherapies for depression in primary care have been found to be effective[55] and result in comparable outcomes to antidepressant medication[56]. Both brief cognitive-behavior therapy (CBT) and problem-solving therapy (PST), ranging from 6-8 sessions, have been found to have moderate effect sizes in reducing depressive symptoms in patients with Major Depression in primary care compared to usual care[7-8]. Unfortunately, in the few studies examining the range of depressive symptoms, such as minor depression and dysthymia, there is minimal evidence that these treatments are efficacious[57-58] In addition, these studies either did not report or did not assess any changes on SI, or excluded those individuals reporting SI, so that their possible effect on SI above and beyond reducing depressive symptoms is impossible to determine. Another significant limitation to this research is that a majority of the studies have been conducted on middle-aged females[8], limiting generalizability to other populations. Thus, there remains a health services research gap with respect to identifying, modifying and testing brief depression interventions in primary care.

The most significant barrier to providing such empirically-based brief psychotherapies for depression in primary care is treatment duration. Both brief CBT and PST typically range from 6-8 sessions lasting 30-50 minutes, with a median of 6 sessions[8]. This is in strong contrast to the typical session format used by MHPs

in VA primary care settings, which is 1-5 sessions of 15-30 minute duration ([4, 46]; see Relevant Empirical Studies section). This actual practice matches the guidelines for integrated healthcare, which recommend that MHPs work towards a maximum of 4 sessions of 15-30 minutes duration[47, 59]. These authors suggest that the frequency and length of contact with patients be dictated by the severity and/or complexity of a patient's symptoms/needs while striving to maintain open access thereby often resulting in sessions scheduled 2-3 weeks apart[47]. **Limited work has been undertaken to bridge this gap between recommended length and number of treatment sessions and existing intervention formats, especially as it relates to providing evidence-based depression treatments.**

The ease of implementation of these other two efficacious brief psychotherapies (i.e., CBT or PST-PC) within real-world clinical settings is also yet to be determined. Although, they have been implemented by a range of healthcare professionals, researchers have provided little information about the training required or supervision necessary for implementation by various healthcare professionals[8]. In addition, these interventions (CBT and PST-PC) typically have involved healthy individuals without co-morbid medical problems, and involve challenging skills, such as effective problem solving or cognitive reframing.

Behavioral Activation: A Good Candidate for Primary Care Based Depression Treatment

Rooted in behavioral theory and initially a component CBT, behavioral activation (BA) was identified within a dismantling study as effective at reducing depressive symptoms on its own[60], with no differences from traditional CBT at 2-year follow-up[61]. BA focuses on reducing depressive symptoms through the use of values assessment and activity scheduling. A core symptom of depression is the lack of interest or pleasure in most or all activities and activity levels overall have been found to be lower in patients with Major Depressive Disorder compared to normal controls[62-64]. Therefore, BA is designed to engage depressed patients in activities that provide more enjoyment and meaning[65]; thereby increasing the patient's level of reward from experiences[66] and activity levels[67].

Recent work supports the traditional format of BA (i.e., ranging from 7-20 50-minute sessions) as an efficacious treatment for patients reporting severe depressive symptomatology, with effect sizes similar to other psychological treatments (d = .78-.87[9, 68]). BA also is an efficacious alternative to psychopharmacology[69-70]. A 5-12 session version of BA, called Brief Behavioral Activation Treatment for Depression (BATD[71]), has also been found to reduce depressive symptoms[67, 72].

BA is also effective at reducing depressive symptoms across a broad range of intensities (i.e., moderate-severe depressive symptoms) and with a diverse age-range of patients (i.e., younger college students to older adults[9, 68]). Demonstration of BA's effectiveness in reducing depressive symptoms has included a number of population samples that are typically "difficult" to treat, including patients who have significant psychiatric and substance use comorbidities[66-67], those with medical problems such as cancer[73-74] and obesity[75], and those who are cognitively impaired[76]. In addition, BA may help improve overall quality of life, such as general well-being, increased social support, and reduced bodily pain[77]. Significant within the Veteran population is that preliminary research has found that the traditional format of BA is effective toward reducing symptoms of PTSD[15], which helped create the foundation for a currently-funded VA Request for Applications for PTSD treatments for OEF/OIF Veterans[78] (Jakupcak; PI).

A recent meta-analysis concluded that there is too limited empirical work to ascertain whether depression psychotherapies impact SI, although their impact on hopelessness was deemed to be moderate to large[123]. Two large depression trials for older adults (not included in the meta-analysis) found that among those who endorsed SI at baseline, 90% continued to have SI following treatment-as-usual compared to 50% following depression treatment [124,125]. We are not aware of any controlled trials of BA that report its effect on SI. In one uncontrolled study, however, preliminary results in a sample of 32 depressed breast cancer patients suggest that patients who received BA experienced significant reductions in SI and significant increases in hopefulness at post-treatment, which were maintained at 12-month follow-up (D. Hopko personal communication, May 6, 2013). While speculative, it is conceivable that with its focus on increasing pleasurable activities (and, to some extent, social engagement) BA can reduce suicidality by increasing reasons for living, quality of life, and enjoyment in life.

Similar to other brief psychotherapies for depression, there is a lack of rigorous studies examining BA or BATD in the format consistent with what MHPs use in primary care (i.e., 4 or less 15-30 minute sessions). A naturalistic study conducted within a VA integrated primary care setting demonstrated that 2-4 sessions of BA reduced depressive and anxiety symptoms among depressed Veterans at posttreatment and one month posttreatment[79]. Others have shown that a one-session version of BATD was effective at reducing

depressive symptoms in moderately depressed university students compared to controls[80]; however, they did not use a clinical sample. In addition, an uncontrolled study of brief BATD (approximately 6 20-minute sessions) found BA to be effective in reducing depressive symptomatology in inpatient psychiatric patients[72]. **What remains to be established is whether a brief form of manualized BA delivered in a primary care setting leads to clinically significant benefits compared to clinical services already provided.**

Research examining the efficacy of BA has found small to moderate effect sizes at follow-up compared to post-treatment, suggesting that the effects of BA on depressive symptoms can be lasting. However, follow-up periods have varied across the studies, ranging from one-month to two years[9, 68, 79]. Because MHPs working within primary care settings provide brief interventions to patients who can be reluctant/resistant to engaging within outpatient specialty care, identifying interventions that can reduce depressive symptoms over the long-term is ideal. Other studies examining brief psychotherapies within primary care also significantly vary their follow-up periods; however, the modal follow-up period that studies report is one-year[55].

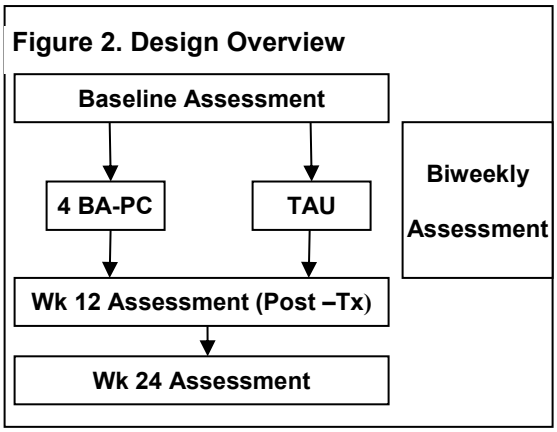
Summary

The high prevalence of depressive symptoms among Veterans in VHA primary care practices coupled with the necessity of delivering (but paucity of existing) effective brief interventions in these settings provides a strong rationale for the proposed study. MHPs working with PACTs need to have evidence-based interventions that meet the needs of their clinical practice, improve the quality of life for Veterans, and help engage those Veterans initially reluctant to mental health care. These interventions need to be versatile enough to be effective with Veterans reporting a range of depressive symptoms and/or medical complexities. BA is ideally suited for modification to the primary care setting due to its: 1) focus on behaviors (similar to other self-management focused interventions in primary care) allowing for easy application with a range of Veterans, including those with co-morbid psychiatric or physical problems, 2) ease of adaptation to each Veteran depending on unique individual factors including psychosocial variables, 3) the uncomplicated skills required to understand and implement BA[71] with a recent study showing a 12-session BA protocol could effectively be delivered by mental health nurses using a 5-day training and supervision[82], 4) evidence supporting its use with a range of depressive symptoms and patient populations compared to CBT or PST-PC, 5) research showing that BA may help reduce symptoms of PTSD by breaking patterns of avoidance, 6) drop-out rates that are lower than CBT[81], 7) preliminary evidence that BA may reduce SI in patients reporting SI (D. Hopko personal communication, May 6, 2013), and 8) research indicating patients receiving BA improve at the same rate as those prescribed an antidepressant and improve significantly more per treatment week than those in cognitive therapy[70].

Methods

Design Overview

The proposed study is a single blind randomized, controlled trial (N=144) with two conditions (4-session BA-PC or TAU) that uses an intent to treat design. Following an initial telephone assessment session, all patients who agree to participate and who meet all inclusion criteria will be asked to participate in the study. As depicted in **Figure 2**, all Veterans will complete a baseline assessment. Eligible Veterans will be randomized in equal proportions to one of two conditions (4-session BA-PC or TAU). All Veterans will complete biweekly brief telephone mood assessments for the first 12 weeks. These brief biweekly assessments can also be completed in-person, if they align with another assessment or if the participant prefers to meet in-person. Comprehensive assessments will occur at 6 weeks and 12 (post-treatment), as well as at 24 weeks. After 12 weeks (post-treatment), all participants will be allowed to seek additional psychological treatment, if desired.



Settings

This study will be implemented in four different primary care clinics in VISN 2 (Syracuse VAMC, Canandaigua, Buffalo VAMC's, and Rochester Outpatient clinic). We will seek Buffalo IRB approval as well.

Study Population

Power analyses revealed that a total of 144 Veterans (72 Veterans per group) will need to be randomized to provide 80% power to detect a medium effect of the intervention on depressive symptoms at the 12-week post-

treatment time point, while accounting for a 30% attrition rate across the 12-weeks. Using the previously collected data to give indication of our screening rates and rates of eligibility and consent to enroll in the trial, we expect to be able to recruit 4-5 eligible patients per month across a 33-month recruitment time period resulting in the ability to recruit approximately 165 Veterans. Ultimately, we would need to conduct telephone screens on approximately 335-379 depending on the specific eligibility (38%-43%) rate used from our preliminary study.

Recruitment will occur using four methods: 1) Direct referrals from PACT team providers and staff, including integrated MHPs when meeting with patients who score positive on the PHQ-2 (> 2) or indicate symptoms of depression, 2) Referrals from the Behavioral Telehealth Center, a primary care service designed to provide telephone assessment of mental health concerns of primary care patients, of patients who report depressive symptoms as measured by the PHQ-9 and who indicate interest in hearing about research studies, 3) Flyers within primary care clinics waiting rooms for interested patients experiencing depressed mood, 4) Following a primary care provider's approval, communication via letters sent to primary care patients who have reported depressive symptoms during a recent appointment (identified via chart review) or who have scored positive on the PHQ-2 within the past month. These letters will describe the study and alert patients that a member of the research staff will be calling them within 1-2 weeks to ask about their interest in participating in a research study (see letters of support). One of two methods will be used to identify patients with positive PHQ-2 screens within the past month: 1) via an information technologist within VISN 2 who will pull this data (i.e., patient name, address, social security number, date of birth and telephone number) or 2) information will be requested and extracted from the VA Corporate Data Warehouse (CDW) and placed within VA Informatics and Computing Infrastructure (VINCI; see below for more information on the VINCI).

Inclusion Criteria

Initial Eligibility Screening: Veterans: a) aged ≥ 18 years, b) seeking or receiving primary care services at the Syracuse, Canandaigua VAMC's and Rochester Outpatient Clinic; and c) reporting depressive symptoms by screening positive for depression on the PHQ-2 (> 2) are eligible.

Baseline Assessment: Veterans: a) reporting at least moderate symptoms of depression, scoring greater than or equal to a 10 on the PHQ-9; b) who are either on a stable antidepressant dose for ≥ 6 weeks or are not taking antidepressants, c) who have been receiving a stable course (i.e., regular scheduled sessions) of outpatient psychotherapy for anxiety disorders, including PTSD, or substance use disorders for ≥ 3 months, and d) who have had no more than one session with the integrated MHP discussing depression as this initial session tends to involve primarily assessment in past 4 weeks (see Relevant Empirical Studies) are eligible.

Exclusion Criteria

Initial Eligibility Screening: Veterans: a) unable to demonstrate an understanding of the informed consent by not being able to answer 5 comprehension questions; b) non-English speaking; and c) who are currently engaged in psychotherapy targeting depressive symptoms are ineligible.

Baseline Assessment: Veterans who: a) are reporting imminent risk of suicide, as evidenced by the suicide assessment identifying the Veteran as imminent risk and in need of intensive treatment, such as hospitalization, b) have an unstable psychiatric condition (e.g., active psychosis or current mania) or who have a history of Bipolar I or II disorder and are in need of more intensive treatment; c) have recently started antidepressants or have not reached a stable dose (< 6 weeks); d) are currently receiving or currently completed (< 1 month) inpatient or intensive outpatient (e.g., partial hospitalization) programs for a mental health disorder and therefore currently engaged in significant mental health treatment likely targeting changes in mood symptoms; and e) who have recently started psychotherapy for an anxiety disorder or substance use disorder (< 3 months) are ineligible.

Procedure

To verify initial eligibility, Veterans will be asked to complete the PHQ-2 to confirm some level of depressed mood. Upon completion of the PHQ-2, Veterans will be asked a series of questions to determine whether they are currently engaged in any type of mental health treatment focusing on depressive symptoms. Because our recruitment methods will only initially identify Veterans who may be experiencing significant depressive symptoms and are not currently engaged in mental health treatment targeting depressive symptoms, this study will be conducted in two parts with two separate consent forms. The first part (Initial Eligibility Screening) will involve a brief initial telephone assessment, the purpose of which is to learn about the Veteran's mood and current strategies he/she is using to improve his/her mood, including participation in treatment. If the Veteran meets the inclusion criteria for the second part of the study, then he/she will be asked to participate. If

interested, the Veteran will be scheduled for an in-person baseline assessment session and will complete the second informed consent, which will describe the purpose of the study examining the effectiveness of a 4-session BA intervention. See **Table 1**. If the Veteran is ineligible for the second part of the study because they recently started or changed medications, but interested in participating we will ask the Veteran if it is alright if we call them back in 3-4 weeks as research shows a large number of patients discontinue antidepressants before reaching 4 weeks. We will explain that as they have recently engaged in treatment or modified an existing treatment that this is not the best time to participate in a study. However, if they are interested, we would be happy to call them back and re-evaluate their eligibility after they have had several weeks to adjust to the treatment. When we call them back, we will have to re-administer the PHQ-9 and ask about his/her treatment/medication regimen to verify eligibility at that time.

Initial Eligibility Screening

The initial assessment will primarily occur over the telephone; however, any Veteran requesting to be seen in person can also complete the assessment during an in-person visit. During the initial assessment, patients will complete an informed consent process and then be asked to verbally complete: a) a demographics questionnaire, b) the Personal Health Questionnaire-9 (PHQ-9)[39] assessing depressed mood, c) the MINI International Neuropsychiatric Interview modules for current mania and psychosis symptoms commonly used by the BHL to assess these same symptoms, and d) a medication and treatment history questionnaire assessing their history of bipolar disorder, engagement in treatment, and use of antidepressants.

At the end of the screening session, research staff will review the various services available for all Veterans at their local VA. For those patients who are eligible to continue to the second part of the study, staff will also briefly describe the study. Research staff will facilitate a referral to any option chosen. All participants will be thanked for their time and will be sent $15 for completing this telephone assessment.

Baseline Assessment (Week 0)

Those patients who meet eligibility criteria and are interested in participating in the second part of the study will be scheduled for an in-person baseline assessment. Following informed consent and HIPAA waiver, research staff will confirm eligibility by examining the Veteran's CPRS record to ensure that he/she meets eligibility criteria.

As shown in Table 1, participants will be asked to complete self-report assessments, including those assessing mood, quality of life, SI, insomnia, and environmental reward from activities. Participants will be compensated $40 for completing the in-person session.

Randomization

Those participants eligible to continue in the study (based on CPRS review) will be called after their baseline appointment by a member of the research team to schedule their next in-person session based on being randomized in equal proportions to one of two interventions (4-session BA-PC or TAU) using a stratified block random assignment based on two factors: 1) "mild to moderate" (PHQ-9 score between 10-15) or "severe" (PHQ-9>15) depression and 2) presence or absence of SI (SSI≥1).

Assessments

All participants will be asked about depressive symptoms every two weeks for the first 12 weeks over the telephone or in-person. Participants will also be asked to complete more comprehensive telephone and in-person follow-up assessments at 6, 12, and 24 weeks (as shown in Figure 1 and Table 1). During these assessments, participants will be asked to complete the same questionnaires as during the baseline assessment and several additional measures dependent on the assessment as identified in Table 1 focused on patient receptivity and medication/treatment history.

All assessment sessions will be led by research assistants blind to condition and take place primarily (unless requested otherwise) via the telephone except the baseline, 12, and 24 weeks (see Table 1). The 12-week assessment will occur over the telephone if unexpected circumstances prevents the Veteran from being able to come in to the medical center. All research assistants will track any non-study care given to participants as that may be a potential confounding variable to our examination of treatment effect[88].

At baseline, 12, and 24 week sessions, information will be collected from the medical chart of each participant regarding his/her current medical problem list, medications, engagement with mental health care, including types of interventions that they may or may not have participated in during the study as monitored by the VA electronic medical record system.

Treatment As Usual Condition

TAU will involve the Veteran receiving an appointment with the integrated MHP at their primary care clinic. At this encounter, the MHP can choose to deliver whatever interventions they deem necessary. In addition, the MHP and Veteran can work together to identify whether and when they would like to meet again during the 12-week period of the active portion of the study. As recommended by Freeland et al[88], it is unnecessary to force the TAU condition to have the same amount of attention unless the purpose is to examine specific and nonspecific effects, which is not the case in this study.

BA-PC Intervention

Intervention Description. A revised 4-session BA-PC manual was created with the help of Dr. Hopko, one of the original authors of the Brief Behavioral Activation Manuals (see Appendix 4). BA-PC will focus on 1) providing feedback regarding his/her experience of symptoms of depression, including the severity; 2) helping the Veteran understand the theoretical foundation for BA, the research behind it, and why it will help reduce symptoms of depression; 3) identifying activities (or lack thereof) within the Veteran's life that may be helping to maintain depressive symptoms as well as any current behaviors that might be eliciting positive reinforcement of depressive behaviors; and 4) identifying new value-based activities that may elicit positive affect within a variety of major life domains (e.g., family, physical, etc.).

Patient Treatment Adherence. A fundamental component of BA is establishing specific measurable goals regarding his/her engagement in activities at the end of each session. Therefore, patient adherence to the BA intervention can be monitored by examining the proportion of the number of goals completed versus the number of goals identified as homework by the interventionist and patient at the end of each session. Then, individual patient adherence can be calculated for each session and overall patient adherence can be calculated for each intervention condition. These calculations will help us understand basic patient adherence to the modified brief forms of BA-PC, which will be used as an indirect reflection of patient receptivity.

Therapists & Therapists Training. Advanced-level clinical psychology graduate students or Masters-level MHPs working as research assistants will implement the 4-session format BA-PC. They will participate in a 2-day workshop to establish training in BA-PC led by Drs. Hopko and Funderburk. Each research assistant will have to demonstrate proficiency within a role-play of BA-PC, observed by Drs. Hopko and Funderburk. All BA-PC intervention sessions will be audio-taped and Dr. Funderburk will meet weekly with the research assistants to provide supervision of the BA-PC based on review of audio-taped sessions, session materials, and ad hoc supervision issues raised by research assistants. In addition, Dr. Hopko will also provide monthly telephone supervision regarding the implementation of BA-PC.

Therapist Treatment Fidelity. To monitor high treatment fidelity within BA-PC and to ensure TAU has low fidelity to BA-PC, research assistants will audio-tape all sessions. For integrated behavioral health providers, a research assistant will come to the scheduled session with the audiotape recorder and then collect the recorder when the session is done. Research assistants will immediately download the files to the secure X: drive and delete them from the audio-recorders. In the event of audio-recorder failure or to accommodate behavioral health providers' preferences, the provider would receive either a paper questionnaire (see Appendix 6) with a sealable pre-filled out envelope or an encrypted email with a link to fill out the questionnaire (see Appendix 6 for template email). No identifiable information will be included on the questionnaire. If the paper questionnaire is completed, providers will return it to research staff either in-person or via VA interoffice mail to research staff within the same VA location. Reminder emails will be sent to providers to help ensure this information is collected. The online document will be hosted on psychdata.com, which has a high level of security (see Appendix 6 for more details). The Principal Investigator, Dr. Funderburk, has used the psychdata.com server successfully for IRB-approved, secure online data collection in several prior studies (e.g., Veteran Treatment Preferences, Clinical Interventions Used by Behavioral Health Providers in Primary Care). Only de-identified data will be stored on the psychdata.com server, so there are no changes to the original Data Security Agreement. Data from the questionnaire will be downloaded on a weekly basis and saved on the secure X: drive. Independent raters, who have mental health training and are trained in BA-PC, will review the audiotapes and asked to complete a treatment checklist identifying what elements of BA-PC were present and how long the provider spent discussing them during the course of the session. This checklist will also incorporate items from the OPTION (Observing Patient Involvement) scale[130], to assess for shared decision-making during TAU and BA-PC sessions. The Treatment Fidelity Checklist will be based on an established measure used for traditional BATD treatment fidelity[74] and ask raters to report whether elements of other interventions commonly used in primary care (see Relevant Empirical Studies) are also discussed during the session (see Appendix 5). Feedback will be regularly given to research assistants on ratings to ensure BA-

PC treatment fidelity. In the event of audio-recorder failure during BA-PC treatment sessions, research assistants will fill-out a version of the Treatment Fidelity Checklist. This version of the checklist will require research assistants to specify whether each session-specific element of BA-PC was present and to enter specific notes, in lieu of ratings, pertaining to each section of each session for which the document is used (see Appendix 7).

Intervention Format. Using preliminary data and established guidelines on the typical formats of interventions MHPs can use in primary care, all interventions sessions for the 4-session BA-PC will be designed to be short (approximately 20-30 minutes) and occur approximately 2-3 weeks apart, mimicking the MHP's schedule in primary care in an effort to maintain open access. Therefore, the first two BA-PC interventions should occur in the first 6 weeks and the second two should be both BA-PC interventions should be completed by the 12-week assessment. All interventions are designed to be conducted in person; however, they will be conducted over the telephone if the Veteran experiences an emergency making it difficult for them to travel to the VA (e.g., snowstorm, car troubles). This follows the typical approach integrated behavioral health providers use if a Veteran would like to continue to meet. As this will not be the primary format and will only be used in rare occasions, it will not be included in the informed consent.

Measures

Table 1 summarizes the assessment time points and measures included.

Initial Screening Telephone Assessment:

Participants' Background Information will be collected using the *Demographic Questionnaire* that will ask participants to report on information such as: age, gender, race, educational background, occupational status, etc.

Medication and Treatment History will be collected using a self-report questionnaire that was modified from the Behavioral Health Laboratory's core assessment[44] to assess the Veteran's past and current engagement in VA and non-VA outpatient specialty care services, including psychopharmacological treatment for mental health symptoms, including depression. In addition, it will ask the Veteran about current strategies for improvement of mood. It will be used to determine initial eligibility.

It will also be given at multiple assessment time points to monitor engagement in treatment at 12 and 24 weeks.

Depressive Symptoms will be assessed using the *Patient Health Questionnaire-9 (PHQ-9)*[92], which is a 9-item self-report questionnaire that assesses the frequency of depressive symptoms over the past two weeks with a specific focus on the symptoms necessary to meet criteria for DSM-IV diagnosis of Major Depressive Disorder. Individuals scoring 10 or above are identified as experiencing moderate symptoms, and those scoring 15 or above are identified as experiencing severe depressive symptoms[92]. Kroenke, Spitzer, and Williams found the PHQ-9 to be both reliable and valid in a sample of 6,000 patients in 8 primary care clinics and 7 obstetrics-gynecology clinics[92]. The total score of the PHQ-9 has also been used as indicative of depression severity and is sensitive to clinical change[92]. It will be used to determine initial eligibility (i.e., inclusion criteria: Veteran scores > 10 on PHQ-9).

It will also be given at the baseline assessment (week 0) to determine status for the stratified block random assignment. The PHQ-9 will also be administered at the other assessment time points as the primary outcome measure for depressive symptoms.

Mania will be assessed using the MINI International Neuropsychiatric Interview modules for mania[97], commonly used by the BHL to assess symptoms of bipolar. It will be used to determine initial eligibility eliminating those with current manic symptoms.

Psychosis will be assessed using the psychosis portion of the DSM-IV Structured Clinical Interview[98], as it is often identified as the "gold standard" for assessing psychosis. It will be used to determine initial eligibility during baseline assessment.

Week 0: Baseline Assessment:

Suicidal Ideation Intensity will be assessed using the Beck Scale for Suicidal Ideation (SSI)[99], which is a 19-item interviewer-administered rating scale designed to assess current intensity of SI by asking about

the patient's specific attitudes, behaviors, and plans to commit suicide. The SSI has demonstrated high internal consistency and concurrent validity with the clinician-administered assessment among both inpatients and outpatients[99]. The SSI has been found to have moderately high internal consistency with Cronbach coefficient alphas at .89 and high interrater reliability with correlations at .98[100]. For our primary SI outcome, we will use the total score for the SSI as a continuous measure of intensity of SI.

Quality of Life will be assessed through the use of two measures to assess various dimensions of quality of life and be used as our secondary outcome measures surrounding quality of life.

The *Short-Form-12 (SF-12*)[101] is a 12-item questionnaire that assesses an individual's perceived health status with higher scores indicating higher perceived physical and mental functioning. Research has found high test-retest reliability and internal consistency[101]. The total score on the mental health functioning subscale will be used.

The *Quality of Life Inventory (QLI*)[102] is a 16-item self-report questionnaire that assesses life satisfaction across multiple domains in 16 areas (e.g., work, love, family, etc.). Participants are asked to rate items on a 3-point Likert scale indicating importance and satisfaction across each domain. Research has found it has a high level of internal reliability, construct validity, and validation within clinical samples[103]. Total scores range from -6 to +6 because total scores are calculated by averaging satisfaction ratings assigned nonzero importance ratings. The total score on the QLI will be used.

Insomnia will be assessed using the *Insomnia Severity Index (ISI*)[104], which is a widely used 7-item Likert scale that assesses sleep disturbances with items asking about difficulty initiating/maintaining sleep, daytime consequences, anxiety and satisfaction with sleep. It has found to be valid and reliable as a measure of sleep disturbance[105]. The ISI total score will be used as one of our secondary measures assessing subjective sleep outcome.

Symptoms of PTSD will be assessed using the *PTSD Checklist – Civilian version (PCL-C),* which is a 17-item questionnaire that assesses how bothersome participants have found a particular problem/symptom to be in the past month, using a 5-point scale. Research has found it has good psychometric properties.[127] The PCL-C total score will be used as a secondary outcome measure assessing PTSD symptoms.

Symptoms of Anxiety will be assessed using the *Generalized Anxiety Disorder-7 (GAD-7),* which is a 7-item self-report scale that assesses the frequency of restlessness, worrying, and other symptoms of anxiety over the past two weeks. The scale has good reliability and construct, criterion, factorial, and procedural validity.[128] The GAD-7 total score will be used as one of our secondary measures assessing subjective symptoms of anxiety.

Levels of Environmental Reward will be assessed using the *Environmental Reward Observation Scale* (*EROS*)[106], which is a 10-item 4-point Likert scale that assesses the positive affect and reward associated with environmental experiences. It has been found to have strong internal consistency and test-retest reliability[106]. It is frequently used within studies examining behavioral activation since levels of environmental reward associated with activities is a focus of the BA-PC interventions. The total score on the EROS will be used as a secondary outcome measure.

Brief Pain Inventory (BPI). The BPI (Cleeland, et al., 1994) is a widely used self-report measure that assesses pain intensity (e.g. severity, location, chronicity) and pain-related functional disability (e.g. work, relationships with others). The BPI includes 11 items that can detect significant changes in pain severity in longitudinal analyses (Kroenke, et al., 2009). The BPI has been widely validated, showing good reliability and construct validity (Tan et al., 2004).

Tobacco Use Questionnaire. This is a brief, 11-item questionnaire comprising an assessment of current smoking status, nicotine dependence via the Fagerström Test for Nicotine Dependence (FTND)[131], and readiness to quit smoking.

Biweekly Assessments

Depressive symptoms will be assessed using the PHQ-9 and item #9 will be used to assess suicidal ideation for safety purposes.

Antidepressant Medication Changes will be assessed by asking the Veteran whether he/she is

continuing to take the specific dosage of the antidepressant medication daily they reported taking at baseline. If not, information will be gathered to identify whether they have decreased the medication, stopped the medication, or increased the medication.

6, 12, and 24 Week Assessments

***Treatment* Satisfaction and Acceptability** will be assessed with two instruments.
The *Client Satisfaction Questionnaire (CSQ)*[109] is an 8-item self-report questionnaire developed to assess patient satisfaction with medical and mental health treatment on a 1 to 4 Likert scale, with higher scores related to a higher level of satisfaction. For example, Veterans will be asked "How would you rate the quality of service you received?" on a four point scale ranging from poor (1) to excellent (4). Using the anchor points of the scale, each item needs to be rated a 3 or 4, yielding a total score of at least 24 or above to demonstrate a good level of satisfaction. The scale has a high degree of internal consistency and correlates highly with therapists' ratings of perceived client satisfaction[109]. Each item rating and the total CSQ score will be used to evaluate participants' satisfaction with the service (i.e., 4-session PC-BA and TAU).

The BA Acceptability Interview is an 18-item interview that was designed for this study to assess the Veteran's satisfaction with the specific components of the BA-PC intervention (including the patient education handouts), the acceptability of the intervention, and importance of each element of the intervention to the Veteran on a Likert scale. Open-ended questions will be used to elucidate additional comments about each Likert-scaled item. Veterans will also be asked to comment on the format of the intervention (i.e., length and number of sessions) and modality (in-person, internet, or telephone) for the primary care setting (see Appendix 5). This measure will be administered by the research assistant delivering the intervention at the last BA-PC session (to allow the assessment research assistant to stay blind to condition). It will be used to give us additional information on the acceptability of each component of the BA-PC intervention and collect information on future implementation.

Treatment Engagement will be assessed using two variables collected via CPRS record review and supplemented by the Treatment History questionnaire: 1) number of BA-PC and TAU sessions will be summarized (both conditions will likely have a similar upper limit as BA-PC will optimally provide 4 sessions and research on TAU suggests for those patients seen after an initial visit, the average number of sessions is 3) and 2) whether or not the participant had engaged in specialty care as assessed at week 24.

Therapeutic Alliance will be assessed using the Working Alliance Inventory (WAI)[129]. The WAI is a 12-item self-report measure that assesses three different domains of the therapeutic alliance, including agreement on therapeutic tasks, agreement on goals of therapy, and development of a therapeutic bond.

Table 1. Schedule of Assessment Measures

	Time (weeks)							
	0	2	4	6	8	10	12	24
SUBJECTIVE ASSESSMENTS	P	T	T	T	T	T	P	T
1. Symptoms of Depression								
a. PHQ-9*	X	X	X	X	X	X	X	X
2. Intensity of Suicidal Ideation								
a. SSI	X			X			X	X
3. Quality of Life								
a. SF-12	X			X			X	X
b. QLI	X			X			X	X
4. Insomnia Severity								
a. ISI	X			X			X	X
5. Symptoms of PTSD								
a. PTSD-CL	X			X			X	X
6. Symptoms of Anxiety								
a. GAD-7	X			X			X	X
7. Level of Reward/Positive Affect from Experiences								
a. EROS	X			X			X	X
8. Pain								
a. Brief Pain Inventory	X			X			X	X
9. Patient Adherence**	X			X			X	X
10. Treatment Receptivity								
a. Client Satisfaction Questionnaire				X			X	

b. BA Acceptability Interview***		X	
11. Therapeutic Alliance			
a. WAI		X	
12. Mental Health Treatment			
a. Medication and Treatment History Questionnaire*		X	X
c. Medication and Treatment via CPRS*		X	X
13. Tobacco Use			
a. Tobacco Use Questionnaire	X		

Note. P=in person assessment; T=telephone assessment
*These measures are also given in the initial telephone screening assessment.
**This is calculated after session 2, 3, and 4 of BA-PC
***This measure will be administered at the last BA-PC session and sealed in an envelope to allow for confidentiality and for other research staff to stay blind to condition.

Data Analysis and Statistical Considerations

The data analytic strategy emanates from the primary aim and is in line with the method used to estimate the sample size necessary to adequately test the primary hypothesis. Initial analyses will be conducted using a series of 2 (Condition: TAU vs. BA-PC) vs. 2 (Time: baseline, week 12) repeated measures ANOVAs. The primary analysis will be conducted using the intent-to-treat approach; participants who are randomized will be analyzed according to their assigned group regardless of amount of treatment received. 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).

Aim 1 (a, d): To evaluate the efficacy of a BA-PC in reducing depressive symptoms compared to TAU. MLM will be used to test the primary null hypothesis that no differences exist in the rate of change in depressive symptoms measured by the PHQ-9 between BA-PC and TAU 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 (e.g., week 0 PHQ-9 total score) and rate of change in the primary outcome (e.g., PHQ-9 total score). If the alternative hypothesis is confirmed, there would be a significant cross-level interaction between group and time of assessment suggesting a greater rate of improvement across time among participants randomized to BA-PC condition relative to TAU.

Below is the multi-level composite equation that will be utilized to model depressive symptom severity. The true depression score for the i^{th} person at the j^{th} time point is a linear combination of a between-subject main effect for group, a main effect for time, and a cross-level interaction term between group and time allowing for the fixed effect slope estimate to vary between groups. Random effects include an intercept and slope. Both level-1 and 2 (subject) residuals are assumed to be normally distributed.

$$Dep_{ij} = \underbrace{\gamma_{00} + \gamma_{01}\text{Group}_i + \gamma_{10}\text{Time}_{ij} + \gamma_{11}\text{Group}_i * \text{Time}_{ij}}_{Fixed} + \underbrace{\mu_{oi} + \mu_{1i}\text{Time}_{ij} + \varepsilon_{ij}}_{Random}$$

Our composite equation assumes a linear trajectory across time, based on our hypothesis of maintaining steady improvement in depression severity throughout the 12-week study period. This assumption may not be true given the timing and number of BA-PC sessions. We propose two alternative theory-driven models to capture an immediate effect from BA and possibly an effect that may weaken during subsequent weeks. Exploratory graphical methods such as subject specific outcome trajectory plots and transformations will be used to assess the linearity (or lack thereof) across time. Non-constant trajectories such as a quadratic time effect and piecewise-linear (PWL) models will be explored to determine the most parsimonious model. Since a linear time model is nested within a quadratic, the likelihood ratio (difference in -2log-likelihood) test can be used to test model fit. In the case where a quadratic provides a better fit than a linear model, consideration will be given to the magnitude of the quadratic effect as well as parsimony. Since a constant rate of change model is not nested within the PWL model, log-likelihoods cannot be compared to assess model fit. However, the Akaike Information Criterion (AIC) statistic (-2LL + 2*# of parameters) can be used to assess fit among non-

nested models. Below is a composite equation that includes two time segments (TS1, TS2) as well as cross-level interactions between time segment and group.

$$Dep_{ij} = \underbrace{\gamma_{00} + \gamma_{01}\text{Group}_i + \gamma_{10}\text{TS1}_{ij} + \gamma_{20}\text{TS2}_{ij} + \gamma_{11}\text{Group}_i * \text{TS1}_{ij} + \gamma_{21}\text{Group}_i * \text{TS2}_{ij}}_{Fixed} \underbrace{\mu_{oi} + \mu_{1i}\text{TS1}_{ij} + \mu_{2i}\text{TS2}_{ij} + \varepsilon_{ij}}_{Random}$$

(d) The above models will be especially useful for assessing sustainability of long-term improvement up to 24 weeks after randomization. An issue of analyzing long-term follow-up data is the rate of "missingness". Methods described below pertaining to missing data will be inspected and, if plausible, used in conjunction with MLM to compare rates of improvement between the primary 12-week study period and long term follow-up. If the reliability of estimates during the long-term follow-up period are poor due to a high rate of missing data, simple means and confidence intervals will be calculated and used for descriptive purposes.

While eligibility criteria require a stable history of depressive medication use or non-use, patients may change (drop, add) medications during the twelve week study period. While randomization should equalize patient characteristics between groups and other research has found it has no effect on the relationship between BA and changes in depressive symptoms[74, 79], medication change during the course of the trial will be assessed and if necessary it can be examined as a time-varying variable. If a sufficient number of patients are on two or more medications during the course of this trial, we will assess the association (i.e. linear vs. nominal) between the number of medications and depressive symptoms using the likelihood ratio test. Then, the number of depressive medications (in stacked format) will be entered into our model primarily to adjust the other coefficients (time, time*group) for the potential confounding effect on the rate of change in depressive symptoms between groups, due to medication.

Aim 1 (b): To evaluate the efficacy of a 4-session BA-PC in improving other secondary subjective outcomes compared to TAU. Similar to our primary depression outcome, secondary outcomes (i.e., sleep, quality of life, level of environmental reward from experiences) measured at baseline, week 6, and 12 will be analyzed by forming a MLM.

Aim 1 (c): To evaluate a higher level of treatment engagement. For the number of treatment sessions completed, non-parametric methods, such as Kolmogorov-Smirnov, will be used to examine differences between BA-PC and TAU conditions. For those participants continuing to experience moderate-severe symptoms at week 12, we will use chi-square techniques to examine rates of engagement in specialty care using data collected at 24 weeks.

Aim 2: To evaluate Veteran receptivity and adherence to a 4-session BA-PC. Treatment receptivity will be measured using the CSQ, BA Acceptability Interview, and patient adherence. For the CSQ given at week 6 and week 12, each of the eight items will be summarized by calculating the proportion of patients selecting a 3 or 4 (excellent) within each randomized group. Also, the average summary score and 95% CI at week 6 and 12 will be calculated within the TAU and BA-PC group. For the Likert-scaled items on the BA Acceptability Interview, the mean and 95% confidence interval will be calculated to help summarize participant's receptivity to BA-PC in primary care. For qualitative questions on the BA Acceptability Interview, two raters will read each participant's response and will summarize the responses[114]. Then, the two raters will discuss the summary responses they each identified and will reach a consensus that will inform the format and feasibility of BA-PC. As mentioned in the methods, a measure of patient adherence will be collected at each intervention session (i.e., proportion of the number of goals completed versus the number of goals identified as homework by the interventionist and patient at the end of each session) allowing for an overall patient adherence to be calculated and used as an indirect reflection of patient receptivity.

Aim 3 (a): To evaluate the effectiveness of a 4-session BA-PC in reducing SI

We plan to compare the presence and severity of SI between TAU to BA-PC using MLM for the purpose of generating robust effect size estimates. While p-values are inherently provided by statistical software packages, our emphasis is to calculate means and standard errors at each time point and within each group, thereby focusing on the magnitude of effects, not statistical significance. As alluded to in the Power Analysis section, this study is not necessarily powered for detecting differences in suicidal ideation among groups.

However, SI is relevant to depression and thus will be summarized for exploratory purposes using the most powerful statistical method (e.g. MLM, GEE) given the data characteristics.

Note on Missing Data: One of the advantages of the proposed analytic method is the handling of incomplete outcome data without resorting to listwise deletion of participants. Our analytic method provides unbiased parameter estimates under a missing at random (MAR) assumption. Unfortunately, the validity of MAR cannot be determined from the data. If the MAR assumption does not seem tenable, pattern-mixture models can be used to obtain valid parameter estimates by classifying participants into nominal categories according to the pattern of "missingness"[115]. This nominal variable is then used as a predictor of the response. The associated regression coefficient and the parameter estimates of its interaction with other predictor variables quantify how the predictor-response association differs across the patterns of missing data. For example, a model consisting of a main effect for time, a main effect for the nominal missing data pattern variable and an interaction term will inform us if baseline depression and depressive symptom trajectories differ according to the type of "missingness". Overall population estimates can be calculated by averaging over the patterns of missing data[115] and then statistically compared between groups[116]. A nice example of using a random-effects pattern-mixture model applied to a two group longitudinal study is shown in Hedeker and Gibbons[110].

Patient Safety

Veterans with moderate-severe symptomatology who are eligible to participate in the study may inadvertently delay treatment to remain in the study during the treatment period (12 weeks). As a result, research staff will provide patients a thorough summary of the psychological and pharmacological options for services available to them at the end of the telephone screening session. Dr. Funderburk will assist in linking the Veteran to those services if the patient is interested. At any time during the initial 12-weeks of the study, if the patient indicates interest in seeking psychotherapy, the research staff will immediately help the Veteran with a referral and ask whether the Veteran would consider continuing the assessment portion of the study. In addition, the consent form thoroughly reviews this information.

All Veterans will be instructed in the informed consent and initiation of BA-PC of the limits of confidentiality and the fact that if we feel they may be in imminent danger of harming themselves that we will involve other medical providers/emergency staff to protect their safety. All Veterans will be regularly assessed for SI throughout the study (at each telephone and in-person assessment using item #9 on the PHQ-9 and followed-up with additional suicide risk assessment) and receive emergency contact information for Dr. Funderburk as well as the suicide hotline information at the initial session (see suicide protocol).

Research staff will be intensively trained by Dr. Pigeon, a clinical psychologist, on assessing SI and determining risk level following protocols approved by the IRB. Drs. Pigeon, Funderburk, and Dollar will provide consultation and supervision throughout the study for any patient reporting SI. If the Veteran's SI escalates to imminent risk, we will connect the Veteran with appropriate services and stop the study.

As this study assumes an intent-to-treat design, at any time any patient can discontinue the intervention component of the study yet continue with the assessments. We would facilitate the referral to the appropriate care.

Information on VINCI

VINCI is a secure, central analytic platform and includes a cluster of servers designed to host databases integrated from national VA data sources, such as the Corporate Data Warehouse. This data includes the PHQ-2 screening data from the sites identified in this protocol. Once approved, the data will be placed within this secure environment of VINCI so only IRB approved staff can access the data. To ensure the protection of Veteran data, VINCI maintains compliance with the guidelines set forth by the VHA Handbook 1200.12 and all other applicable VA and VHA policies and regulations. All data will remain within the VINCI environment.

Data Safety and Monitoring Plan

Data Safety. To ensure safety of participants in the study proposed and validity and integrity of data collected, the co-PIs will oversee all data and safety monitoring functions. Both co-PIs will assume responsibility for these activities, but the research team will be advised that Dr. Pigeon will be the primary contact PI overseeing these activities. As described in the Multiple PI plan of this proposal, Drs. Funderburk and Pigeon will meet regularly to monitor study progress and discuss the implementation of monitoring

procedures. Dr. Pigeon will meet regularly with the research coordinator and staff to review monitoring procedures and ensure all efforts are being taken to minimize risks to participants.

To help monitor safety issues, we will have an independent Data Safety Monitoring Board (DSMB). As described below, we will track all negative outcomes and incidents as well as conduct interim data analysis every 12 months after the study has started. The study design will be significantly modified (and even screening stopped) on the advice of the DSMB that the study is creating potential harm to our participants.

Both co-PIs will regularly oversee all aspects of the study, including participant recruitment, informed consent, data collection, management, and analysis, as well as regularly assess the risk/benefit ratio associated with participation in the study. As a result, all research staff will participate in an intensive training to help them understand the importance of reducing the risk for participants and learning how to recognize and report any adverse event or serious adverse event to Drs. Pigeon or Funderburk. Serious adverse events (SAE) may include: death, hospitalization due to worsening depressive symptoms or suicidal ideation, or all life threatening or disabling/incapacitating events among research participants. Adverse events may include (but is not limited to): physical injuries, worsened physical or mental health, or inadvertent disclosure of confidential research information.

In the event of a SAE, the co-PIs will immediately communicate with the DSMB and Institutional Review Boards, followed by a written report in 24 hours. Jointly, we will make a decision whether there is sufficient evidence to necessitate suspension of data collection, further IRB review, modification of the protocol, or other changes to reduce potential risk to participants. Resumption of the study shall be based on the concurrence of the co-PIs, the chairperson of the IRBs, and the DSMB.

In the event that an adverse event that is not an SAE is reported to the co-PIs, they will discuss the event with the DSMB. Immediate evaluation will occur to determine if any extra steps can be taken to minimize the likelihood of that type of adverse event occurring again. If changes can be made, a report/amendment will be written and submitted to the DSMB and Institutional Review Boards.

As part of a standard practice at the Center for Integrated Healthcare, Dr. Pigeon will supervise the implementation of one audit within 4 months after study recruitment and one regularly per year afterwards of the materials collected and produced as part of the study at each site to ensure proper confidentiality and compliance with ethical principles, including informed consents, electronic medical record documentation, questionnaire data, and to make sure that the research staff are following established protocols.

Dr. Pigeon, with support from Dr. Funderburk, will provide an annual summary report of all adverse events to the IRB and the DSMB as part of the annual review. If no adverse events have occurred, the report will state, “No adverse events affecting human participants have occurred during this project year.”

Data Monitoring. To ensure adequate participant recruitment and enrollment, the co-PIs will weekly discuss the current numbers of participants contacted, screened, and enrolled from each site and compare those numbers to the expected based on our preliminary data. If after the first 4 months, it appears we are not reaching our expected N’s, the co-PIs will discuss potential barriers/obstacles and solutions with the DSMB, including the option of replacing or adding another site (e.g., Canandaigua VAMC due to its proximity to staff located at the Rochester clinic, current primary care support, and resources available to the project from the COE), if necessary. Discussions regarding recruitment and enrollment will continue at each meeting with the DSMB to ensure proper implementation of the study.

Data Safety Monitoring Board. The purpose of the DSMB is to review protocols and consent documents for this study, monitor safety issues throughout the study, provide an overview of the quality of the accumulating data, and provide guidance on interim analyses and stopping rules.

The DSMB will be comprised of 3 individuals with no direct involvement in the study or conflict of interest with the research team conducting the clinical trial. The DSMB will include individuals with expertise in: research and monitoring at-risk research participants; research in longitudinal clinical trials with Veterans; and research expertise with mental health and implementing collaborative care models.

The DSMB responsibilities will include:

i. Review and approve, disapprove, or suggest modifications to the study protocols and/or consent documents to assure both scientific integrity and study adherence to human subject protection policies.

ii. Monitor, provide feedback, and report on scientific and ethical issues related to study implementation for the protection of human subjects and advise on ethical issues related to adverse events. The DSMB will

monitor adverse event reports for purposes of determining whether their nature, frequency and severity are consistent with expectations.

The DSMB, in coordination with the co-PIs, will report to the VA IRBs any unanticipated problems involving risks to subject.

The DSMB can recommend remedies or other appropriate actions such as introducing new monitoring protocols, altering inclusion or exclusion criteria, or recommending changes in the informed consent documents.

iii. Ensure that the study protocol maintains patients' confidentiality in a manner that is appropriately balanced with issues of clinical care and safety.

iv. Monitor data regarding effectiveness. The DSMB will review data for outcomes by treatment group. If differences in results between groups appear to be clinically significant, the DSMB will review whether the clinical trial should continue with or without further enrollment of new subjects. The DSMB has the authority to halt the trial as needed.

v. Monitor data management activities. The DSMB may ask to review data relevant to quality control. The DSMB will review requests for interim analyses and approve, disapprove, require additional information, or defer decisions.

At a minimum, the DSMB will convene on an annual basis throughout the study. During the first year, the DSMB will convene after the first 4 months of participant recruitment. DSMB meetings will be held in-person or via video teleconference. The Board Chair and co-PIs will decide upon the format of the meetings. Additional meetings or telephone conferences will be held on the recommendation of the DSMB. The Board Chair and the co-PIs will determine meeting logistics based upon clinical urgency and the availability of DSMB members.

The co-PIs will submit reports to the DSMB one week prior to the scheduled meeting. These reports will include all reported data up and including 14 days prior to the reporting deadline (except for SAEs, which are to be reported within 24 hours of an event). For each meeting at which the study is to be considered or monitored, the co-PIs will present an overall progress statement. This brief statement will contain the assurance that the study investigators have considered the clinical trial's progress and that there is/is not evidence of safety issues that should be addressed by the DSMB.

Interim analyses will be conducted at each of these annual reviews to determine whether the emerging pattern of findings with respect to initial response or subsequent recurrence alters the risk-benefit ratio to the point that the study needs to be discontinued. Interim analyses will be planned in order to detect whether there are problems in recruitment, biases in attrition, other operational problems that affect the integrity of the study, and stronger treatment effects than anticipated that may lead to deliberation of prematurely discontinuing the trial.

The DSMB will be kept apprised of all SAE's and AE's on an ongoing basis and will serve as the final arbiters of whether individual patients should be removed from the protocol. Although research staff, under the supervision of the co-PIs and co-I, are empowered to take whatever immediate action is necessary to safeguard the welfare of individual patients, the DSMB will be called upon whenever possible to render judgments in the advent of a serious adverse event. We acknowledge that there may be rare instances where some emergent situation occurs that was unanticipated regarding the welfare of the participant. In these situations, the VA IRB or the DSMB may be contacted to help resolve the situation.

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