Protocol Title: Improving Function Through Primary Care Treatment of PTSD

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1. SPECIFIC AIMS

Posttraumatic stress disorder (PTSD) is a debilitating and costly mental health condition that heavily impacts VHA. RAND estimated a two-year cost of $4.0 to $6.2 billion US dollars for mental health issues from the current conflicts in Iraq and Afghanistan and estimated that providing evidence-based treatments for PTSD and depression could save about $86.2 million. Even modest reductions in PTSD severity have been related to increased probability of positive function outcomes. Prolonged Exposure (PE) therapy is an effective, first-line treatment for PTSD. However, despite successful PE dissemination efforts in VHA, most Veterans do not access effective psychotherapy for PTSD. Referral to specialty mental health remains the standard of care for PTSD and contributes to low rates of treatment access. The VHA has developed and implemented post- deployment health surveys that screen for PTSD in primary care (PC), but effective PC based PTSD psychotherapeutic interventions have not been established. To address this gap in PTSD care, the study investigators developed a 4-session PE for Primary Care (PE-PC) treatment protocol. A pilot study and randomized clinical trial in military facilities supports the efficacy of PE-PC for PTSD with half of those who received PE-PC no longer meeting PTSD diagnostic criteria. Since functional outcomes are critical to recovery-based mental health care, we intend to extend prior work to include assessing the impact of PE-PC on functioning. The intention of PE-PC is to provide quick access to effective intervention that can impact function in a setting where veterans with PTSD prefer to receive care and enhance referral to specialty mental health for those who need more. Providing a new access point for high quality PTSD care is of key relevance to Veteran function and mental health care and will allow more Veterans access to PTSD care consistent with a primary goal of the **National Research Action Plan (2013) and RR&D Research Priorities to translate clinical research findings into clinical veteran care.**

We will examine the effectiveness (function and symptoms) of PE-PC in VHA primary care mental health integration (PCMHI) clinics. We will randomize Veterans presenting in VA PC with chronic PTSD symptoms [PCL-5 ≥ 28] who meet minimal inclusion/exclusion criteria to receive PE-PC (four to six, 30-minute weekly sessions) or PCMHI treatment as usual (TAU). TAU will include the current standard of PTSD care in PCMHI (medication, referral to specialty mental health, etc.). The type of TAU used will reflect the current practice in PCMHI and will not be constrained in the study design. All care received will be closely monitored and recorded. All Veterans will complete baseline (week 0) and follow-up assessments at weeks 6 (post), 12, and 24. We will examine utilization at 24 weeks prior to randomization and 24 weeks after randomization. Project deliverables include effectiveness, acceptability, and utilization on PE-PC compared to PCMHI TAU. If effective, implementation strategies for PE-PC can be quickly developed and tested using the current dissemination infrastructure in place for the PE Therapy roll-out trainings in discussion with VA stakeholders.

Aim (1): Examine the effectiveness of PE-PC compared to PCMHI-TAU to improve functional outcomes [*Outcomes: functional impairment/quality of life* (WHODAS)].

Hypothesis 1: PE-PC will result in larger increases in *function* than PCMHI-TAU (Week 0 to Week 6) and these differences will be maintained at 12 and 24 weeks post-baseline.

Aim (2): Examine the effectiveness of PE-PC compared to PCMHI-TAU for treatment of PTSD [*Outcomes:* reductions in *PTSD severity* (Clinician Administered PTSD Scale (CAPS-5), PTSD Checklist- 5 (PCL-5) and *depression* (Patient Health Questionnaire-9 (PHQ-9)].

Hypothesis 2.1: PE-PC will result in larger reductions in *PTSD severity* (CAPS and PCL-5(15, 16)) than PCMHI-TAU (Week 0 to Week 6) and these differences will be maintained at 12 weeks and 24 weeks post-baseline.

Hypothesis 2.2: PE-PC will result in larger reductions in *depression* than PCMHI-TAU (Week 0 to Week 6) and these differences will be maintained at 12 weeks and 24 weeks post-baseline.

Hypothesis 2.3: PE-PC will result in a greater proportion of Veterans remitting from PTSD than PCMHI-TAU at week 6, 12, and 24.

Our exploratory aim is to assess potential moderators of improvements in function and PTSD symptoms, including combat experience severity and exposure to life events.

2. BACKGROUND AND SIGNIFICANCE

Posttraumatic Stress Disorder Prevalence, Function, and Impact. In a comprehensive study of mental health (MH) costs related to deployment for the conflicts in Afghanistan and Iraq, RAND reported an estimated two-year cost of $4.0 to $6.2 billion United States (US) dollars and further estimated that providing evidence-based treatments for posttraumatic stress disorder (PTSD) and depression could save an estimated $86.2 million. Impact on function is significant with research estimating annual employer costs of $651 per Veteran with PTSD and modest reductions in PTSD severity related to significant increases in function and probability of employment. Review of Veteran Affairs (VA) patients recently diagnosed with PTSD revealed that only 33% received minimally adequate PTSD care, either medication management or therapy. This despite a multi-site investigation within the VA that found treating PTSD symptoms with an evidence-based therapy (EBT) is an effective way to reduce suicidal ideation, a primary risk factor for suicide and two independent VA studies demonstrating that PTSD treatment is associated with a 50% annual cost reduction due to decreased need for long term MH utilization. Findings indicate a significant need for the continued development and implementation of efficient, accessible, and effective treatment resources. In recognition of these costs for our service members and society, an Executive Order Improving Access to Mental Health Services for Veterans, Service Members and Military Families was issued in 2012 and followed by the National Research Action Plan (NRAP) responding in 2013. NRAP is a cross government agency [National Institutes of Health (NIH), Veterans Health Administration (VHA), and Department of Defense (DOD) priority plan for MH research including PTSD. NRAP identified three priority areas in PTSD including, “Enhance current PTSD evidence-based treatment delivery to be briefer, more durable, and more efficacious” which precisely overlaps with the aims of current project. In addition, the proposal directly fits in Rehabilitation Research and Development (RR&D) Priority areas. Finally, in discussions with national leaders in PTSD treatment in VA and outside of VA, and in the development of PTSD clinical practice guidelines, provision of therapy-based interventions in Primary Care (PC) is a hot topic and recognized gap in service area.

Issues in the Delivery of PTSD Treatments. Prolonged Exposure (PE) therapy has emerged as an effective, first-line treatment for PTSD. A recent meta-analysis substantiated exposure-based therapy as achieving superior PTSD treatment outcomes compared to stress management, supportive, and psychodynamic therapies. In 2007, the Institute of Medicine's (IOM) Committee on Treatment of PTSD published the most comprehensive scientific review to date, concluding that only exposure-based psychotherapy had adequate evidence to support efficacy for PTSD treatments. Tuerk and colleagues demonstrated an average savings of $11,644 in the year after completion of PE for Veterans who completed compared to those who did not. Many studies support the efficacy of PE for PTSD even with very complex patient presentations. Nonetheless, PE is provided in specialty MH settings typically in 8 to 15 weekly, 90-minute, individual sessions. As such, individuals who are unwilling to go to specialty MH or who cannot accommodate the time required for PE are left with few effective treatment options. Veterans with PTSD may be overrepresented in this group. Issues of stigma associated with specialty MH are especially salient for Veterans, who often fear the social and employment consequences of having the label of PTSD. Veterans with PTSD are often reluctant to seek care in specialty MH and many will not accept a referral. Indeed, Possemato and colleagues reported that 67% of patients referred to specialty MH by a VA Primary Care Provider (PCP) either refused or expressed ambivalence. Subsequently, many are serviced solely in PC. Veterans seeking care are also balancing multiple issues following return from deployment— e.g., finding work, returning to school, family difficulties, etc. —that make time constraints for care especially difficult. Hoge and colleagues conducted a survey of service members after return from Iraq and Afghanistan and found that concern about the stigma of MH help-seeking was greatest among those most in need of help. Indeed, only 23% to 40% of those who screened positive for a MH issue had received any professional assistance, with only 13% to 27% receiving assistance from a MH professional in the past year. These issues are not restricted to Veterans of the current conflicts; Lu et al reported that Veterans older than age 30 were less likely to attend specialty MH visits following a positive screen for PTSD. Thus, time-intensive psychotherapy delivered in a setting that is clearly identified as MH is unlikely to reach a significant proportion of Veterans in need of assistance. As such, the population of Veterans with PTSD remains highly functionally impaired.

In addition to issues of Veterans accepting referral to specialty MH, obstacles in availability of PE and other evidenced based therapies (EBTs) in specialty MH continue. Hermes et al. reviewed VHA administrative data to examine the specialty MH care workload in 1997-2005 and 2005-2010. They found both an increase in Veterans seeking care (117%) and an increase in the intensity of care across Veteran eras (more visits per Veteran). Thus, providing a briefer effective therapeutic option may help ease the increased workload required for the increased VHA demand while also increasing the reach of evidenced based psychotherapy for PTSD. Finally, increased access to effective treatment in PC promises to increase function in those who receive care. The PE Training Program has trained over 1700 VA providers in PE. While many clinicians report finding the training and treatment to be highly effective with high intent to use following the training period, many are not treating a high volume of patients 6 months after completing consultation. The most commonly cited reason for seeing few patients include logistical barriers (e.g., no clinic grid time to implement PE, 8-15 weekly sessions). Given the efficacy of PE, it is imperative to find alternate solutions to overcome logistical barriers that prevent its reach to more Veterans. Because many Veterans seek care through PC, a model for PC allows for extension of reach for the current providers as well as training of a new group of VHA PTSD providers who may increase the reach of PE to Veterans.

Increasing Access through brief, PC-Based, PTSD-Focused Therapy. Starting in 2007, VHA initiated system-wide integration of MH providers in PC (care managers, therapists, and medication prescribers). In fiscal year (FY) 2014, there were an estimated 1 million visits to primary care mental health integration (PCMHI) providers completed by nearly 8% of the PC patient population. The initial focus of PCMHI has been to improve the quality of PC-based treatment of depression, anxiety, and problem drinking by increasing same-day access to services and use of evidence-based collaborative care protocols. There has been no national mandate to treat PTSD in PCMHI given the lack of empirical effectiveness data for treating PTSD in PC settings. This remains true even though PTSD is routinely screened for in PCMHI. National data shows that PTSD is diagnosed in 23.0% of VA PCMHI patients (making it the second most common diagnosis after depression). Indeed, among PC patients receiving a new MH diagnosis, receipt of a same day PCMHI contact increased the likelihood of another MH encounter within 90 days, suggesting that they had at least initiated follow-up contact. Among PC patients newly diagnosed with PTSD, same day contact with a PCMHI or specialty MH provider greatly increased likelihood of PTSD treatment initiation at 6 months and a year post diagnosis. With regard to psychotherapy, at 12 weeks post diagnosis 26% of those seen in just PC and roughly 66% of those with same day PCMHI or specialty MH had initiated PTSD treatment. While this increased initiation of treatment, we can further increase access to effective psychotherapy-based PTSD treatment by providing it in the PC setting without necessitating referral to specialty MH. PE-PC could address this gap and fill this identified need and increase the reach of evidence-based PTSD care. Indeed, the PC setting may be an ideal environment for delivery of PTSD treatment in terms of acceptability and reach to Veterans. The VHA has developed and implemented post-deployment health surveys that screen for PTSD in PC, increasing the likelihood that symptomatic individuals will be identified and assessed. Advanced access to services (e.g., appointments same-day or within several days) is prioritized in PCMHI settings and increases likelihood of subsequent visit attendance. The time-limited nature of MH services in PC may also better fit the busy lifestyle of many Veterans with PTSD by providing them an option to receive effective treatment with less transition in care and less time at the VHA facility. PCMHI providers on our research team for the ongoing military clinical trial and VA PCMHI providers who are currently piloting the intervention as program development report that many Veterans prefer to receive PTSD care in PC, as they perceive less stigma and quicker access to care. Of note, the intention of PE-PC is NOT to replace specialty MH evidence-based interventions for PTSD, but to increase reach of PE and provide a much larger population of Veterans with PTSD access to effective first line intervention. For some Veterans, this brief dose will produce symptom improvement or even remission. For others, it may increase acceptability of referral to a higher level of care. Ideally, it would be implemented in a stepped care model where increasing intensity of intervention is applied as a Veteran requires. Testing of a complete stepped care model is beyond the scope of this grant, but would be a reasonable next step once the intervention has been proven effective (see Stepped Care Model in Figure 1).

The current VA/DOD clinical practice guidelines for management of PTSD in PC limit intervention options to prescription of antidepressant medication, supportive counseling, and referral to specialty care. These narrow treatment options often result in a majority of those Veterans who screen positive never receiving the most effective available care. Of those receiving treatment, most were receiving medication only or medication in combination with supportive or psychodynamic treatment. Tanielian et al. found that the most commonly reported barrier to care was concern about medication side effects. In VHA, PCMHI providers most often provide supportive psychotherapy and support for medication adherence in sessions of 40 minutes average duration. While the DOD and VA have actively integrated behavioral health providers into their PC clinics, current behavioral interventions for PTSD in PC are often inconsistent with clinical practice guidelines and lack proven efficacy. In sum, reluctance to take

medication or engage in treatment in specialty MH and lack of effective PTSD treatment options in PC are preventing significant numbers of Veterans with PTSD from receiving adequate care. In a commentary on this state of affairs, Dr. Engel sums up the status of PC services for military personnel and Veterans with PTSD by stating: “To date, virtually all PTSD treatment studies have been completed in specialty settings; without proven PC therapies for PTSD, PC screening may not help those suffering from PTSD and may even do harm by detecting insoluble cases that compete for clinician time and resources….”.

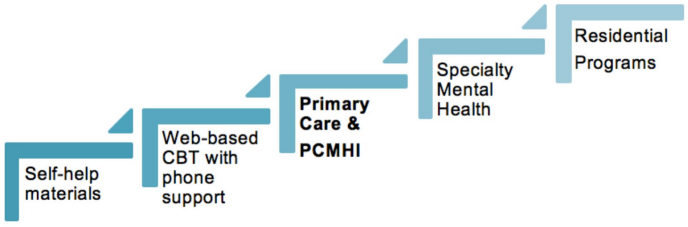
To enhance implementation and fit the intervention fully into the PCMHI clinic, the brief model of PE was required. While some PCMHI teams do allow for use of full protocol PE on occasion, the current staffing models in place for these teams would not allow for the full PE protocol within PC to meet the access needs to the Veterans presenting with PTSD. Further, quick access to brief treatment (typically 30-minute sessions and 6 or fewer sessions) is the hallmark of PCMHI and interventions that are more provider and patient intensive would not fit the model and result in delays and system issues. Developing a brief, PC intervention for PTSD from well-established, efficacious PTSD psychotherapy protocols is an advantageous alternate approach. VHA PCMHI would benefit from the availability of a proven brief psychotherapy for PTSD that is consistent with the PC model of intervention. Schnurr et al found no difference between enhanced case management specific to PTSD (including PTSD psychoeducation) and Treatment as Usual (TAU) in PC among a sample of 195 veterans, and subsequently advocated for the development of effective brief therapy interventions for PTSD that can be delivered in the PC environment. While additional studies using care management for PTSD in VA are ongoing, this approach has some drawbacks compared to PCMHI. Specifically, care management can be much more difficult to implement than collocating therapists because care managers involve greater systems redesign including registry management and supervisory infrastructure compared to collocation. A stepped care model of increasing intensity of intervention based on Veteran response and access to effective treatments, including psychotherapy, is key to providing just-in-time effective treatments. Such a model could represent an efficient use of MH provider expertise and allow the maximum access to effective PTSD psychotherapy. Thus, there is an urgent need to further develop, validate, and disseminate evidence-based psychotherapeutic treatments for PTSD in integrated PC.

To this end, we have developed the PE-PC protocol. While conducting the preliminary studies in military settings, Dr. Rauch and Dr. Cigrang have been contacted by many VHA and DOD providers, policy makers, national leaders and others interested in the program who want to use the protocol. Dr. Norman who directs the VA’s PTSD Consultation Program, also receives frequent questions from PCMHI and community providers asking for efficacious, brief, PTSD treatments for PC. In previous discussions, VA PC Quality Enhancement Research Initiative (QUERI) and QUERI PTSD Coalition leads (the Coalition is no longer in place but members remain active in discussions), including Dr. Mattheiu and Dr. Richie, have reported significant interest in this model as a good fit for an identified gap in VA care that can improve access to PTSD treatment for Veterans. Dr. Rauch has consulted with VHA policy leaders on program structure and study design during grant development for the current proposal. In addition, National Center for PTSD (NCPTSD) leaders, including Dr. Schnurr, Dr. Ruzek, and Dr. Eftekhari have consulted on design of the study and have been critical contributors to program development. Dr. Rauch and Cigrang are also in discussion with Air Force and other military behavioral health program leads to design dissemination and implementation plans.

Conceptual Model of PE-PC for PTSD in VHA. While the current study does not propose to test a full stepped care model of PTSD treatment in VHA due to budget constraints, discussion of how PE-PC could provide a step within such a model is critical to support this study’s innovation and importance.

First, stepped care as applied in VHA is intended to provide Veterans effective MH care at the earliest point of contact and at the lowest cost possible. This occurs by creating steps in care that begin even prior to the Veteran's contact with the VHA system, then move to the Veteran's first or most general contact with VHA in PC, and finally moving to specialty MH (outpatient and more intensive services). These models are believed to provide: 1) increased access to care for a larger number of Veterans, 2) reduced costs to the system through provision of briefer interventions first before moving to costlier interventions, and 3) increased Veteran care choice. Stepped care is consistent with Veteran–centered care in VHA as the patient can direct where they want to receive services for MH while still allowing access to quickly accelerated intensity of care if required due to Veteran non-response or preference. Existing research has provided some support for stepped care models when treating depression, anxiety, alcohol use disorders, and other issues showing increased efficiency and cost effectiveness. PE-PC would be an easily incorporated step in this model of care that is consistent with other available PTSD care steps (such as PE). Specifically, self-help and web-based interventions that include exposure components would be possible first and second steps prior to contact with VA, PE-PC the third step and initial contact with VA, PE in specialty MH, and then residential PE focused (or other Evidence based psychotherapy) programs. While the first couple steps in this model have not yet been fully developed or implemented to date, work is ongoing to create and test both patient directed self-help and web-based versions of effective PTSD care. Thus, the Veteran can proceed through a system with ease of transitions as therapeutic milieu remains the same across steps. The idea of this stepped care model is two- fold: 1) increasing levels of intensity of intervention as the patient does not fully respond to the lower level of care, and 2) providing access to effective interventions where Veterans are choosing to receive their MH care.

FIGURE 1. Proposed Stepped Care Model of PTSD Treatment in VHA



Preliminary Studies By Team Members. The team members have excellent working relationships with most having worked together as VA clinicians in addition to working together on many research projects. As Principal Investigator (PI), Dr. Rauch has significant experience with clinical trial design and conduct with over 18 years in PTSD treatment research. Her experience includes leading a current DOD funded, multi-site PTSD treatment trial in VA examining the efficacy and biological mechanisms of PTSD treatment and a completed VA Clinical Science Research & Development (CSRD) funded CDA-2 award PTSD translational treatment outcomes study. Dr. Rauch and Dr. Cigrang developed the PE-PC protocol with collaborative input from Dr. Foa and others. Dr. Cigrang led and Dr. Rauch is the Co- I on the recently completed first randomized clinical trial (RCT) of PE-PC with active duty service members. Several members have experience in clinical delivery of MH services in VA settings, including PCMHI, PTSD treatment, clinical trials, treatment development, biostatistics, and analysis of large VA administrative data sets. Dr. Ruzek and Dr. Eftekhari have led the VHA PE Training and have extensive expertise in health services implementation and policy. With their formal involvement on the current project, the NCPTSD is closely involved with planning of next steps for dissemination and implementation. Dr. Kara Zivin is an international expert in Veteran functional outcomes and Dr. Myra Kim is an international expert in clinical trials time series analysis. Drs. Kipling Bohnert and Acierno have separately published on relations between factors such as social support and PTSD treatment

services utilization and evaluating associations between receipt of VA PCMHI and other MH care. The recruitment site selected (Dr. Acierno, site lead) has a history of success in recruiting from PC for PTSD trials. This research team has all of the skill necessary to implement this trial. Formal and informal interactions among team members are frequent, further increasing coordination of efforts and the likelihood of successful completion of this trial. Their previous success working on projects as a team and independently along with their expertise supports the feasibility of our accomplishing this multisite trial with high quality.

Pilot Study, Randomized Trial in Military Setting, and VHA Providers with PE-PC. To address this gap in care for Veterans, the study investigators developed the 4-session PE-PC treatment protocol including a PCMHI manual and a patient guide. The protocol was developed based on the investigators' (JC, SR, EBF) clinical and research experience in PC and specialty MH, with review and editing input from nationally recognized experts on PTSD treatment. The protocol comprises those elements of PE that coincide with therapeutic efficacy through mechanistic studies conducted in Dr. Rauch's laboratory and elsewhere (see preliminary work). The protocol is intended for PCMHI providers (psychologists, social workers or psychiatric nurses). A pilot study supports its feasibility and initial effectiveness in military treatment facilities (MTFs). A majority of patients preferred PE-PC to no treatment, medication only, and referral to specialty MH. Indeed, in the pilot study where they were offered PE-PC or referral to specialty MH, none of service members chose the referral. Fifteen active-duty participants who received PE-PC had significantly reduced symptoms of PTSD at one-month post-treatment [$t = 3.8$, $p = .002$, $d = 1.1$] with half no longer meeting diagnostic criteria for PTSD. Additionally, depressive symptoms [$t(15) = 2.6$, $p = .02$, $d = 0.8$] and overall MH functioning improved significantly [$t = -3.4$, $p = .004$, $d = 1.0$] (33). These improvements were maintained at 6- and 12-month follow-up assessments (34). The strength of these pilot study findings is limited by the small sample size and the absence of a control condition.

Preliminary RCT (RCT; PI: Cigrang; Co-I: Rauch) results comparing PE-PC to minimal attention control (MAC, including continuation of any PC initiated treatment) found a significantly larger reduction in PTSD severity (measured by PTSD Checklist (PCL)) in PE-PC than MAC (between group $d = .55$, $p = .02$, $N = 67$) and significantly larger reductions in depression (measured by the PHQ-9). The changes were maintained to 6-month follow-up (full in press manuscript included in appendices; (35)). In addition, the pre-follow-up effect size for PE-PC on PCL was .99 and the Behavioral Health Measure (BHM- used for general function in Air Force Behavioral Health Operations) was .51. Drop from PE-PC was only 12% compared to the typical 20-40% drop in the standard PE protocol (36). Lee et al. showed metanalytic effect size of full PE varied between 1.54 and 2.57 depending on inclusion of cognitive restructuring (37). Of note, exclusions for the PE-PC studies were minimal and included only risk to self for others that required intervention or alcohol or substance use to a level that required intervention to ensure that it fits with the model of PCMHI. Thus, the intervention resulted in reductions that were maintained over time. Providers found the intervention easy to learn and use. Examination of function was not part of this RCT and is critical as a next step.

Outside of the study, Dr. Cigrang and Dr. Rauch have trained 10 VA providers and 5 DOD providers to date using a model of completion of PE training, reading the manual, and phone consultation on at least two PE-PC cases. While some VA PCMHI providers are currently using the protocol in practice in consultation with Drs. Cigrang and Rauch, no VA sites have tested the protocol. Providers using the protocol have found good patient acceptance and response. While Service Members and Veterans have many similarities, potential differences in motivation for treatment and other factors may influence the effectiveness of the protocol. As such, the current military data are encouraging but a trial in VHA

is warranted. Recently, Dr. Norman in her role as lead of the PTSD Consultation Program mentioned the PE-PC program on a national VHA PCMHI call. Following that call, Dr. Rauch received requests from over 80 PCMHI providers asking if they can get trained with the protocol to address a need they have in their PCMHI programs. Current resources cannot meet this demand, but Dr. Rauch has been in touch with VA leaders to discuss how to disseminate in the future if study results support. Dr. Pomerantz and Dr. Paula Schnurr are supporting Dr. Rauch in a design to pilot PE-PC Roll Out. A few additional PCMHI providers are now going through the training program with success. Clearly, more formal evaluation is warranted.

PTSD Therapy Initiation by Location of Services. As mentioned above and lead by Dr. Bohnert, many on our team recently conducted a study examining the prevalence of PTSD therapy initiation by location of services for a 30% random sample of all VHA PC patients with positive PTSD screens (n=21,427). Within one year of a positive PTSD screen, 53% of those in PC, 85% of those in PCMHI, and 84% of those in specialty MH started therapy. While provision of MH services same day shows a positive impact on initiation of treatment, there is still 15% in the same day group and 47% of those who receive standard PC services who have not sought PTSD treatment. Moreover, treatment in the PCMHI setting may be ideal in promoting continuation and further engagement in MH care for PC patients with PTSD. These numbers amount to thousands of Veterans in PC requiring PTSD care, highlighting the burden of PTSD in the PC setting and the gap in service provision that PE-PC may address potentially resulting in increased function.

PTSD and Effective Therapy Mechanisms. In addition to research to improve access to effective treatment, Dr. Rauch's other primary line of research is mechanisms of change in effective PTSD treatment. She has received funding and lead multiple translational treatment outcomes studies and published influential papers in this area. She is currently the lead on a large DOD PTSD translational Treatment Outcomes trial. Her expertise in this area was used throughout treatment development with focus on extinction processes and how to maximize effective exposure and change in trauma related cognitions that drive effective PTSD treatment.

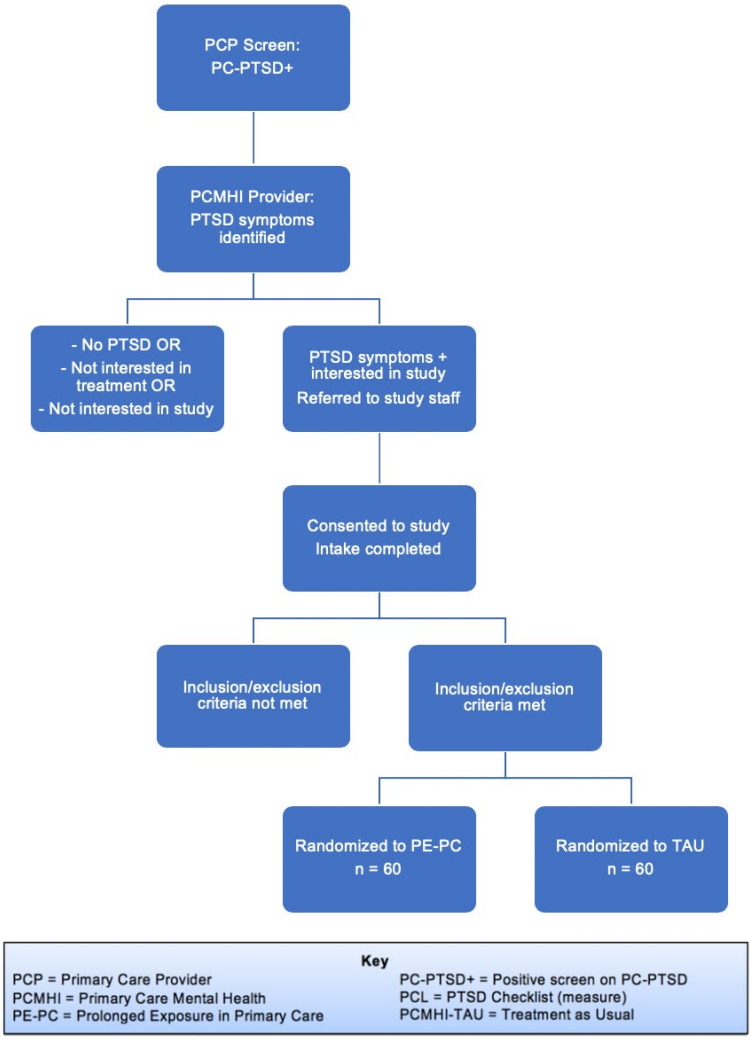
3. STUDY DESIGN

We will conduct a RCT to evaluate improvement in function with PE-PC compared to PCMHI-TAU among Veterans with PTSD symptoms in PC (see Figure 2 for RCT study flow). Veterans presenting in PC with chronic PTSD symptoms of at least 3 months duration who meet minimal inclusion/exclusion criteria will be randomly assigned to PE-PC (four to six, 30-minute in person or telehealth sessions) or PCMHI-TAU over 4-6 weeks. TAU will include the current standard of PTSD care in PCMHI (medication, referral to specialty MH, etc.). The type of TAU used will reflect the current practice in PCMHI and will not be constrained in the study design. All care received will be closely monitored and recorded. All Veterans will complete a baseline assessment (week 0) prior to randomization and follow-up assessments at weeks 6 (post), 12, and 24 post-baseline. Primary outcome will be the total score of World Health Organization Disability Assessment Schedule (WHODAS). Secondary outcomes will be Brief Inventory of Psychosocial Function (B- IPF), Clinician Administered PTSD Scale-5 (CAPS5) and Patient Health Questionnaire-9 (PHQ-9). If WHODAS shows floor or ceiling effect, the overall impairment score of the B-IPF will be used as a primary outcome measure.

To achieve these objectives, the study will have two phases. Phase one will include regulatory start-up and review, as well as study team training for coordinators, PCMHI providers, evaluators, and the rest of the PCMHI team. Dr. Cigrang and Rauch have an established training protocol and will augment with

training case recording ratings to establish competence prior to the therapist seeing randomized study patients. This process will be facilitated since the recruiting site already has many of the staff as providers. Phase two will be an RCT of functional outcomes for PE-PC compared to PCMHI-TAU in PC patients with PTSD. Veterans who present in VHA PC with PTSD symptoms who meet minimal inclusion criteria will be randomly assigned to receive PE-PC or PCMHI-TAU. Primary outcome will be function of WHODAS) assessed at baseline, week 6, week 12, and week 24. Utilization of MH and overall VHA services will also be examined. Secondary outcomes will include PTSD severity (CAPS5) and depressive symptoms. RCT outcomes will be examined using linear modeling.

FIGURE 2. Study Design



Treatment Conditions.

1. **<u>Experimental Condition: Prolonged Exposure for Primary Care (PE-PC).</u>** PE-PC will be provided by the PCMHI or research provider in four to six, 30-minute appointments scheduled approximately once a week over 4-6 weeks (to accommodate scheduling and missed appointments). PCMHI providers of PE-PC will include research clinicians, VA psychologists, social workers, and psychiatric nurses who have completed the PE training program and are on the IRB personnel list. Treatment will follow the PE-PC manual and Veteran workbook developed in the pilot

study, with minor modifications that will occur in our first 3 months of the study for use in VHA. Treatment content was drawn from the PE model. PE components include: imaginal exposure, in vivo exposure, psychoeducation, and processing. These four components are all included in PE-PC at a lower "dose" based on repetition or duration of session. Breathing was not included based on dismantling research showing no benefit and possible interference with outcome in other anxiety disorder, such as panic disorder. At the first 30-minute appointment, the PCMHI provider will review the "Confronting Uncomfortable Memories" activity workbook to be completed at home and brought back for use in subsequent appointments. The workbook asks the Veteran to write a detailed first-person narrative of the event associated with the greatest level of current distress, including recollection of personal thoughts, feelings, and physical reactions. Emotional processing questions are also included. In addition, the PCMHI provider will plan for in-vivo exposure activities between appointments. The Veteran will be instructed to complete the memory exposure for 30 minutes each day between appointments. At the second 30-minute appointment, the PCMHI provider will review the Veteran's exposures, problem-solve any implementation difficulties, and process the exercises. The Veteran will then read the narrative and his or her answers to the emotional processing questions out loud and they will process the exercise. Practice continues between sessions. This appointment format and content are repeated in the subsequent appointments. At the end of treatment, the provider and Veteran will review treatment progress assisted by results of the PCL-5 administered at baseline and during the final appointment. Possible outcomes of this collaborative review are to conclude treatment at four-six appointments or refer the Veteran to specialty MH care for more intensive treatment.

Provider Training. Drs. Cigrang, Rauch, and Eftekhari have an established training protocol and will augment this protocol with training case recording ratings to establish competence prior to therapists seeing randomized study patients. Dr. Eftekhari as the lead for the PE Therapy Roll Out has extensive experience in fidelity assessment and training to criterion. Dr. Cigrang has been leading the implementation of PE-PC in MTFs in his pilot study and randomized trial. He has years of experience training military providers in this model. Evident within this team is extensive experience working with trauma survivors and expertise in training providers in rapport building within this population as well as manualized therapy components. Dr. Foa is the developer of PE and will provide her expertise and input into the design and implementation of training. Dr. Rauch worked with Dr. Cigrang and Dr. Foa on the development of PE-PC protocol. She has been a PE trainer since 2000. Therapists will be trained to a minimal 85% competency on the PE-PC fidelity manual elements prior to seeing randomized cases. While this is a high bar, the brief intervention requires a high level of competence.

Evaluation of PE-PC Fidelity. Treatment fidelity will be assessed by review of a randomly selected 10% of recorded session tapes by a trained fidelity evaluator. In addition, training tapes will be rated for fidelity to ensure therapists are competent prior to their receiving randomized cases. Dr. Wangelin will lead weekly ongoing supervision for PE-PC therapists for the duration of the trial to further ensure consistent therapist competence and fidelity. Dr. Wangelin was trained in PE by Dr. Rauch and has extensive experience in delivery of and supervision in PE therapy, both in the context of RCTs and routine VA clinical settings.

2. **Control Condition: Treatment as Usual Condition.** Veterans assigned to PCMHI-TAU will receive standard PCMHI care for PTSD in PC that does not include any PTSD-specific therapy in PCMHI but may include referral for specialty care (including specialty MH), medication management or general supportive contact while awaiting referral. All PTSD care received during the study will be

collected and monitored as TAU. TAU will include the current standard of PTSD care in PCMHI (medication, referral to specialty MH, etc.). The type of TAU used will reflect the current practice in PCMHI and will not be constrained in the study design. All care will be recorded when a research assistant (RA) conducts a monthly standardized Computerized Patient Record System (CPRS) records review of all MH care received. Each encounter in CPRS will be noted for all randomized patients. Encounter current procedural terminology (CPT) codes, billing codes, duration or contacts will be tracked. No shows and cancellations will also be tracked. Finally, psychoactive medications will be tracked on a monthly basis as well, including medications prescribed, changes, and whether the prescriptions have been filled. While this is most relevant for the TAU condition, theses monthly treatment reviews will be conducted on all enrolled Veterans to ensure we can compare rates across groups and note compliance with study requirements.

4. INCLUSION AND EXCLUSION CRITERIA / STUDY POPULATION

Veterans presenting in PC with chronic PTSD symptoms (PCL-5S ≥ 28) of at least 3 months duration who meet minimal inclusion/exclusion criteria will be randomly assigned to PE-PC (four to six, 30-minute sessions) or PCMHI-TAU over 4-6 weeks. Non-veterans will not be included in the study. All Veterans will complete a baseline assessment prior to randomization and post- treatment and follow-up assessments at Weeks 6, 12, and 24 post-baseline. Interview assessments will be completed via phone or face-to-face depending on patient preference. Self-reports will be completed via paper and pencil or online via REDCap. Potential Veteran participants will be any era Veterans with PTSD symptoms and desire treatment for this issue. Age range will include 18 to 70. Ralph H. Johnson VAMC (CHS and surrounding CBOCs) PCMHI will conduct the study.

Inclusion Criteria:

1. Any era Veterans seeking care in VA PC for PTSD symptoms (PCL-5 ≥ 28).
2. Age 18-70.
3. English speaking.
4. Report significant impairment in function related to PTSD symptoms as noted on intake WHODAS.
5. Report that they want treatment for PTSD.

Exclusion Criteria:

1. Other primary clinical issue that would interfere with PTSD treatment.
2. Level of suicidal risk as determined by the Columbia Suicide Severity Rating Scale (C-SSRS) that requires intervention.
3. Severe cognitive impairment that, in the judgment of the investigator, makes it unlikely that the patient can adhere to the study regimen.
4. Psychosis or unmanaged bipolar disorder.
5. Moderate to severe substance use disorder in the past 8 weeks.
6. Patients who are currently receiving talk therapy for trauma- related symptoms. Inclusion/Exclusion criteria will initially be determined by the PCMHI provider at the first contact and will be confirmed by the Independent Evaluator (IE) at the Baseline assessment following consent.

Medication Stabilization. Participants meeting inclusion criteria will be asked to maintain medications at current dosages when medically appropriate. Participants who have not initiated new psychotropic prescription medications in the previous 2 weeks will complete the baseline assessment battery. Potential participants who have recently begun trials of psychotropic prescription medication will be required to wait 2 weeks prior to completing the baseline assessment battery to ensure medication stabilization, at which point the assessment battery will be administered (or re-administered if applicable). This re-administered battery will be used for pre-treatment data in analyses.

6. NUMBER OF SUBJECTS

To account for attrition during treatment (estimated at 15%), and loss to follow-up (estimated at 10%), and consented screen fails (estimated at 30%) we inflate the sample size to approximately 267 subjects to achieve a final sample size of approximately 120 subjects: 267 less 30% consented screen fails = 187; 187 less 15% attrition = 147; 147 less 10% loss to follow-up = 120 total participants completing all measures.

7. SETTING

Charleston VA Medical Center and surrounding CBOCs.

8. RECRUITMENT METHODS

Research staff will display flyers and posters at the PC clinic and other high-traffic areas. PC providers will be informed of the study and how to refer Veterans to the PCMHI provider for treatment of PTSD in the PC setting. The study PCMH provider will be available to referrals from the PC providers as per the standard PCMH procedures. Flyers will direct interested people to contact research staff for information or to inquire about the study with their PCP. Veterans who see flyers for this study and express an interest in being screened and treated for PTSD in PC will be directed to see the study PCMHI provider at one of their scheduled walk-in clinics. Provider guidelines for conducting the initial screening of referred patients and discussion of treatment options including study participation is included in the PE-PC Provider manual under heading “Contact 0.” In addition, Veterans are routinely screened for PTSD symptoms by their PC provider as per VHA requirements. Individuals who screen positive will be asked if they are interested in participating in research. If so, study staff will screen for PTSD symptoms and significant impairment in function from these symptoms, as well as a desire for treatment to address these symptoms. Potential participants will then meet with a member of the research team and have the study explained to them in a safe and private location with the opportunity to ask any questions. Research staff and the on-site PI will also deliver periodic briefings to PC providers to encourage assessment of PTSD symptoms and increase referrals to PCMHI. Research staff and investigators will seek opportunities to brief larger groups such as health fairs, staff meetings, etc.

Minority and Female Recruitment. Inclusion of minorities in PTSD research with Veterans is recognized as being of critical importance. Based on our previous and ongoing RHJ VAMC studies, we estimate that approximately 40% of the sample will be African Americans; 8-10% Hispanic, and 4-6% Asian American; 10% are expected to be women.

9. CONSENT PROCESS

Informed consent will be administered by approved individuals trained in human subjects regulations and informed consent procedures, with appropriate VAMC and University training certifications on file and up to date. These individuals will first be asked to read the treatment protocol, and will then attend a training for study personnel given by the PI and other team members on how to provide information about the study and obtain consent for participation in the study (i.e., informed consent), and will role play until the PI determines excellent competency in this area. This is so that each person collecting informed consent is familiar with all study aspects.

All patients will complete intake assessment with study staff. As reported in the inclusion/exclusion criteria, those patients who report clinical symptoms that suggest therapy for PTSD is not in their best interest at this time will be excluded from the study and alternate care provided as appropriate. Patients who appear to meet criteria for entry into the study will be informed of the study and if interested will review consent with study personnel (PI, study coordinator, or study evaluator). During review of consent, study staff will detail study procedures and ensure that patients understand. Study staff will ensure that potential participants understand the study and are interested and able to complete study procedures prior to signing consent. Patients will receive emergency contact information for use in case of acute exacerbation of symptoms in the consent document. Patients will be informed that they can withdraw from the study at any time and receive alternate care outside of the study in outpatient psychiatry. Patients who report imminent suicidality or intolerance for study procedures at any point during the protocol may be withdrawn from the study and receive alternate care as appropriate (i.e., inpatient hospitalization, treatment in outpatient psychiatry, etc.). Consent will be written, signed, and documented in CPRS.

Timing and Location of Informed Consent. After communicating with the PCMHI provider, potential Veterans will meet with a member of the research team and have the study explained to them in a safe and private location with the opportunity to ask any questions. Informed consent will be collected in research offices where potential candidates will be invited to learn about the study and that they will have a 50-50 chance, like a coin toss, to be assigned to either condition. Informed consent will be collected in a private, interruption free environment. Potential candidates will not be required to make a decision to participate at this initial contact, though that possibility will be available. If they wish to discuss participation with significant others, they will be encouraged to do so. If any potential volunteers are illiterate, the consent form will be verbally read and explained in the presence of a witness.

To reduce the burden of participating in research we may use VA approved teleconsent methods.

After discussing teleconsent procedures during screening, study staff will mail a paper consent form to the patient along with a self-addressed, stamped envelope and instructions on how to access the videoconference platform. At the scheduled day and time of consent, staff will contact patients via videoconference from a VA device (computer, laptop, tablet or phone) and begin the teleconsent session. During the teleconsent video session, project staff will explain the purpose of the research, the nature of the intervention, potential benefits and risks, the voluntary nature of participation, and the data collection procedures. The study staff and the consent form will make it clear that the individual's eligibility for services will not be affected by the decision to participate in the study. They will be informed that they are being asked to participate in a research study. They will be told the nature of the procedures, informed of risks associated with their participation, asked to read the consent form, and encouraged to ask questions or discuss any pertinent issues. If patients agree to consent, they will be asked to sign applicable areas of the consent/HIPAA form. Research staff will ask patients to hold up the signed forms to the camera so that the consenter may take a screen shot of the signature. These

images will be stored on the secure VA research network. Participants will then be asked to mail back the completed, signed consent form in the return envelope provided.

Per VA Directive 6609 instructions for mailing sensitive materials, study staff will attach a notice with the following language on on the front of any mailed consent paperwork, and instruct participants to attach it to the completed paperwork to be returned:

NOTICE!!!

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

To mitigate risk, study staff will instruct the participant to only sign those areas of the consent/HIPAA that must be in the participant's handwriting. Other areas of the forms (such as the name of the participant and date at the top of each page of the consent) will be completed by study staff once the paperwork is returned. Note that study staff expects this form of consent to be rare, and will only be offered to participants with unavoidable barriers that prevent them or study staff from consenting in person. Absolutely no study procedures will begin until study staff completes the consent process.

Randomization Procedures. A randomized block randomization schedule will be generated. Participants will be randomly assigned (1:1) to one of the two study conditions. After determining eligibility, enrolled patients will be randomized to treatment groups using a web-based computer generated randomization scheme. The randomization results then will be recorded on the master tracking table. Randomization will occur at the patient level. Once a patient is randomized and attends the first session, he or she will be entered into the study and included in the intent-to-treat analysis plan. The only members of the research team who will be aware of randomization assignment will be the project therapists, the research assistant and coordinator, and the statistical analyst in charge of randomization.

Compensation for Participation. All participants will receive $50 for the baseline assessment. After randomization, participants will receive $50 for the 6 week assessment, $50 for the 12 week assessment, and $50 for the 24 week assessment for a combined total of $200. The VA will either directly deposit the compensation into the participant's bank account, or if they do not have a bank account, participants can pick up their check from the agent cashier inside the Ralph H. Johnson VAMC. It can take up to 60 days to receive compensation.

10. DATA MANAGEMENT

Data Collection. All data will be in the form of interview and self-report questionnaires for psychological outcomes included with this document. Demographic data will be collected, but no uniquely identifying participant data will reside with, or be linked to actual responses to questionnaires. Patients will complete clinical interviews and self-report measures assessing emotional state and symptoms at intake (Baseline/Week0), week 6, week 12 and week 24. Week 0 measures are only re-administered if

time since baseline is over 4 weeks. All assessments will be audiotaped and study personnel will listen to a randomly selected 20% to ensure reliability over the course of the study. We will also collect administrative data to examine utilization of VA care the 6 months prior to randomization and 6 months following treatment.

The study assessments will be administered online through the Charleston VA's academic affiliate, Medical University of South Carolina (MUSC) REDCap™ (Research Electronic Data Capture) software. REDCap™ is a software toolset and workflow methodology for electronic collection and management of research clinical trial data. It provides secure, web-based flexible applications, including real time validation rules with automated data type and range checks at the time of entry. The underlying database is hosted in a secure data center at MUSC, a secure environment for data systems and servers on campus, and includes redundancy, failover capability, backups and extensive security checks. The system has several layers of protection including user/group account management, "Data Access Groups" which allow data to be entered by multiple groups in one database with segmented user rights for entered data, audit trails for all changes, queries and reports, and Secure Sockets Layer (SSL) encryption. The administration of study assessments will be conducted and monitored by the study staff through a password-protected REDCap account. Only research team members will have access to the data. Data will remain on REDCap and will be uploaded to the VA secure network until it is verified as de-identified per HIPAA regulation. All paper forms will be held in a locked filing cabinet in the recruiting Site PI's locked research offices. Study data will be collected by study ID only via REDCap. REDCap data will regularly be backed up and exported to the VA secure server. At the study's conclusion, the electronic crosswalk file linking study IDs with patient identifiers will be destroyed per MUSC and VA policy.

See Table 1 for a summary of the assessments and timing of administration. Assessments will be administered in person whenever possible. However, in order to accommodate participant schedules and/or instances in which a participant may have left the local area at the time of a follow up assessment, we may collect full or partial assessments in person or via phone or electronic data capture using a secure link to the HIPAA-compliant REDCap database. Reasonable efforts will be made to collect all data as described in this protocol, but we expect some participants may not be able to complete part or all of any given follow-up assessment.

Table 1. Research Materials.

Instrument	Wk 0	Wk 6	Wk 12	Wk 24
1. LEC	X			
2. CAPS5	X	X	X	X
3. WHODAS	X	X	X	X
4. C-SSRS	X	X	X	X
5. Health Interview		X	X	X
6. Demo & Military Service Characteristics	X			
7. B-IPF	X	X	X	X
8. PCL-5*	X	X	X	X
9. PHQ-9*	X	X	X	X
10. PTCI	X	X	X	X
11. CES	X			
12. CEQ	X	X	X	X

13. MINI (AUD/SUD modules only)	X			
14. COVID-19 Research Therapy Impact Questionnaire		X	X	X

*These measures will be administered for PE-PC treatment sessions as well as all assessment time points.

1. [Primary Outcome] World Health Organization Disability Assessment Schedule (WHODAS): The WHODAS is a brief assessment instrument (36-item version) used to assess health and disability across six domains of functioning: cognition, mobility, self-care, getting along, life activities and participation. The WHODAS has excellent psychometric properties, including high overall internal consistency (α = .96) and test- retest reliability (0.98).
2. Brief Inventory of Psychosocial Function (B-IPF): The B-IPF is a recently developed brief self- report of function. Since the measure is new, we will examine the measure's utility within this patient population and its sensitivity to show treatment change coincident with the well-established WHODAS.
3. Clinician Administered PTSD Scale-5 (CAPS5): CAPS is an interview measure of PTSD severity and the primary outcome measure for the study. Current PTSD will be assessed by IEs in relation to the trauma that is currently most upsetting. The CAPS5 has excellent psychometrics and requires about 45 minutes to complete. 20% of CAPS will be rated by a second rater to ensure reliability.
4. PTSD Checklist – Stressor-Specific Version (PCL-5): The PCL-5 is a 20-item self-report measure of PTSD severity in the past month with 4 subscales: Intrusion symptoms (items 1- 5); Avoidance symptoms (items 6-7); negative cognitions and mood symptoms (items 8-14) and Hyperarousal symptoms (items 15-20). Each item ranges from 0 (not at all) to 4 (extremely). Cut points and psychometrics are pulled from the most recent studies on the new PCL-5.
5. Patient Health Questionnaire – 9 (PHQ-9): The PHQ-9 is a 9 item, well-validated measure of depression and secondary outcome. The PHQ-9 assesses symptoms of major depression in the past two weeks from 0 (not at all) to 3 (nearly every day) and has excellent internal and test-retest reliability as well as construct and criterion validity. The PHQ-9 was demonstrated effective in detecting treatment changes in depression in PC settings.
6. Demographic & Military Service Characteristics: This form assesses standard demographics (ethnicity, sex, age) and military service information (e.g., rank).
7. Columbia-Suicide Severity Rating Scale (C-SSRS): C-SSRS will be used to assess past suicide ideation. The C-SSRS will be administered by an IE.
8. Posttraumatic Cognitions Inventory (PTCI): The Posttraumatic Cognitions Inventory (PTCI) is a 36-item self-report of negative thoughts about the self, negative thoughts about the world, and self-blame. The scale has good psychometrics and change in these thoughts has been related to change in PTSD symptoms with treatment.
9. Health Interview: The Health Interview includes items regarding general health, hospitalizations, current and past psychiatric medications, utilization of MH services, utilization of outpatient medical services, and caffeine and tobacco use. Items will be minimized to prevent redundancy with information pulled from medical record and other sources. After treatment, we also ask about changes in military status and important life events since the last interview.
10. Combat Experiences Scale: CES is a seven-item measure of combat exposure severity and enquires about the frequency of various combat experiences. Total scores range from 0 to 41. The CES has demonstrated good reliability and will characterize the sample and be considered as a potential moderator.
11. Life Events Checklist (LEC): LEC is a 17-item measure of self-reported potentially traumatic life events endorsed as happened to me, saw it happen to someone else, and heard about it. LEC (e.g.,

number of life- events) will be used to characterize the sample and be considered as a potential moderator.

12. Credibility and Expectancy Questionnaire (CEQ): The CEQ is a 6-item measure that was designed to assess treatment expectancy and rationale credibility of interventions examined clinical outcomes studies. The scale has demonstrated high internal consistency and test-retest reliability.
13. Mini-International Neuropsychiatric Interview (MINI): The MINI is a brief structured interview that assesses the criteria for DSM-V Axis I diagnoses. The MINI exhibits similar sensitivity and specificity to more time-intensive structured psychiatric interviews. The MINI will be used to screen for severe alcohol and/or substance use.
14. Mental health and medical services utilization: Receiving the PE-PC intervention may lead to a change in the health care utilization pattern for VA patients. Therefore, we will collect utilization data for all VA health services received by the study patients 24 weeks prior to study enrollment as well as the 24-week period of study enrollment. This will allow us to analyze both within-patient and between-patient changes in resource utilization patterns due to the intervention. We will use data on patient clinical status, health services use, and pharmacy use obtained from VA Decision Support Systems (DSS) Medical SAS Outpatient and Inpatient data, and the National Patient Care Database (NPCD). We will also use Non-VA Medical Care (formerly Fee Basis) files to incorporate financial and limited clinical information on covered care provided to VA patients outside of VA facilities. Outpatient visits will be defined as a clinical encounter with a VA MH clinician (e.g., psychologist, psychiatrist, social worker), PC provider (for MH brief intervention or psychiatric medications), VA tele- psychiatrist or tele-psychologist, or community (non-VA) MH provider. As a part of PCMHI care, each PE-PC sessions will be included as an outpatient encounter. Each PE-PC sessions will be recorded and considered as an outpatient encounter. We will examine the number of outpatient MH visits and the number of MH inpatient admissions. Medical services utilization will be defined as the number of PC outpatient visits, ED, and inpatient medical admissions during follow-up.
15. COVID-19 Research Therapy Impact Questionnaire: Ten-itme questionnaire which assesses impact of the COVID-19 pandemic on research participation and daily life.
16. Other Covariates. We will assess patient comorbidity burden during the 24 weeks prior to enrollment using the Charlson Comorbidity Index (CCI).

Evaluator Training. All evaluators will be blind to treatment condition and will be trained to criterion on CAPS5 prior to study start. Interviews will be recorded for use in recalibration and interrater reliability assessment. All IEs will complete bi-monthly recalibration assessment reviews for CAPS5.

Protection of Patient Confidentiality/Disposition of Data. Protection of participant confidentiality is an important component of subject protection. The main potential risk to subjects is violation of their confidentiality. We will take careful precautions to maintain confidentiality for all subjects, using procedures we have used with similar previous studies: The investigators and the research team will sign a confidentiality agreement with the Charleston VAMC that no identifying information of specific individuals will appear in any internal reports prepared for the VA or external documents (e.g., peer-reviewed publications, presentations). All study data related to psychological outcomes (i.e., the participant responses to questionnaires) and demographics will not have any unique identifying data commingled or attached in any way. There will be no linkage between a volunteer's identity and their responses. The master list of participants (again, not linked to any participant responses) will remain on the VA secure network in an encrypted folder, and the document itself will be encrypted with a password for an added measure of protection. All data will be stored in locked files or on encrypted computers in the PI's research offices.

When study results are published or presented, only aggregate reports of the results will be used and subjects' identity will not be revealed. All analyses will be conducted on de-identified data only. All paper documents will be securely stored in locked filing cabinets. Access to research records (paper and computerized) will be restricted to the project staff. Specifically, access to de-identified study data will be limited to named project investigators, the project coordinator, VAMC audit personnel, and MUSC IRB audit personnel. The list of participant names will be kept separate from all data and will be available only to on-site project staff.

Data will be maintained per VA protocols, and not less than two years prior to permanent storage. We will seek guidance regarding VA policies for maintenance terms of psychological data to determine the exact period of time that will elapse upon completion of which all study records will be stored permanently.

Data regarding sensitive information such as HIV status or illegal residency will not be collected. Rather, only demographic and psychological outcome data will be collected. However, State and Local authorities do require reporting of potentially suicidal or homicidal behavior. These exceptions to confidentiality will be clearly explained to volunteers during the informed consent process.

All investigators and project personnel have completed a certified program of instruction in the protection of human subjects in research, such as the VA website tutorial, NIH website tutorial or the University of Miami CITI course.

Data Protection. Data will be coded using an assigned number. Data collected on paper will be placed into locked cabinets in study offices at the Ralph H. Johnson or surrounding CBOC. Electronically captured data, as well as audio/video recordings, will be uploaded to a secure database. Every member of the research team will be trained and monitored about how to handle and protect both medical and research records. Furthermore, the research team strictly controls access to study data. These audio files will only be used for the purpose of fidelity to ensure the treatment is being delivered in accordance with the treatment manual for this study only. Upon study termination, and once the data has been analyzed to the fullest extent by the researchers, the audio and video files will be deleted from the secure server if in accordance with VA and MUSC policy.

Data Management Plan. Data will be coded using unique research identifications (IDs). All source documents will be labeled using the research ID and will not include identifying information. Data collected during assessment or treatment will be stored in a secure location (locked file cabinet in a locked room) and will be entered in the data management system. Raw study data will be manually entered from original and securely stored. Paper forms will be retained at the study site in secure storage per VA policy. Every member of the research team will be trained and monitored about how to handle and protect both medical and research records.

Data Sharing. Only data without identifiers will be shared between sites and all data will be retained on the VA network and REDCap.

Data and Safety Monitoring Board. The DSMB will be made up of three members: Primary Care provider, biostatistician, and a PTSD treatment researcher. They will meet a minimum of twice per year during the period of study recruitment to review data for quality, assess patient progress through the study, and examine adverse event data.

Data Analytic Plan. Baseline variables will be examined to compare PE-PC and PCMHI-TAU groups using t- tests and chi-square as appropriate. Baseline variables found to be potential confounders in the relationship between treatment and outcomes will be included as covariates in outcome analyses. Although patients will be randomized to intervention groups, other potential covariates are trauma era (Vietnam, Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF)/Operation New Dawn (OND), Persian Gulf), baseline function level, PTSD or depression severity, and demographic characteristics.

Hypothesis 1.1: PE-PC will result in larger increases in function than PCMHI-TAU (Week 0 to Week 6) and these differences will be maintained at 12 and 24 weeks post-baseline. Effectiveness will be defined as a group difference at 6 weeks, and maintenance will be defined as whether there is still a group difference at 12 and 24 weeks and whether gains relative to baseline have not been lost. To examine the effectiveness and maintenance of a brief PE-PC protocol compared to PCMHI-TAU alone, we will use a unified linear mixed-effects model with WHODAS total scores at 0, 6, 12 and 24 week as the dependent variable. Mixed-effects analyses do not require the assumption of homogeneity of variance in the treatment groups, permits flexible specification of the covariance matrix of the repeated measures and gives unbiased estimate with incomplete data assuming missing at random. The model will include each participant as random intercepts and will adjust for other potentially confounding patient characteristics identified in baseline analysis. Primary predictors will be PE-PC group indicator and time (either as a continuous variable in weeks or as indicators each for 6, 12 and 24 weeks), and interactions of treatment group by appropriate time variable. In this model, time can be modeled in a variety of ways, and a graphical exploration of the cross- sectional means of the outcome by treatment group at each assessment time will guide the decision. For example, if time shows a non-linear effect (e.g., lack of maintenance at 24 weeks), we can model time as categorical indicators for each assessment time and will include interaction terms of PE-PC group indicator by time indicator. Based on the model coefficients and contrasts of the coefficients, outcome at 6 (for effectiveness), 12 and 24 weeks (for maintenance) can be compared separately between groups, and a significant drop in function from 6 to 12 and from 6 to 24 weeks within PE-PC group can be tested for any loss in initial gain (another type of maintenance) if 6 week gain is found to be significant. If no significant loss of initial gain is seen (e.g., no significant difference across the three interaction effects), we will test for the time-averaged PE-PC effect during 6-24 weeks by dropping the interaction terms, and including post randomization time indicator and its interaction with PE-PC group indicator where the coefficient of the interaction term will be interpreted as the time-averaged PE-PC effect during period 6 to 24. Although not our main hypothesis, within each treatment group, improvement from baseline in outcome at each follow-up will also be determined based on the model. Residuals will be examined for ceiling or floor effects, and if ceiling or floor effect is evident, we will consider reanalyzing function using the dichotomized WHODAS total score (using hierarchical logistic regression model and recognizing that our study will likely not have adequate statistical power for H1 based on the dichotomized response), and will also repeat the primary analysis using the overall impairment score of the B-IPF.

The study will have both drop-outs and lost to follow-up. We will prepare a consort flow diagram to describe disposition of Veterans at each stage of the research. We expect about 10% loss at 6 weeks. This estimate may seem low but the period of follow-up is short and patients will be followed regardless of treatment completion to fully model response. Primary analytic cohort will be intent-to-treat. Every effort, including follow-up phone calls, will be made to collect follow-up data to reduce missingness to a minimum. We will also collect the reason for missing data such as “patient refusal” or “scheduling complication” to have a better understanding of the mechanisms of missingness. We will check for pattern of missingness, compare rate of missingness at each follow-up time and dropouts between

groups, and compare reasons for dropout between groups. We will also check if dropout depends on covariates and will include those covariates in the models described above; the analysis using linear mixed-effects model will give us an unbiased estimate assuming missing at random. When data are missing for items within scales, we will use recommended imputation procedures.

Hypothesis 2.1-2: PE-PC will result in larger reductions in PTSD severity (H2.1: CAPS and PCL-5 (49, 50)) and depression severity (H2.2) than PCMHI-TAU (Week 0 to Week 6), and these differences will be maintained at 12 weeks and 24 weeks post-baseline, larger reductions in depression than PCMHI-TAU (Week 0 to Week 6) and these differences will be maintained at 12 weeks and 24 weeks post-baseline. We will use a similar analytic approach as for Aim 1 using a linear mixed-effects regression model for each outcome measure with both baseline and all follow-up assessment data as the dependent variable. The model will include PE-PC group indicator, follow-up time indicators, and interactions of treatment group by follow-up time indicators. Statistically significant interaction terms with negative parameter estimates will provide evidence for significantly greater symptom reduction at each follow-up time in those randomized to PE-PC compared with PCMHI-TAU group. Similar to the analytic approach described for Aim 1, maintenance will also be assessed as drop at 24 weeks in improvement gained at 6 weeks, and this will be assessed for both PTSD and depression symptoms using appropriate contrasts based on the coefficients from the linear mixed-effects model.

Hypothesis 2.3: PE-PC will result in a greater proportion of Veterans remitting from PTSD than PCMHI-TAU at week 6, 12, and 24. Remission will be defined as CAPS5 below 20. We will report proportions remitted in each treatment group with confidence intervals. To compare remission between two treatment groups at 6, 12 and 24 weeks, we will use a generalized linear mixed-effects regression with logit link The dependent variable will be the repeatedly assessed remission at 6, 12 and 24 weeks, and the primary predictor will be the PE-PC group indicator and indicators for 12 week and for 24 week time, and the interactions of follow-up time indicators by treatment group can be used to test if the relative odds of remission between the two intervention groups differ across the follow-up times. The model will be adjusted for baseline function score and symptom severity as well as site.

For the exploratory aim to assess potential moderators of improvements in function and PTSD symptoms, potential moderators include combat experience severity, and exposure to life events. We will extend the primary mixed-effects model to include these measures and their interaction terms with PE-PC arm to understand and assess if the treatment effect differs by the level of these potential mediators. We will also extend the mixed-effects model by including PTCI as a time-dependent covariate to explore if increased self-efficacy, as assessed by PTCI, is associated with decreased function or symptom. Lastly, in the control (PCMHI-TAU) arm, we will include the use of specialty care during prior six weeks as a time- dependent covariate to see if it explains improvement in function or symptom in the control group. This exploration will provide us with an examination of whether contamination of participating study providers' referring control patients to specialty care might explain some of the improved function or symptom in control group, which might in turn have led to reduced effects of PE-PC.

Power Analysis. We propose to enroll 120 patients (60 per group) and considered power to detect a clinically meaningful difference in primary outcome at 6 months. The sample size is expected to have 80% power to detect a 0.54 standardized effect size with 0.05 two-sided tests for the outcome of WHODAS total score, assuming 10% lost- to-follow-up at the primary endpoint of 6 weeks post-baseline. This estimate of loss to follow-up may seem low but the period of follow-up is short and patients will be followed regardless of treatment completion to fully model response. The between-

group standardized effect size of 0.54 is approximately a medium effect size and is meaningful for both function and symptoms, and we consider this effect size minimally detectable with PE-PC based on our preliminary data. If no differential trends between arms is present over the 24 weeks follow-up time, we will be able to detect a smaller standardized effect size of 0.49 as a time-averaged between- arm difference with a 0.05 level two-sided test assuming within-person correlation of 0.6 and an overall 20% loss to follow-up by week 24 based on our preliminary data. For binary outcome of remission, we do not have preliminary data, but we note that we do not expect to have adequate power unless the between-arm difference in remission is very large; for example, the study will have 80% power to detect a difference of 69% vs. 42% with a 0.05 level two-sided test.

11. WITHDRAWAL OF SUBJECTS

Participation in the study may be discontinued by the principal investigator if continued participation is considered a danger to a participant's welfare. Reasons for discontinuation can include: 1) serious adverse event; 2) clinical worsening for any reason that is deemed to necessitate non-study psychological or psychiatric treatment; 3) exacerbation of PTSD, anxiety, or depressive symptoms that the participant cannot tolerate; or 4) discontinuation would be in the participant's best interest. Participants deemed candidates for discontinuation will be discussed with the therapist and the supervisor and will be brought to the attention of the PI for final decision.

Participants who are discontinued from the study for any reason will be scheduled for a final evaluation within one week and given appropriate treatment referrals. If participants are discontinued due to a serious adverse event, they will continue to be followed clinically by the therapist and/or member of the research staff until the adverse event is resolved or becomes stable. If participants are discontinued for a medical or psychiatric reason, they will be given the opportunity to either complete the balance of their therapy sessions or to receive a full course of all sessions after the condition has resolved or stabilized and the endpoint assessment has been completed. The reason the participants are discontinued from the study and any referrals made will be documented. Participants will be told they will be contacted for post-treatment assessments whether or not they complete the trial.

12. RISKS TO SUBJECTS

Foreseeable Risks. The risks for study participants include psychological risks and loss of confidentiality. Psychological risks may involve changes in symptom intensity or frequency, or feelings of stress while working through the treatment protocol or during study assessments. To minimize, all research staff interacting with patients will either be mental health staff or be supervised by VA investigators who are also experienced VA mental health clinicians. All research staff will be fully trained in VA research privacy and confidentiality policy as well as data management policy and practice within VA. Potential breaches in confidentiality of participants' protected health information are another potential patient risk. Our research team has considerable experience in maintaining the confidentiality of study datasets and will have procedures in place to ensure data confidentiality. All investigators and study staff have completed training in the requirements for handling protected health information as outlined by the Health Insurance Portability and Accountability Act (HIPPA).

Risk Management and Emergency Response. All risks will be minimized through full disclosure to patients of all procedures at the time of consent as well as during all sessions. Participants will be monitored closely by study staff and the study will be stopped if participants report a desire to pause or stop any procedure.

Suicidality will be closely monitored. When any concerns over suicide risk are raised, the provider will follow the VA clinical policy for management of risk. This includes completion of the Columbia Suicide Scale Severity Rating Scale (C-SSRS) at each symptom assessment and when significant concerns are raised. The provider will follow up with the VA Safety Plan for Reducing Suicide Risk for those who are positive for items 1 or 2. If the Veteran already has a Safety Plan, it will be reviewed at each additional visit where significant risk of self-harm is reported (items 3, 4, or 5 are endorsed). Participants deemed to be an acute risk for suicide based on the C-SRSS will be removed from the protocol and transferred to an appropriate level of clinical care (i.e., inpatient hospitalization).

The study team, including clinical care providers who are part of this team, will be available by page at any time to address any concerns or issues as they may arise for the participant. Participant privacy will be protected through ensuring they are willing to complete procedures (interviews, forms, etc.) in the laboratory or private office. In addition, participant confidentiality will be protected through storing consent and other information with PHI in a separate location from study data. Only the research staff will have access to the study data via secure website. Throughout the study, IRB and HIPAA guidelines will be followed to ensure privacy of patient data. As soon as patients sign the informed consent, they will be assigned a unique study ID number. A file matching participants' identifying information and their study ID will be stored in a password protected file on a secure server. The crosswalk file containing patient identifiers will remain on the secure VA network in a password protected study file. No physical copies of this ID list will be maintained. Confidentiality will be protected by restricting access to the research data to authorized study personnel only. Data will be stored on dedicated servers and in study folders that can only be accessed by specified study personnel. A minimum necessary rule for access to private information will be used to allow a limited number of research staff to have access to patient identifiable data. The identifiers will be maintained as long as data collection activities are ongoing, and up to 5 years following the completion of the study in compliance with VA policy. The training of all study staff will include VA training on privacy, confidentiality, and all VA polices related to data management and security. All research procedures will be reviewed and signed off according to the IRB procedures for protection of human subjects in research.

Study data will be collected by study ID only via REDCap. When needed for analysis, REDCap data will be securely exported to the VA secure server. At the study's conclusion, the electronic crosswalk file linking study IDs with patient identifiers will be destroyed. All research data will be presented in aggregate form only. The study assessments will be administered online through the Charleston VA's university affiliate MUSC REDCap™ (Research Electronic Data Capture) software. REDCap™ is a secure, web-based application designed to support data capture for research studies. The administration of study assessments will be conducted and monitored by the study staff through a password-protected REDCap account. Only research team members will have access to the data. Data will remain on REDCap and on the VA secure network until it is verified as de-identified per HIPAA regulation. All paper forms will be held in a locked filing cabinet in locked research offices.

13. POTENTIAL BENEFITS

Veterans will receive treatment for PTSD and reductions in symptoms are expected for both PE-PC and PCMH- TAU based on previous study results. In addition, the knowledge gained from the study may directly lead to improvement in the care they receive. Risk/Benefit comparison: The risks are minimal and few beyond that expected with the Standard of Care for PTSD treatment and the benefits are significant given the potential information we can learn about a PC based PTSD treatment.

Importance of Knowledge to be Gained. The knowledge gained will help us to understand the effectiveness and acceptability of a brief version of an effective PTSD treatment for PC. If effective, this intervention will greatly increase the reach of effective PTSD interventions and increase both access and Veteran choice for PTSD treatment. This knowledge may serve to improve the care of other Veterans and non-Veterans with PTSD and improve dissemination efforts.