

Peer Social Support During In Vivo Exposure for PTSD: A Program to Address Dropout from Prolonged Exposure

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Study Protocol and Statistical Analysis Plan

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Principal Investigator:

Wendy A. Muzzy, MRA, MLIS
Principal Investigator, MUSC
Research Instructor

Co-Principal Investigator:

Ronald E. Acierno, Ph.D.
Co-Principal Investigator, Ralph H. Johnson VA Medical Center
Research Health Scientist, VAMC

1.0. PROTOCOL TITLE

Peer Social Support During In Vivo Exposure for PTSD: A Program to Address Dropout from Prolonged Exposure

2.0. ABSTRACT

Post-traumatic Stress Disorder (PTSD) is a significant problem for Veterans and Active Duty personnel. Although effective treatments for PTSD exist (e.g., Prolonged Exposure, PE; Cognitive Processing Therapy; CPT) and have, at great expense, been widely disseminated by VA and DoD, *over of those 30% who start treatment subsequently drop out prior to completion*. In our first preliminary study we addressed published survey data from Veterans indicating that dropout was related to logistical barriers such as travel time, cost, and stigma associated with care from mental health settings, and so overcame these barriers by delivering treatment via home-based telehealth. *However, dropout remained virtually unchanged*. Veterans in our study who dropped out of treatment, including that delivered via home based telehealth, were interviewed and a majority responded that they would (a) consider returning to treatment and (b) would be more likely to complete treatment *if a peer who had themselves successfully completed treatment were available to help them with exposure homework*. In keeping with this feedback, our second preliminary study examined the feasibility of using peers to (a) encourage Veterans who had dropped out of PE to return to treatment and (b) offer support during in vivo (real world) exposure therapy homework assignments (e.g., as they would during 'gym workouts'). Preliminary findings indicate that such an approach is feasible, and potentially effective, in that over 50% of dropouts from PE agreed to return to treatment and 30% of these actually did so immediately. We will evaluate whether the opportunity to receive social support during in vivo exposure therapy homework from Veterans who themselves have successfully completed PE (i.e., the therapeutic equivalent of an exposure therapy 'workout buddy') is effective in *reversing* dropout and *improving* PTSD outcomes; and, secondarily, to determine whether this program is particularly helpful for those receiving PE via telemedicine.

3.0. OBJECTIVES/SPECIFIC AIMS/RESEARCH QUESTIONS

This study seeks to address the problem of dropout from evidence-based treatment for PTSD. We will evaluate whether the opportunity to receive social support *during in vivo exposure therapy* assignments from Veterans who themselves have successfully completed PE (i.e., the therapeutic equivalent of an exposure therapy 'workout buddy') is effective in **reversing** dropout and **improving** PTSD outcomes. To achieve this objective, we will use a between group, randomized controlled repeated measures design comparing PE+Exposure Workout Buddy vs. PE+Peer General Support (i.e., the standard VA Peer Support program methods involving a peer who does NOT engage in any support during *in vivo* homework) to evaluate the 'PE+Exposure Workout Buddy' adjunctive therapy component in terms of its ability to increase likelihood that Veterans will (a) return to and complete treatment & (b) evince reduced PTSD symptomatology at post-treatment and 3- & 6-month follow-up. An exploratory objective is to determine whether the hypothesized differential advantage of the workout buddy program is more pronounced for Veterans who receive PE via telehealth vs. receiving PE in person, as data from Preliminary Study #1 indicate that this may be the case.

Objective 1a. To determine relative differences in treatment dose obtained, measured in terms of the number of sessions completed upon return to treatment, in response to 'PE+Exposure Workout Buddy' vs. 'PE+Peer General Support' in individuals who have previously dropped out of evidence based treatment for PTSD.

Hypothesis 1a. Treatment 'dose', measured in terms of number of sessions completed post randomization, will be greater for participants in the PE+Exposure Workout Buddy condition compared to PE+Peer General Support.

Objective 1b. (Exploratory) To determine if differences are amplified or diminished with respect to prior identified risk factors such as age, race, gender, substance use, or social support.

Hypothesis 1b. This enhanced dose/adherence will be observed for the PE+Exposure Workout Buddy condition within each risk factor previously associated with dropout (i.e., age, race, gender, and substance use).

Objective 2a. To determine differential effectiveness, measured in terms of therapeutic gains over time on measures of PTSD symptomatology, of 'PE+Exposure Workout Buddy' vs. 'PE+Peer General Support' with therapy dropouts in (i.e., 'treatment outcome').

Hypothesis 2a. Treatment 'outcome', measured in terms of PTSD symptom reduction scores, will be significantly more improved for participants in the PE+Exposure Workout Buddy relative to PE+Peer General Support condition at each assessment point (post treatment, 3-month and 6-month follow-up).

Objective 2b. (Exploratory) To determine if differences are amplified or diminished with respect to race, gender, age, substance use, or social support.

Hypothesis 2b. Relatively greater gains in the PE+Exposure Workout Buddy condition will be observed across race, gender, and age groups at post treatment, 3-month and 6-month follow-up. Self reported levels of social support will mediate gains.

Objective 3. (Exploratory) To determine the presence of an initial signal of differential dose and effectiveness of ‘PE+Exposure Workout Buddy’ when delivered in traditional in person (face to face) vs. telehealth formats. *(Note, the parameters by which this objective will be achieved are naturalistic insofar as this variable is not subject to randomization because participants who had received telehealth PE (about half of our clinic population) or in person PE prior to dropout (and thus prior to this study) will continue to receive treatment in the same modality upon randomization to either condition).*

4.0. MILITARY RELEVANCE

Maintaining force strength is of paramount importance during times of conflict. Up to 24% of OEF/OIF Veterans meet criteria for PTSD and 35% report significant PTSD symptoms. These disorders manifest while these individuals are still DoD service members, and as such, current characteristics of combat, and subsequent shortcomings in current treatments for PTSD, particularly with respect to treatment retention, significantly affect force strength. Our best treatments can return personnel to nearly pre-trauma performance at about 65-75% effectiveness. A large proportion of those who fail to respond to treatment do so not because treatment was ineffective, but because they were unable or unwilling to complete treatment. That is, they dropped out of treatment prior to completion. If the present intervention, which builds upon the teamwork and leadership skills implicit in military training, is effective in retaining individuals in treatment who otherwise would drop out, then we may well be able to dramatically cut the dropout rate from our most effective class of treatments, and thus significantly enhance our ability to sustain force strength.

Moreover, from the perspective of future costs in terms of human suffering and mental health care, effective intervention is key. This is because PTSD does not seem to remit over time, and each year that effective intervention is delayed is characterized by functional impairment, depression, and increased health care costs to the Veteran, the DoD and the VA. These improvements to dropout prevention from evidence based therapy for PTSD, in addition to reducing effects of untreated PTSD, will contribute directly to the health and well being of service members, enhancing mission readiness and preventing unnecessary force depletion and care expenses. As such, military significance of this project is great, both in terms of directly enhancing force readiness, as well as reducing economic and human suffering costs borne by the DoD and its members.

5.0. BACKGROUND AND SIGNIFICANCE

We will evaluate whether the opportunity to receive social support during in vivo exposure therapy homework from Veterans who themselves have successfully completed Prolonged Exposure (PE) (i.e., the therapeutic equivalent of an exposure therapy ‘workout buddy’) is effective in (a) reversing PE dropout and (b) improving PTSD outcomes in a sample of Veterans who have previously dropped out of PE. This will be accomplished by comparing ‘PE+Exposure Workout Buddy’ to ‘PE+Peer General Support’ who does NOT engage in any support during in vivo homework, the treatment typically offered Veterans who drop out from evidence based PTSD care, in a Randomized Controlled Trial.

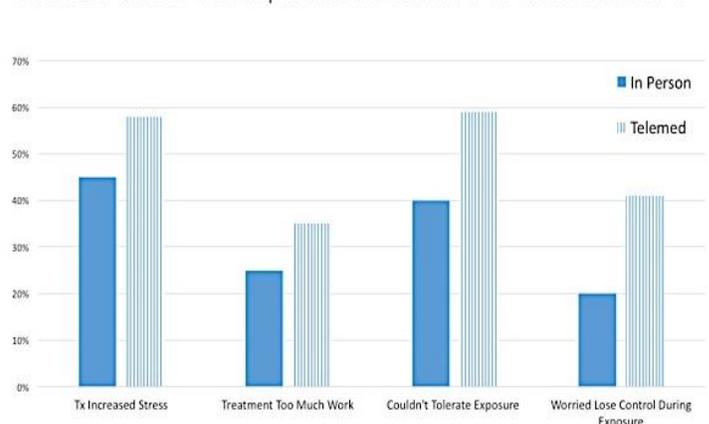
- Post-traumatic Stress Disorder (PTSD) is a significant problem for Veterans and Active Duty personnel.
- Effective Treatments (e.g., Prolonged Exposure, PE; Cognitive Processing Therapy, CPT) exist and have, at great expense, been disseminated by the Departments of Veterans Affairs (VA) and Defense (DoD).
- Despite treatment effectiveness, over 30% of those who are identified, referred, and successfully access evidence based psychotherapy for PTSD treatment drop out prematurely.
- In a prior DoD study we addressed findings that dropout is related to logistical barriers such as travel time, cost, and stigma associated with care from clinic-based settings by delivering treatment via home telehealth. However, dropout remained virtually unchanged at 26%.
- In Preliminary Study #1, Veterans who dropped out of treatment, including that delivered via home telehealth, were surveyed and half responded in the affirmative to a statement that they would have had a better likelihood of completing treatment if a peer who had completed treatment were available to help them with exposure homework. In Preliminary Study #2, 52% of a clinic sample of Veterans who dropped out of PE indicated that they “would be interested in trying exposure therapy for PTSD a second time if they could do so with the assistance of an exposure workout buddy.”
- To serve these dropouts from PE therapy, we developed and began initial feasibility testing of the ‘PE+Exposure Workout Buddy’ program in which Veterans who have recently completed PE and no longer meet criteria for the disorder meet patients at exposure sites in the community to offer support during exposure.
- The present study is to use a randomized controlled repeated measures design to test the hypotheses that the in vivo ‘exposure workout buddy’ adjunctive component to PE will increase the likelihood that Veterans who have dropped out of PE will (a) return and complete treatment and (b) evince reduced PTSD symptomatology relative to a general support peer.

Preliminary Studies:

Preliminary Study #1: Dropout from Exposure Therapy for PTSD in Telehealth Vs. In Person Treatment (See Hernandez-Tejada et al., 2014 for a full description of Preliminary Study 1).

All participants met DSM-IV criteria for PTSD. Of the 258 participants in our DoD study who were randomized to either telehealth or in person conditions and received at least one exposure therapy treatment session, 69 (26.5%) withdrew from treatment. All were male, 27.7% were Vietnam Veterans, 27.7% Persian Gulf Veterans, and 44.7% were OEF/OIF Veterans, with no significant differences in theatre in terms of treatment medium. Surprisingly, rate of dropout from telehealth (28.7%, n = 35) was not significantly different from that of in person treatment (25.0%, n = 34) ($\chi^2=0.45$, p = 0.30). Forty-seven of the 69 (68.1%) treatment dropouts (27 telehealth; 20 in person) agreed to provide data regarding reasons for dropping out of treatment. Age ranged from 21-70 years, and there were no significant differences in terms of age, education, employment, marital status or baseline symptom severity between conditions.

Problems with In Vivo Exposure: In Person PE Vs Telemedicine PE



Results: Considering travel logistics and their relationship to dropout, ANOVA indicated a significant (and entirely expected) difference between in person and telehealth participants, with in person participants reporting more problems with bad weather, parking, transportation, and work/family obligations ($\bar{x} = 22.5$) compared to telehealth ($\bar{x} = 19.6$) ($F_{(1,45)} = 5.20, p = 0.027$). No other significant differences were noted for any other factor, including Treatment Demands (in person $\bar{x} = 16.2$, vs. telehealth $\bar{x} = 15.6$; $F_{(1,45)} = 0.34, p = .560$); Perceived Relevance of Treatment (in person $\bar{x} = 20.9$, vs. telehealth $\bar{x} = 20.7$; $F_{(1,45)} = 0.01, p = 0.906$), or Relationship with Therapist (in person $\bar{x} = 9.1$; telehealth $\bar{x} = 9.0$; $F_{(1,45)} = 0.04, p = 0.847$). However, when Veterans who dropped out of exposure based treatment were asked specifically about their experiences during imaginal and in vivo exposure homework, differences between in person and telehealth groups did emerge, and both groups reported significant difficulty, *particularly with in vivo exposure trials*. Specifically, while only 20% of in person and 31% of telehealth based treatment dropouts reported they “could not tolerate thinking about the trauma”, 40% of in person and 58% of telehealth treatment dropouts reported they “could not tolerate assignments to go out in public.” Moreover, 20% of in person but 41% of telehealth based Veterans reported that they “worried about losing control during exposures.” (See graphical illustration of these data.) Overall, these preliminary data suggest that dropouts had problems with in vivo/situational exposure homework, and that participants in the telehealth condition who dropped out of treatment were having more difficulty with specific aspects of exposure therapy compared to those receiving exposure therapy in person. Along these lines, Hernandez-Tejada, et al (2014) noted that when treating PTSD in general, and particularly when offering exposure based treatments via telehealth, interpersonal support offered during exposure trials by other Veterans could be helpful. Actually, this “exposure homework workout buddy” idea was not so much our own as it was a direct and repeated approach *suggested by the Veterans who had dropped out of treatment* and who were interviewed regarding their reasons for doing so. Specifically, when we contacted aforementioned Veterans, approximately 50% indicated that they would have been likely to remain in treatment had they the support of another Veteran during in vivo exposure homework (see Preliminary Study #2). While novel in its application to PTSD treatment, peer assistance is a technique currently used successfully by other health and mental health specialties (e.g., *cancer*: see Meyer et al., 2015; *serious mental illness*: see Corrigan et al., 2014)).

Preliminary Study #2: Offering Treatment Dropouts a Chance to Return to PE Treatment with an Exposure Therapy Workout Buddy: Feasibility of Recruitment of Patients and Peers

The Veterans’ suggestion to combine the beneficial aspects of social support with the effectiveness of exposure based treatments for PTSD (e.g., one Veteran described it as ‘the best of supportive group counseling with the best of PTSD treatment’) represented no less than a “Eureka” moment for our research team, insofar as we recognized that combining peer support with exposure therapy might directly impact, in a cost effective manner, the treatment retention issue confronting patients of VA and DoD. Indeed, variations on this theme are evident in-group delivery of exposure therapy for PTSD (see Smith, Porter, Messina, Beyer, Defever, Foa, & Rauch, 2015). Our approach to leveraging peer support is directly in line with the recent VA/DoD implementation of “Peer Support Programs” (Money et al., 2011) across the country. We predict that this support will help to address dropout associated with exposure therapy, particularly when delivered via telehealth, an increasingly prevalent modality in VA/DoD.

Toward this end, we developed the ‘*PE+Exposure Workout Buddy*’ program, explained at length in the *Treatments* section below. It is important to note that Veterans serving as ‘workout buddies’ are not

replacing therapists or performing therapy; rather they are simply providing support and encouragement akin to that derived from others during group psychotherapy, such as during group delivered PE (Smith et al., 2015). PE Workout buddies are Veterans who have completed PE and no longer meet criteria for the disorder, and who have volunteered to meet Veterans engaged in PE (in this case, Veterans who have dropped out of PE, but returned at the offer of a PE workout buddy) at their situational exposure homework site to offer encouragement and support in addressing a previously discussed and agreed upon exposure hierarchy item. Our preliminary qualitative interviews with Veterans in this program indicate that this enhances PE treatment in two ways: first, Veterans appear more likely to attempt in vivo exercises if they know a fellow Veteran is waiting at the site of their exposure homework (i.e., when they 'don't feel like' doing the exposure homework, they are nonetheless more likely to leave their house and drive to Wal-Mart for the exposure assignment if they know the Workout Buddy is there waiting). Second, they are more likely to complete the exposure homework item if they have the encouragement and support of another Veteran during the process.

For this preliminary feasibility study, we re-contacted 82 Veterans who had dropped out of exposure based treatment for PTSD (either from two ongoing treatment outcome studies or from VA PTSD clinic services) and offered them the opportunity to attempt PE again, this time with the assistance of an 'exposure therapy workout buddy'. We also asked clinicians to contact individuals who had successfully completed treatment and no longer met criteria for PTSD who might be interested in serving as a PE Workout Buddy.

Feasibility Results: Fully 52% (n=43) of the 82 dropouts indicated that they "would be interested in trying exposure therapy for PTSD a second time if they could do so with the assistance of an exposure workout buddy," and 30% (13) of these immediately completed informed consent to re-initiate treatment. Given the strong support from Veterans who had dropped out of treatment for the peer support solution, we next attempted to identify peers who might be good candidates to serve in this capacity (e.g., offer to meet patients at in vivo homework locations to offer support and encouragement). Thirteen potential exposure therapy workout buddies were contacted, 85% (11) agreed to enroll in the program as a volunteer, and 8 have completed the brief training, indicating that recruitment of peers does not appear problematic. Note each peer agreed to accompany up to 4 different patients over a 6-month period, and the future dissemination potential of the program from the perspective of Veterans volunteering to help other Veterans appears strong.

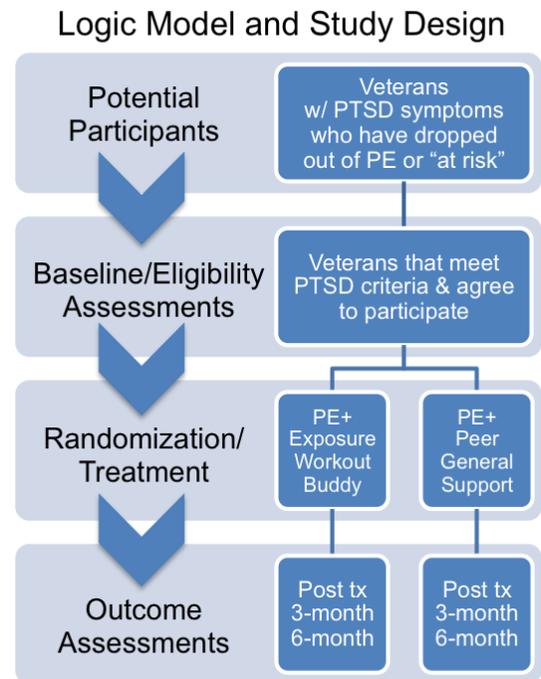
As noted above, 13 Veterans who dropped out of treatment agreed to return to PE with an exposure workout buddy and 12 have contributed baseline pilot study data. Two Veterans have already completed PE treatment with the social support assistance of a workout buddy and the remaining 11 are in the process of treatment, engaging in standard PE with their therapist, and meeting peers in the community to complete in vivo exposure therapy assignments. We polled participants (both those who had completed the PE+Workout Buddy program, and those who were in the midst of treatment) as to their satisfaction and general experiences. 100% reported that they were either "very satisfied" or "extremely satisfied with the program. All participants reported that they would strongly recommend the program to a friend. 100% of participants agreed with the statement that "the peer was dependable," and 100% indicated in the affirmative to the statement "the peer addressed important issues in their health care." Zero adverse events were reported, by patients, peers, or therapists. *Thus, the feasibility of the program, measured in terms of the successful resolution of the logistics of peer recruitment, peer training, peer and patient coordination with each other and with the therapist for in vivo exposure therapy homework assignment meetings, and most importantly, patient willingness to return to treatment (52%), overall appears very strongly supported.*

6.0. RESEARCH DESIGN

Using a 2-arm, randomized controlled trial with repeated measures at baseline, post treatment, and 3- & 6-month follow-up we will compare PE+Peer General Support to PE+Exposure Workout Buddy intervention, in which peers who have successfully completed PE PTSD treatment and no longer meet PTSD symptom criteria are paired with Veterans who have recently dropped out of treatment to help the latter complete exposure homework assignments to determine if this pairing affects the following 2 primary endpoints: (1) treatment dose/completion and (2) treatment outcome. Exploratory aims are to determine if the program results in (3) differential treatment completion and outcomes for telehealth vs. in person-delivered PE treatment, as preliminary data indicate that the exposure workout buddy adjunctive component may be more relevant to Veterans receiving PE via telehealth, a treatment delivery format of increasing prevalence in VA and DoD settings. See Logic Model Diagram for study design illustration. **NOTE:** (a) whereas telehealth delivered

psychotherapy involves a therapist at one site and a patient at a second, all exposure workout buddies will be located near patients and workout buddy interactions with participants take place in person, in the community (b) Peers will NOT be conducting any therapy or substituting for the therapist, who will continue to deliver treatment. Rather, workout buddies will simply be meeting patients at community exposure assignment sites such as the parking lot of Wal-Mart, & accompanying them during exposure, which typically simply involves staying in a location until anxiety subsides. General support peers follow the VA standard Peer Support model and roles. General support peers make telephone contact with Veterans, and meet with them informally in person when Veterans arrive for their appointments. They will remind and encourage participants to attend appointments, check up on them once per week via telephone and ask about current treatment progress, life stresses, opportunities, problems and successes, and offer general support and advice regarding VA programs.

Veterans (participants and peers) with PTSD will be recruited from the Charleston VA Medical Center catchment area. Participants will have been assigned to exposure therapy for PTSD and either started treatment, or dropped out before treatment; peers will have successfully completed exposure therapy for PTSD. Note, Charleston VA Medical Center treatment providers for PTSD all offer both in person and telemedicine based treatment, and equal numbers of patients in both treatment modalities will be enrolled (approximately 10 and 10). Those eligible to participate will also include Veterans who are identified as “at-risk” of dropping out, Veterans who are uncomfortable completing in vivo exposure activities, and those who may have PTSD symptoms, but at the sub-threshold level. Participants will receive 8-12 weekly sessions of exposure therapy treatment with assistance of a PE Peer, who will meet them at least once per week for in vivo exposure therapy assignments, for 3-4 weeks at the beginning of treatment. All participants and peers will be consented. Participants will be assessed at



baseline, post-treatment, and 3- & 6-month follow-up. Participants who demonstrate clinically significant and adequate gains prior to the 8th session will be eligible for early termination if they achieve a 24-point reduction from baseline PCL on two consecutive measurements. This criterion has been established in prior exposure therapy trials to guard against the potential of misclassifying early responders as treatment dropouts.

Peer Selection. Therapists will be asked if they have any patients who have completed treatment and did very well, both overall and with in vivo exposure therapy components. Therapists are directed to contact these patients, inform them about the peer program, and ask them if they would like Dr. Acierno, a VA clinician and researcher, to discuss the program further, outline the nature of expectations, including confidentiality, and research characteristics, and schedule a 2 hour training. Thus, initial nominations for the program are based on therapist impressions of successful candidates AFTER they have completed treatment. As such, the therapists know candidates' strengths. Peers, who undergo training and subsequently indicate their willingness to serve as a peer will have their names added to our database, which is housed on a secure VA server. Note, peers will be trained that confidentiality is key, and we will explain confidentiality in the same way as is expected when individuals participate in supportive group therapy. That is, this is a supportive intervention of peers as is found in supportive group therapy, with which Veterans are very familiar, and that all discussions held during such interactions are confidential, as is all information, including identifying information, learned about another participant, through participating in this project.

7.0. RESEARCH PLAN

7.1. Selection of Subjects

7.1.1. Subject Populations. Participants will be 100 Veterans of OEF, OIF, OND, Persian Gulf, or Vietnam conflicts with PTSD; peers will be 50 Veterans from the same conflicts. As the Charleston VA also serves Active Duty personnel, a small proportion of participants will be from this subgroup. Participants will be male or female, aged 18 years and above, who have dropped out of evidence based treatment for PTSD (PE) after completing 1-7 sessions and *who still have PTSD* (in the literature on PE, the first session is sometimes session 0, during which treatment components, including exposure, are explained. A significant proportion of dropout occurs at this point, and thus we intend to include these individuals as participants to maintain relevance of study findings).

7.1.2. Source of Research Material. Self-report scales, session attendance data, and interviews will be used to evaluate clinical and process outcome at pre-treatment, immediate post-treatment, 3-month, and 6-month follow-up; with the exception of session attendance, process outcomes will be evaluated at post-treatment and 3- & 6-months. These timeframes have been selected because they correspond to assessment structures of prior studies of PTSD, and because they represent critical timing points for the diagnosis. In pilot testing of the assessment battery, 95 minutes was the average time of completion; however, all participants will nevertheless be informed that the assessment will require approximately 2 hours and will be allowed to take a break from assessment at the approximate 30-minute point. All assessments will be audiotaped and study personnel will listen to a randomly selected 20% to ensure reliability over the course of the study.

In addition to these regular battery-based comprehensive assessments, the PCL-5 and Patient Health Questionnaire will be repeated every week, before the session begins, to allow a more in-depth evaluation of the longitudinal trajectory of PTSD symptom severity over the active treatment period. Moreover, in instances of premature study exit, participants will be asked to complete a PCL-5 and Patient Health Questionnaire at that point in time in order to obtain more valid exit point data. As in our prior studies, the more complete PCL-5 trajectory will be used to facilitate multiple imputation of missing data for treatment dropouts for related outcomes.

Clinical Outcomes. The following interview and self-report measures have been widely used in the clinical evaluation of adults with PTSD, and will be used in the present study. They will be collected at baseline, post-treatment, and 3- & 6-month follow-ups. The PCL-5 and Patient Health Questionnaire are also collected every other week during treatment.

1. Clinician Administered PTSD Scale-5 (CAPS-5; Weathers et al., 2013): PTSD diagnoses will be ascertained using the CAPS-5, considered the gold standard in PTSD assessment. The CAPS is a 30-item, structured interview that corresponds to the DSM-5 criteria for PTSD. For each diagnostic item, standardized questions and probes are provided. Questions focus on symptom presence, the onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning and improvement in symptoms.
2. Mini International Neuropsychiatric Interview 7.0 (MINI 7.0): The MINI is a standardized structured interview used to assess psychiatric diagnoses according to the DSM-5. The MINI is similar in sensitivity, specificity, and inter-rater reliability to more lengthy diagnostic interviews, such as the SCID (Sheehan et al., 1998). Major Depression, Panic, and Substance Dependence diagnoses will be evaluated via this structured interview.
3. PTSD Checklist-5 (PCL-5; Blevins, Weathers et al., 2015): The PCL-5 is a new version of the PCL, among the most commonly used self report measures of PTSD symptoms and intensity. The PCL-5 is structured to correspond to the DSM-5 PTSD criteria. The 20-items are scored on a 0-4 Likert scale for each symptom corresponding to “Not at all” to “Extremely”. Total scores range from 0 to 80. Initial psychometric data are encouraging. With college student samples, Blevin et al found PCL-5 scores exhibited strong internal consistency ($\alpha = .94$), test-retest reliability ($r = .82$), and convergent ($r_s = .74$ to $.85$) and discriminant ($r_s = .31$ to $.60$) validity. With Veteran samples, Bovin et al (2015) found that the PCL-5 had good internal consistency ($\alpha = .96$) and test-retest reliability ($r = .84$). Moreover, signal detection analyses using CAPS-5 indicated a cutoff score of 31-33 on the PCL-5 optimally categorized PTSD diagnosis.
4. Selected scales of the Deployment Risk and Resiliency Inventory (DRRI; King, King, & Vogt, 2003). The DRRI is collection of self-report measures assessing 14 key deployment-related risk and resilience factors with demonstrated implications for Veterans' long-term health.
5. Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, & Williams, 2001): The Patient Health Questionnaire -9 is widely used, well-validated measure of depression severity with high internal consistency (alpha $.83$ to $.92$; Cameron, Crawford, et al, 2008), and is correlated strongly with other depression measures (Kroenke et al., 2001). Its 9 items assess affective and somatic symptoms and correspond to diagnostic criteria for MDD.
6. Veterans RAND 12-Item Health Survey (VR-12; Kazis, 2000, 2004). The VR-12 is a valid and reliable instrument to measure quality of life and/or functional status in veterans. It will be used to track changes in general mental and physical health functioning (i.e., functional status or general health functioning).

7. Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman & Kupfer, 1989): The PSQI assesses the quality and patterns of sleep. It differentiates “poor” from “good” sleep by measuring seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month.
8. Brief Inventory of Psychosocial Functioning (B-IPF; Marx et al., 2013). The Brief Inventory of Psychosocial Functioning (Marx et al. 2013) is a 7-item self-report instrument measuring respondents’ level of functioning in seven life domains: romantic relationship, relationship with children, family relationships, friendships and socializing, work, training and education, and activities of daily living. Respondents indicate the degree to which they had trouble in the last 30 days in each area on a 7-point scale ranging from “0 = Not at all” to “6 = Very much.”

Additional Co-variables. In addition to demographic and baseline levels of the clinical outcome variables that will serve as adjustment co-variables and putative effect modification variables in proposed analyses, we will assess the level of combat exposure of participants at baseline using the Combat Exposure Scale (CES; Keane, Fairbank, Caddell, Zimering, Taylor, & Mora, 1989) because combat exposure intensity has been related to treatment response in past studies, including our own (see Price, Gros, Strachan, Ruggiero, & Acierno, 2013). The CES is a 7-item self-report measure that assesses wartime stressors experienced by combatants. Items are rated on a 5-point frequency (1 = no or never to 5 = more than 50 times), 5-point duration (1 = never to 5 = more than 6 months), 4-point frequency (1 = no to 4 = more than 12 times) or 4-point degree of loss (1 = no one to 4 = more than 50%) scale. Respondents are asked to respond based on their exposure to various combat situations, such as firing rounds at the enemy and being on dangerous duty. The total CES score (ranging from 0 to 41) is calculated by using a sum of weighted scores, which can be classified into 1 of 5 categories of combat exposure ranging from "light" to "heavy." Further, we will administer the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993), a 10-item screening questionnaire with three questions on the amount and frequency of drinking, 3 questions about alcohol dependence, and 4 questions about problems caused by alcohol. The Drug Abuse Screening Test (DAST-10; Skinner, 1982) will also be administered to all participants. The instrument contains 10 items that serve as a brief clinical screening and treatment evaluation for substance use. The DAST-10 items are structure in a “yes/no” format. Staff will gather a prior treatment history at baseline via the “Previous PTSD Treatment Information” measure, an eleven-item questionnaire detailing previous treatment history in the VA. Finally, current treatment will be assessed using the “Existing Treatment” questionnaire, which queries about current participation in research studies, treatment received, and medication information.

Process Outcomes. During data collection of clinical outcomes, we will also examine the following measures immediately post-treatment, and at 3- & 6-month follow-up (only treatment credibility will be assessed at mid-treatment, after treatment has been explained):

1. Session Attendance, Session Frequency Limits, Definition of Treatment Completion, and Study Attrition This is, of course, a primary outcome variable related to AIM 1a and 1b of this study, and examines impact of the exposure workout buddy program on ‘treatment dose’ delivered, measured both in terms of total new treatment sessions attended and % completing treatment in each group. To this end, we will keep careful records of session attendance and study dropout. A treatment dropout will be defined as any patient who does not complete a total of at least 10 new sessions of treatment OR who leaves treatment prior to a reduction of PCL-5 Scores below

the clinical cutoff posted by the VA National Center for PTSD of 33 obtained in two consecutive PCL-5 scores. A treatment completer will be defined as completing 10 or more sessions; or when no additional treatment is needed due to treatment gains, two consecutive PCL-5 scores below 33 will reflect these gains. The overall limit to number of sessions in either group will be 15 (so as to prevent outliers in session frequency affecting 'dose' between group analyses). It is expected that most patients will occasionally miss a session or fail to complete their homework assignments. These will not be considered dropouts; patients will be allowed to make-up sessions as long as they re-enter treatment within a 4 week period. Patients who miss all 4-treatment sessions during a 4-week period will be considered dropouts (i.e., if a patient, during treatment, does not attend the next session within 4 weeks of the last session completed, they will be considered a dropout). *Note MEASUREMENT ISSUE: participants who completed a greater number of sessions prior to original dropout may be expected to achieve clinical outcome goals in fewer sessions than those completing one or two sessions prior to dropout. Hence, the 'dose' variable of Aim 1a and b, measured in terms of overall number of new sessions, is confounded by 'prior dose', or the number of treatment sessions received prior to study initiation. Therefore, in addition to number of new sessions completed, we will also assess number of treatment completions, measured in terms of completing at least 10 sessions or achieving clinical gains on the PCL-5 reflected by scores below 33 on two consecutive PCL-5 measurements as specified above.*

2. Treatment Credibility (Peers after 1st patient experience; Participants prior to session 2) To assess differences in outcome expectancy, treatment credibility scales developed by Borkovec and Nau (1972) will be used. Four of the questions will be used for this study, with 10-point Likert scales. These include questions regarding how logical treatment seems, how confident they are about treatment, and expectations of success.
3. Treatment Adherence Treatments in both groups will require patients to carry out "homework assignments." These forms will be collected and monitored each week during treatment. The percentage of returned, completed forms will be computed as an indicator of adherence to homework assignments.
4. Modified Charleston Psychiatric Outpatient Satisfaction Scale (CPOSS-VA; Frueh et al., 2002): (Patient, following their last treatment session) Patient satisfaction is an important treatment outcome variable, closely associated with clinical outcomes (Druss et al., 1999). This measure also asks about specific components of the workout buddy program (e.g., the quality of communication, ease of use, willingness to use treatment) in order to allow in depth analysis of potential causes of differences in workout buddy effectiveness for in person vs. telehealth delivered PE (AIM 3). The CPOSS-VA is 16-item measure, with a Likert scale response format, based on a general measure of patient satisfaction (Pellegrin et al., 2001). In a sample of Veterans preliminary data showed excellent reliability ($\alpha = .96$) and good convergent validity with anchors (Frueh et al., 2002).
5. Barriers to Therapy Scale (Modified) Assesses logistic, interpersonal and anxiety based barriers.
6. COVID-19 Research Therapy Impact Scale; Ten item questionnaire which assesses the impact of the COVID-19 pandemic on research participation and daily life.

Preliminary Economic Outcomes. Workout-buddy Related Capital Costs: Incremental costs of the intervention relative to the comparator are the relevant costs for decision making, thus preliminary estimates for this new program will be obtained here. These costs primarily include workout buddy training time and materials, and extra therapist time required to coordinate exposure hierarchy logistics

for initial meetings, as well as therapist time to collect feedback regarding exposure trials from peers in between sessions.

7.1.3. Inclusion and Exclusion Criteria. Participants will be 100 Veterans of OEF, OIF, OND, Persian Gulf, or Vietnam conflicts with PTSD; peers will be 50 Veterans from the same conflicts. Participants will be male or female, aged 18 years and above, who have dropped out of evidence based treatment for PTSD (PE) after completing 1-7 sessions and who still have PTSD (in the literature on PE, the first session is sometimes session 0, during which treatment components, including exposure, are explained. A significant proportion of dropout occurs at this point, and thus we intend to include these individuals as participants to maintain relevance of study findings). Participants who are considered “at risk” of dropping out will also be included; this is defined as having failed to complete 3 sessions of exposure therapy within any 6-week period, verbally indicating major anxiety about exposure activities, and/or populations identified at higher risk of dropping out of exposure therapy.

Actively psychotic or demented persons and individuals with both suicidal ideation and clear intent will be excluded; however, to maximize generalization of results, other forms of psychopathology will not be a basis for exclusion. All structured interviews will be audiotaped to calculate inter-rater reliability on a randomly selected 20%. Based on clinic data and data from our two prior DoD/VA PE treatment outcome studies, we will have satisfactory minority representation: 35-50% African American, 8-10% Hispanic, and 4-6% Asian American; 10% are expected to be women.

Participant Eligibility Criteria. Study inclusion and exclusion criteria are as follows:

Inclusion Criteria:

1. Adult male or female over the age of 18 that has served, or is currently serving, in the military.
2. Either diagnosis of PTSD as determined by a Clinician Administered PTSD Scale for DSM-5 (CAPS-5) clinical interview or CAPS-5 severity ≥ 25 , and a PCL-5 score of ≥ 25 .
3. Attempted PE treatment in the past, but did not complete treatment (defined as dropping out from treatment or refusal to engage in in vivo exposure assignments) OR identified as “at-risk” of dropping out of current exposure therapy treatment (defined as failure to complete 3 sessions of therapy within any 6 week period, verbally indicating that they are not comfortable with the exposure activities, and/or populations identified at higher risk of dropping out of exposure therapy)

Exclusion Criteria:

1. Active psychosis or dementia at screening.
2. Suicidal ideation with clear intent.
3. Concurrent enrollment in another clinical trial for PTSD or depression.

Peer Eligibility Criteria. Study inclusion and exclusion criteria are as follows:

Inclusion Criteria:

1. Adult male or female over the age of 18 that has served, or is currently serving, in the military.

2. Successful completion of exposure therapy treatment in the past and willingness to act as peer in the program.
3. PCL-5 score of 32 or lower.

Exclusion Criteria:

1. Active psychosis or dementia at screening.
2. Suicidal ideation with clear intent.

Medication Stabilization. Participants meeting inclusion criteria will be asked to maintain medications at current dosages when medically appropriate. Participants who have not initiated new prescription medications in the previous 4 weeks will complete the baseline assessment battery. However, potential participants who have recently begun trials of prescription medication will be required to wait 4 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.

7.1.4. Recruitment Process. The Ralph H. Johnson Veterans Affairs Medical Center (RHJ VAMC) catchment area is home to a very large number of PTSD treatment outcome studies, as well as to several studies on suicide, depression, and anxiety. Moreover, the nationally known PTSD Clinic conducts only evidence-based psychotherapy, with an emphasis on PE, and was the first to offer this treatment via telehealth and via home based telehealth. As such, all RHJ VAMC Mental Health Clinic staff are cross trained in research referral to study staff for all potential participants, and research staff are housed alongside clinic staff. More relevant to the present application, as there are a large number of providers conducting PE in both clinic and research treatment settings (19 current full time PE providers each providing both in person and home based telehealth PE), the number of PE dropouts meeting inclusion criteria and available for recruitment to this study is quite large (our current roster of dropouts just in the past 6 months is over 250, representing about 30% of cases).

We have obtained (for our PE+Exposure Workout Buddy pilot study) and currently maintain Institutional Review Board (IRB) and Veterans Affairs Research and Development (VA RD) approval for clinical research staff to approach all Veterans who have dropped out of PE with an invitation to participate in the pilot feasibility workout buddy study. Each week, representatives from each of the 8 research teams attend a case staffing with all PTSD Clinical Team (PCT) clinicians to review new cases, their appropriateness for research participation, study cross referral, and to review dropouts from PE. Names will be obtained at these staffings for re-contact by research clinicians. As we are the only study including PE dropouts, recruitment via this pathway has been strong for the pilot study, and will continue to be significant for this project.

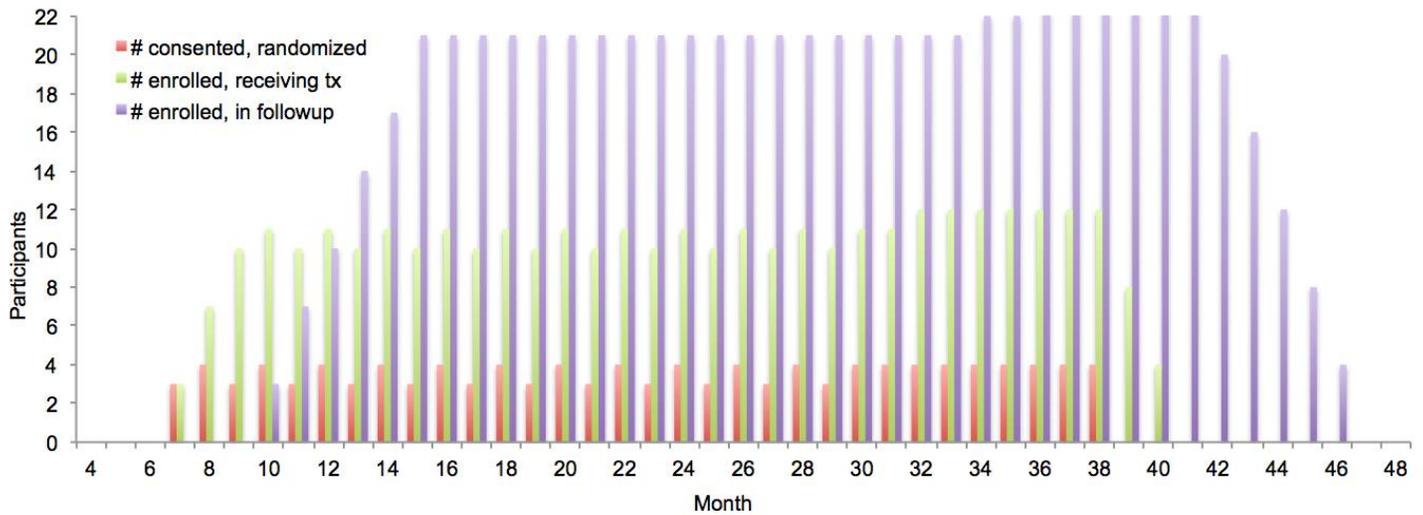
Related to the question of whether or not participants meeting inclusion criteria are available, is whether those available participants will actually agree to return to treatment. Our pilot study data, described above, indicate that 52% of those who have dropped out of PE agree to return with the assistance of an exposure workout buddy, and 30% of these sign consents to do so immediately. The willingness of Veteran PE dropouts to consider returning to treatment upon hearing of the workout buddy program was extremely encouraging.

In addition to direct contact with recent dropouts from therapy provided by the 19 active clinicians, we will list this study among those listed in our consortium institution's (Medical University of South Carolina) "active research projects" web page and weekly newspaper research recruitment sections. Third, primary care and mental health providers of Veterans for whom PTSD is suspected may also refer to the study. In the latter scenario, the Veteran will be informed that researchers at the VA are evaluating a treatment to help those who have dropped out of PE and the Veteran will be asked for permission to release contact information only to study personnel. If this verbal consent is given and a referral made, project staff will contact potential candidates. Participants who do not meet inclusion criteria will nonetheless be offered services through the RHJ VAMC Mental Health service. Our final recruitment strategy will be to run a series of advertisements in relevant local newspapers.

Recruitment Steps: Potential participants will be contacted by study staff when recruitment derives from the weekly PTSD clinic staff meetings. Potential participants who respond to brochures, or who are referred by other providers will be directed to the study coordinator for face-to-face explanation of the study in a private treatment room at either the RHJ VAMC, CBOC, or MUSC leased space where they will review informed consent and have all questions answered. If for any reason the study coordinator and patient cannot meet face-to-face, participants may be contacted via telephone to discuss study parameters. After informed consent has been collected, the initial assessment interview will be scheduled within 7 days by our trained interviewers (who are NOT the therapists for the study). All potential participants will first complete the entire assessment interview either face-to-face, via telephone, or via Tandberg if the assessor and patient are located at two different CBOCs; immediately after the assessment interview, participants meeting inclusion and exclusion criteria will be randomized to condition by the study coordinator using the randomization protocol designed by the study statistician and informed of this outcome. Participants will be told to expect a telephone call from their counselor to start treatment within 7 days. Additionally, we will mail letters of invitation to patients from Dr. Acierno's former research studies who dropped out of treatment, as well as Veterans who began treatment in the PCT clinic but did not finish.

Recruitment and Enrollment Targets: See the chart on next page for the anticipated participant recruitment.

Minority and Female Recruitment. Inclusion of minorities in PTSD research with Veterans is recognized as being of critical importance (Frueh et al., 1998). Based on our previous and ongoing RHJ VAMC studies (Acierno, 2015), 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.



7.1.5. 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 1-day 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.

Timing and Location of Informed Consent. Informed consent will be collected in research offices (VA and MUSC offices) where potential candidates (both Peers and patients, as both will provide data) 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 PE+Exposure Workout Buddy or PE+Peer General Support conditions. 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 consentor 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 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.

7.1.6. Subject Screening Procedures. Following consent, a baseline assessment and screening will take place with an interviewer or study coordinator to determine the participant's eligibility. The initial consent and screening will require 2-3 hours. For individuals that do not meet study inclusion criteria, the study staff will assist with coordinating appropriate care outside of the study. Individuals meeting the study inclusion and exclusion criteria will be randomized into one of the two treatment groups.

7.1.7. Compensation for Participation. All participants will receive \$30 for the baseline assessment, \$30 for the post-treatment assessment, \$35 for the 3-month follow-up assessment, and \$45 for the 6-month follow-up assessment for a combined total of \$140. Compensation may also be available in the form of Wal-Mart gift cards for peers who complete exposure activities with Veterans.

7.1.8. Treatment Procedures. Participants will be randomly assigned to one of the two study conditions: 1) Experimental Condition: PE+Exposure Workout Buddy (i.e., a peer who specifically offers social support during in vivo exposure homework) or 2) Control Condition: PE+Peer General Support (i.e., a peer who does NOT engage in any support during in vivo homework, but offers support according to standard VA peer support models).

Participants will be randomly assigned (1:1) to one of the two study conditions. After determining eligibility, enrolled patients will be assigned to treatment groups by study staff using a web-based

computer generated randomization scheme through REDCap, an application designed to support data capture for research studies. Study personnel will be able to obtain randomization assignment by completing a REDCap survey verifying inclusion/exclusion criteria. Randomization will occur at the patient level. Once a patient is randomized, 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 the statistical analyst in charge of randomization. Moreover, we will take the following steps to minimize contamination between the two arms of the study: 1) patients in the intervention and control arms will be instructed not to share intervention materials with friends or other clinic patients; 2) patients will be given instructions not to disclose their treatment assignment to any other healthcare providers; and 3) per standard practices for MUSC-VA research, providers will be informed of their patients' participation, but will be blinded to condition.

1. Experimental Condition: PE+Exposure Workout Buddy. The experimental treatment is a modified version of PE insofar as social support in the form of 'workout buddies' for in vivo exposure homework is added to the protocol. Specifically, PE is a manualized treatment (Foa et al., 2007) that includes the following components: (a) psychological education about the common reactions to traumatic events and presentation of the treatment rationale (sessions 1 and 2), (b) repeated *in vivo* exposure to trauma-related stimuli such as people, places, things, or situations that trigger memories of the traumatic event but are realistically safe (in vivo exercises are assigned as homework during sessions 3 through 11), (c) repeated, prolonged, imaginal exposure to traumatic memories (imaginal exposure is implemented during sessions 3 - 11; patients listen to session audiotapes for homework between sessions), and (d) relapse prevention strategies and further treatment planning (session 12).

PE is based on emotional processing theory, which suggests that traumatic events are incompletely and inaccurately encoded in memory as "fear networks." Gradual exposure to corrective information via the confrontation of (i.e., exposure to) conditioned trauma-related stimuli within a safe and therapeutic environment results in a competing and antithetical memory structure that inhibits the conditioned fear response. PE relies on two primary therapeutic tools: in vivo exposure and imaginal exposure. During in vivo exposure, the patient confronts feared, but safe, stimuli or cues that elicit trauma-related distress. During imaginal exposure, patients are guided by therapists and "revisit" the traumatic event, providing a detailed verbal account that includes sensory information, thoughts, feelings, and reactions experienced during the traumatic event.

Consistent with the spirit of the new VA mandate to use peers in specialty clinics such as PTSD clinics, we will offer those individuals who indicate that they have decided to drop out / have dropped out of treatment (e.g., stopped attending sessions) the opportunity to have a peer (see description of peer and training below) who has been through treatment successfully, and no longer holds a PTSD diagnosis, help them to complete in vivo exposure trials as an 'exposure workout buddy,' by offering social support during exposure homework.

Peer Selection. For the pilot feasibility study, a large number of peers volunteered and were trained. Most of these peers have indicated that they will be available for this study. We will use identical methods to recruit and train peer exposure workout buddies as proved feasible in the

pilot study. Specifically, therapists will be asked if they have any patients who have completed treatment and did very well, both overall and in particular with in vivo exposure therapy components. Therapists will then be asked to contact these patients, inform them about the exposure workout buddy program, and ask them if they would like Dr. Acierno, a VA clinician and researcher, to discuss the program further. Upon being contacted, Dr. Acierno will outline the nature of expectations and research characteristics, and schedule a training session. Thus, initial nominations for the program are based on therapist impressions of successful candidates AFTER they have completed treatment. Peers who are candidates for the workout buddy program will be consented, evaluated for presence of PTSD diagnosis via the CAPS 5, and only those who no longer have the PTSD diagnosis will be permitted to participate in this study. Peers will also serve in the capacity of general peer support for the comparison condition, but will be explicitly directed NOT to meet the Veteran during in vivo exposure assignments. In fact, the only meetings between general VA support peers and patients take place at the VA, as is standard with VA peer programs (further description of duties below)

Peer Exposure Assignment 'Workout Buddy' Training. NOTE: Peers are not therapists or therapist replacements, and the major activities of the peers are to simply meet Veterans at in vivo exposure homework sites and offer encouragement and support. To illustrate, this is like a workout buddy agreeing to meet you at the gym. This person is not a physical therapist or trainer, rather, they are just a peer who agrees to go to the gym and offer verbal support during gym activities. This is exactly the role of the peer: to offer verbal support during in vivo exposure activities that have been agreed upon. Thus, logistics and *limits* of responsibility, not skills, are the primary focus of training. Much time is spent emphasizing appropriate rules of confidentiality, self-disclosure (which is instructed to be limited), boundaries and safety procedures. As mentioned, analogies have been very helpful: that of peer and participants as 'workout buddies' and that of peer and participant having the same relationship and responsibilities to one another as group therapy patients. These analogies are applied as described below. Each peer will attend a 2-hour training meeting with the PI Acierno and Co-I Hernandez-Tejada. During this meeting, the rationale for in vivo exposure will be reviewed, and the benefits of having a supportive partner, friend, or exposure workout buddy during in vivo exposure will be outlined. Training will explicitly include content wherein peers will be clearly informed that they are **not** engaging in the role of therapist or providing therapy; rather, their role is equivalent to that of a supportive group member in traditional group counseling (with which many Veterans are familiar), only this support is given in the context of exposure exercises. In such a situation, group members offer each other advice and support on how to achieve stated goals. In the present case, the stated and agreed upon goal will be the in vivo exposure therapy assignment. As with group counseling members, peers are trained in the importance of confidentiality, and are **not** paid or compensated for their time (they are reimbursed for fuel). This clarifies that they are not in the role of a compensated therapist while also speaking to the sustainability of the program, a position underscored by the fact that we have had such a high Peer volunteer rate (85% of those approached) (see Preliminary Study #2). Limits to personal responsibility will be clearly outlined, and peers will be well educated that neither the outcome of the treatment, nor the disposition of the patient is their responsibility. We will review potential negative outcomes, including patient suicide, and apply the limits of personal peer responsibility to each. Moreover, we will make it explicitly clear that exactly and only those roles and responsibilities found in group

counseling sessions, including support, respect, and confidentiality, are in place here, with the exception that meeting locations are offsite and without therapist direction.

Workout Buddy Logistics & Supervision: Getting Started. Our pilot study experience allowed us to refine methods of initiating the exposure workout buddy program to the following steps: Once patients have agreed to re-initiate treatment, the available peer in closest proximity to the patient will be asked by the project coordinator to call in to the next therapy session. During the session, the therapist will make introductions and the peer will listen to the patient and therapist review the next item of the in vivo exposure hierarchy in depth. The location, timing, outline, description, and parameters of the in vivo exposure therapy assignment will be reviewed and will be clear to patient, peer, and therapist. Once this clarity has been achieved, peer and patient will finalize arrangements to meet at a set time and place to engage in this exposure trial and will be directed to arrange at least 1 such meeting per week for 3-4 weeks. The analogy of a workout buddy will be used, insofar as the role of the peer is to be present and encourage the Veteran during his or her exposure efforts. For patients who dropped out of treatment prior to developing and engaging in hierarchy item exposure, the workout buddy 'session call in' will be delayed until this hierarchy is established. Once established and reviewed, the peer will call into the next session and discuss logistics of meeting patient at the exposure hierarchy item location with patient and therapist.

Note that with respect to peer behaviors, these are PRECISELY the procedures we encourage and have used when delivering exposure-based therapies in group settings (see Smith et al., 2015) and to those with supportive family members. Specifically, we encourage group members to work together during in vivo exposure trials in between sessions to offer encouragement and praise for successful completion. In this instance, we are borrowing that effective aspect of group therapy and applying it in dyads to patients who have dropped out prematurely from exposure based treatment.

As with the feasibility trial, peers will not be matched on gender or age, except in cases of Military Sexual Trauma, for which peers are matched on gender. Peers will be selected on the basis of geographic proximity to participants. After the participant, workout buddy peer, and therapist hold a conference call to review logistics of in vivo exposure trials, therapists will speak with only the participant to assure that he or she continues to want to participate with a peer exposure workout buddy. Over the following weeks, this 'check-in' with participants will be repeated and the therapist will ask the patient to comment on any problems or benefits associated with in vivo exposures that were accompanied by a peer workout buddy to obtain a progress report of how exposure trials are going, and to determine if there were any issues that should be discussed. Similarly, following the first scheduled in vivo session, the therapist will contact the peer to review how the exposure homework went. Subsequently, peers, patients, and therapists will hold five-minute telephone check-ins during treatment sessions to assure that exposures are going well according to both patient and peer. In the event a peer is not available to call in during a treatment session, the therapist will contact them after the session. This investment of therapist time has not been a problem in the feasibility trial, and will be precisely measured. Finally, during the first therapist call with the peer, the therapist will ask if the peer would like to continue with the participant and if there are any issues or problems. If a peer indicates that they prefer to no longer work with a participant, a different workout buddy will be recruited. If two workout buddies

indicate for any one participant that they prefer not to work with that participant, the peer workout buddy program will be terminated for that participant, and therapists will include these interpersonal events as topics of therapeutic focus appended to subsequent PE sessions. This has not occurred in our previous feasibility trial.

To ensure that participants are not currently experiencing significant PTSD symptoms when serving as peers, a PCL will be administered at the baseline assessment, of which peers must score below 32. Of note, a score higher than 32 does not necessarily indicate only elevated PTSD symptoms because this measure contains questions related to depression; therefore, the PI may determine eligibility based on PTSD versus depression symptomology. In these instances, peers will be offered “booster” sessions by their previous therapists from which they received their initial exposure treatment. Booster sessions will consist primarily of emotional processing and/or confronting current life stressors which may contribute to current elevated PTSD symptoms. Peers will be administered frequent PCL measures to assure that scores remain lower than the threshold, and may be offered booster sessions at any time during their participation in the study.

In Vivo Exercises with Peers. As detailed above, each peer workout buddy will undergo a 2-hour training to review expectations, responsibilities, *and most importantly, limits of responsibilities.* Specific discussion of engaging in only those activities the workout buddy feels comfortable performing is held. Specific review of excluded activities will also be held. All workout buddies engage only in hierarchy items jointly determined by the therapist and participant, with assent of the workout buddy. No new, or unscheduled exposure activities, initiated on the part of the workout buddy or the participant are permitted. Workout buddies are directed to communicate with participants if either party feels or seems to feel uncomfortable with the activity in question. The difference between discomfort arising from conditioned anxiety that is part of PTSD and discomfort arising from feelings that the situation is inappropriate are discussed as part of peer training.

Only situational activities, in clearly safe places, will be included in the in vivo exposure participation events by workout buddies. This will be determined by review with therapist and workout buddy. If EITHER party feels there is more than minimal risk, the activity will not be included. Note: risk of anxiety on the part of the participant is not a justifiable reason to exclude an activity; indeed, producing and dealing with such anxiety in a supportive environment is the point of in vivo exercises. It is impossible to list every possible activity that should be avoided vs. included. However, several common activities, listed below, are **excluded**:

- activities involving driving together on the part of either the exposure workout buddy or the peer as driver (public transportation, such as taking a bus together is permitted);
- activities in or around private residences of the participant or exposure workout buddy;
- activities involving weapons (e.g., shooting range);
- new or previously unlisted or unscheduled activities; and
- activities that are associated with risk or danger as defined per therapist and or peer workout buddy.

Workout buddies and participants are told that the workout buddy program is **only** in place for a given patient for 3-4 weeks, at least once per week, and is a means by which to allow participants to progress to their own, independently conducted in vivo exposure trials. Thus, 'phase out' of the program is built in from the beginning. Workout buddies will focus on helping participants engage in those exposure exercises that typically are social in nature. Again, any exposure trials, such as driving, that require the participant to engage alone, or from which workout buddies are specifically prohibited will not be the target of this program.

2. Control Condition: PE+Peer General Peer Support. Participants in this condition will receive PE (see above) and be assigned a peer support volunteer who will NOT engage in any support during the in vivo homework. The primary purpose of the peer in this condition is to emulate standard VA PTSD peer support procedures. Therefore, in this conditions peers provide general support, such as reminding and encouraging participants to attend appointments, meeting with them at the VA 2-4 times per month to assess general progress, checking up on them once per week via telephone and asking about current treatment progress, life stresses, opportunities, problems and successes, and offering general support with VA programs. The PE component of this treatment will be matched to experimental condition in terms of session number and duration (12 sessions); treatment completion will be defined as for the experimental condition (minimum 10 sessions **or** pre-specified reductions in PCL score at two consecutive sessions; see above). Counselors will deliver treatment according to the same schedule as the experimental condition, once weekly for 75-90 minutes.

Treatment Providers Training, and Supervision. Treatment providers for both conditions will be master's level counselors with at least 2 years of experience providing evidence based counseling to adults. All providers will perform both treatments in equal measure to control for non-specific therapist effects, as with our prior three PE treatment outcome studies. All project therapists have already engaged in training through the prior PE studies and workout buddy pilot study. However, for new therapists, providers will undergo a 4-day PE workshop and a 4 hour PE+Exposure Workout Buddy Training with Drs. Hernandez-Tejada and Acierno. During the project, therapists will follow the treatment manual and will undergo regular peer supervision directed by Dr. Birks.

Treatment Integrity and Adherence. The present study will obtain a quantitative measure of protocol adherence through a checklist of specific procedures scheduled in the treatments outlined above. In order to ensure that treatments are competently administered in accord with protocols as written, all sessions will be audiotaped, and 20% of these will be randomly selected and rated for competence and adherence by co-investigators. This will also allow us to study any differences between conditions on specific and non-specific factors, such as length of therapy, therapist empathy and rapport. Raters, blind to treatment condition, will rate the tapes independently to allow for the computation of inter-rater reliability. To evaluate adherence, rating forms were developed based upon the treatment manual to determine if the therapist appropriately covered the content of each session (i.e., demonstrated the particular behavior described in each item). To evaluate competence, rating forms were developed to assess how well the therapists accomplished a range of relevant tasks for each. These rating forms use 7-point Likert scale response formats, and are modeled after the therapist rating forms used in other studies of cognitive-behavioral treatments, including our own treatment outcome studies.

Treatment integrity can also be challenged by the introduction of non-study treatments. That is, participants may seek additional treatment on their own during follow-up data collection periods. This is particularly a problem if one treatment does not “work” and participants naturally look elsewhere for help. Individuals cannot ethically be prevented from seeking treatment. Therefore, we will assess, at post treatment and during follow-up periods, whether participants have obtained additional mental health treatment. Participants who do receive additional treatment will be compared to others within their treatment conditions that do not receive such additional intervention. Any differences noted will result in relevant adjustments to data analytic procedures (e.g., reporting data summaries of individuals receiving other treatment).

Attrition and Retention. As study participants may have already dropped out of PE treatment once and may arguably be more likely to do so again in the future, this study has been powered to offset a projected 35% dropout rate during treatment, and a 10-15% loss to follow-up during the 6-month follow-up period. Patients who attend at least 10 sessions or evince two consecutive weeks with PTSD Clinical Checklist-Military Version (PCL-5) scores below 20 (note, the National Center for PTSD suggested cutoff is 33 (Weathers et al., 2013)) will be considered completers. Participants will be allowed to make-up sessions when appropriate or necessary within a 4-week window. Make-up sessions for subjects in both conditions will be handled in the same manner: when feasible, these sessions will be scheduled for later the same week. We will minimize drop out from the study by providing monetary compensation for completing baseline, post treatment, and 3, 6-month follow-up assessments (but not treatment sessions). Additionally, following the informed consent process, we will request additional contact information (two family members and/or friends) who would know how to get in touch with the participant if we are unable to do so with his/her primary contact number. We will also specifically ask for e-mail and cell phone contact information. This information will be updated at each assessment time point. We also will employ the following strategies to maintain study participation: 1) We will stress the importance of attendance during the first session and educate patients regarding the treatment process, treatment participation, and (for the experimental group) partnering with a workout buddy for exposure trials; 2) Study personnel will send letters ahead of telephone and/or e-mail scheduling contacts and make reminder telephone calls to participants on the day or evening prior to each session; 3) Study personnel will coordinate care, as needed, with participant’s case managers, psychiatrists, social workers, and other care providers who have acted as referral agents for the study; 4) Study personnel will be flexible in accommodating participant schedules for treatment sessions; and 5) Project staff will meet weekly to review scheduling activities and problem solve regarding strategies and approaches that may increase successful follow-up and retention.

7.2. Drugs, Dietary Supplements, Biologics, or Devices. N/A

7.3. Study Procedures. The following study procedures will be followed:

- A member of the research team will explain the purpose of the study to potential participants. Potential participants will be asked to read and sign the consent.
- If the participant has been referred from another study and already undergone baseline testing, the participant will be asked as part of the consent process to use these assessments rather than repeating the assessment battery.
- If the participant is newly referred to this study or declines use of previously completed assessments, he or she will meet with an evaluator and complete the assessment questionnaires.

- The results of these screening procedures will be reviewed to determine whether it is appropriate for the participant to continue in the study. If it would not be appropriate for the person to continue in the study, a member of the research team will discuss the reasons why and, if needed, coordinate appropriate follow-up outside of this study.
- Once all the baseline testing is completed and eligibility is determined, the participant will be randomized to either condition.

All therapy and evaluation sessions will be audio recorded. Therapy sessions will be audio recorded for the patient to be able to complete homework during sessions. Assessments will be recorded to ensure that study staff is correctly following the study procedures; a randomly selected subset of these tapes will be reviewed by research experts who are part of the research team. Participants will have the option to accept or deny the use of video/audio recording during evaluations and therapy at informed consent. Agreeability to recording will have no bearing on participant eligibility.

7.3.1. Collection of Human Biological Specimens. N/A

7.3.1.1. Laboratory Evaluations and Special Precautions. N/A

7.3.1.2. Specimen Storage. N/A

7.3.2. Data Collection. All data will be in the form of 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.

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.

7.3.2.1. Instrumentation. See the table at Section 7.1.2 above for a summary of the assessments and timing of administration. All measures are being administered for research purposes. 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. Assessments completed via phone or remote electronic data capture will not include psychophysiological measures. 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.

7.3.2.2. Data Storage and Access.

Participant Identification. A file of research identification numbers and associated social security numbers will be stored separately on paper and on computer, for purposes of audit by the VAMUSC IRB, if necessary.

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 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.

7.3.3. Human Biological Specimen (Biomarker) Processing. Not applicable. This study will neither be collecting specimens nor conducting laboratory evaluations of biomarkers.

7.4. Statistical Consideration

7.4.1. Sample Size Estimation. For the continuous longitudinal clinical, functional, and process outcomes for Primary Aims, with 50 subjects randomized to each intervention group, we will have 89% power to detect at least a 0.3 standardized (sd units) effect size between the two intervention groups assuming 4 time points (baseline, post-treatment, and 3- & 6-month follow-ups), and; intra-class correlation no greater than 0.5; level of significance ≤ 0.05 , two-tailed. A standardized effect size of 0.35 sd (Cohen's d, "small" effect) is equivalent to a raw effect size of 2.8 raw scale units for PCL-5 (assuming pooled sd for post treatment PCL-5 scores is 8.1, from preliminary data). For the dichotomous process outcome completer/dropout, with 50 subjects per group, the study will have 85% power to detect a relative improvement in retention for the experimental condition of 20%. Power will be 89% for the continuous 'dose' received measure of number of sessions attended, assuming an effect size of 0.3 for the experimental condition. We make these conservative effect size predictions based on the fact that we intend to use Intent to Treat (ITT) analyses for primary outcomes for which group average treatment effects are lower compared to completer analyses.

To account for dilution effect of ITT analyses, "administrative" dropout, i.e., those who drop out immediately upon randomization (do not receive a treatment or return for a post baseline visit), and the need to impute missing data, we will 'over recruit' by 15% to achieve a final ITT sample size of 58 participants randomized to each treatment group (i.e., ITT N = 116, Completer N = 100).

7.4.3. Data Analysis.

Preliminary Descriptive Analyses. Satisfaction and process measures will be summarized for patients and peers. Baseline values for demographic, war theatre, clinical, and other putative prognostic variables will be compared for imbalance across the two randomized treatment conditions and across the non-randomized, exploratory conditions (in person vs. telehealth delivered PE+Exposure Workout Buddy vs. PE+Peer General Support). These analyses will identify potential confounding variables to be used as covariates in subsequent analyses and will include race/ethnicity, age, psychiatric comorbidity, and initial disease severity. To investigate potential limits on generalizability, we will compare characteristics of participants who prematurely exit and/or are protocol non-adherent (i.e., they dropped out again) against those who were completers/protocol adherent. Characteristics of patients who do not complete the study or do not adhere to treatment will be compared for both conditions.

Objective 1a: To determine the differential impact on treatment dose received of 'PE+Exposure Workout Buddy' vs. 'PE+Peer General Support' in individuals who have dropped out of evidence based treatment for PTSD in terms of the number of sessions completed following randomization to either treatment. Objective 1b. To determine if this differential dose received is amplified or diminished with respect to prior identified risk factors such as age, race, gender, or substance use.

Analysis Issues for Objective 1: As mentioned in the Measures section, 'dose', or number of new sessions received is likely confounded by 'prior dose', or number of pre-dropout sessions received prior to initiation of this study. Nonetheless, the basic question of treatment dose as measured by number of new sessions completed after receiving the experimental treatment is important and will be obtained. However, to deal with this potential confound, (a) number of sessions completed prior to dropout will serve as a covariate in subsequent analyses & (b) 'dose' will also be examined dichotomously, in terms of between group proportions of treatment completers (defined as completing 10 or more new sessions OR 2 subsequent PCL5 scores below 33).

Analysis Plan for Objective 1: We will adopt a relatively direct analytic approach for this first objective. Specifically, if preliminary descriptive analyses reveal baseline differences in psychopathology or other potentially confounding variables, including number of sessions completed prior to dropout (i.e., prior to entry into this study) these will serve as covariates in ANCOVA, which will be used to compare average dose received in terms of number of treatment sessions in each group. These ANCOVAs will be repeated with race and gender as between group factors to determine if any interaction is present between treatment condition and these demographic characteristics. A similarly direct approach will be taken for the dichotomous variable of treatment completion, for which we will initially use chi square analyses for bivariate examination of treatment completion in terms of each demographic variable and each treatment condition, followed by logistic regression in which those variables producing significant chi square relationships to this outcome will be included in regression models. We will use 95% confidence intervals (CI) for single proportions to estimate the proportion of participants who complete treatment *within* each intervention group. We will also estimate the difference in completer proportions between groups using 95% CI for difference in proportions. In addition, frequency distributions describing participants' reasons for discontinuation of study participation will be developed. In this way, the effect of each treatment condition on 'dose', measured in terms of overall number of sessions completed, and in terms of proportion of participants completing at least 10 sessions / achieving clinical cutoff will be described.

Objective 2a. To determine differential effectiveness of 'PE+Exposure Workout Buddy' vs. 'PE+Peer General Support' who does NOT engage in any support during in vivo homework with therapy dropouts in terms of therapeutic gains over time on measures of PTSD symptomatology (i.e., 'treatment outcome'). Objective 2b. To determine if differential effectiveness is amplified or diminished with respect to race, gender, age or substance use.

Analysis Issues for Objective 2. The primary analyses for this objective will use the ITT sample, which will consist of all participants who are randomized to either PE+Exposure Workout Buddy or PE+Peer General Support. Patients will not be discontinued from the study assessments because of non-adherence and all patients will remain in the study assessment protocol unless

consent is withdrawn or there are concerns regarding patient safety. We will adopt several approaches to dealing with missing data for the intent-to-treat analysis set: for continuous outcomes, we will employ mixed effects models (GLMM, MEM) which allow for measurement of subjects at different time points and missing data (Hedeker & Gibbons, 2006); for single endpoint imputation, we will use the multiple imputation methods of Little and Rubin (1987). We will model the dichotomous outcome, missing/not missing post treatment score, using logistic regression to determine if missingness is related to treatment condition. In a secondary analysis, the results of analyses using treatment completers (completer analyses) will be compared with results using the full set of all randomized participants (ITT analyses) to test sensitivity of study conclusions to dropouts.

To address possible Type I errors due to the number of analyses: (1) for the primary analyses, we specify *a priori* the primary measures corresponding to the stated *a priori* hypotheses (with other measures being considered secondary/exploratory) and maintain the significance level (alpha) at 0.05 for analyses involving the primary study variables; and (2) for secondary analyses using additional outcome variables and combat exposure measures, we will adjust p-values using a Bonferroni-type correction for multiple outcomes and will report both unadjusted and adjusted p-values. Secondary outcomes and exploratory analyses will be evaluated qualitatively in terms of consistency with primary results and cautiously in terms of statistical significance of results. The sensitivity of the study results to adjustment for multiplicity of outcomes will be evaluated.

Analysis Plan for Objective 2. Our primary outcome is the PCL5 continuous score for PTSD. Clinical (CAPS, PCL-5, Patient Health Questionnaire), functional (SF-36), and process (treatment credibility scales, patient satisfaction, session rating scale, service delivery perceptions, retention in treatment) outcomes will be compared using the generalized linear mixed models (GLMM) approach. In addition to accommodating a wide range of distributional assumptions [continuous (e.g., PCL-5, CAPS, Patient Health Questionnaire), dichotomous/categorical (e.g., binomial), ordinal (e.g. patient ratings), count (e.g., number of missed homework assignments (Poisson), the approach accommodates multilevel data (clustering) such as repeated measurements of subjects, missing data, time-varying covariates, and possible cluster effects within sites or clinics through inclusion of random effects in the model (Hedeker & Gibbons, 2006). For the continuous outcomes, for example PCL5, GLMM is equivalent to a linear mixed effect model (MEM) approach. MEM analyses estimate individual change in outcome for each subject in addition to estimating average change in outcome within each intervention arm. *Covariates, such as initial severity as measured by the PCL-5, age, race, and comorbid illnesses will be added to the model to adjust for putative confounding variables.* Unadjusted and covariate-adjusted least squares means for continuous outcomes will be compared at relevant time points (e.g., immediate post end-of-active-intervention and 6-month end-of-study time points) using appropriate model contrasts and the Tukey-Kramer adjustment for multiple comparisons. We will first assess trends in the outcome profiles over the full study period (active + follow-up). In these analyses, we will allow slopes to differ depending upon whether it is active or follow-up phase. In secondary analyses, we will also assess separately the active phase and the follow-up phase (3- & 6-months) trajectories to remove from the active phase results the complicating issue of intervening events in the follow-up phase. Intervention specific patient satisfaction items will be described separately within each intervention group

using standard descriptive analyses (e.g., means, proportions along with corresponding confidence intervals). Global satisfaction level (e.g., overall satisfaction level) will be compared between intervention groups using the GLMM process described above. Mediation effects of perceived level of social support on outcome will also be examined.

Estimation of effect sizes. The magnitude of treatment group differences (effect sizes) for outcome variables will be estimated using 95% confidence intervals (CI). Effect sizes will be used to evaluate clinical significance of treatment group comparisons.

Exploratory Objective 3. To determine the presence of initial signals of differential dose and effectiveness of 'PE+Exposure Workout Buddy' when delivered in traditional in person (face to face) vs. telehealth formats. *(Note, the parameters by which this objective will be achieved are naturalistic insofar as this variable is not subject to randomization because participants who had received telehealth or in person PE prior to dropout and thus prior to this study will continue to receive treatment in the same modality upon randomization to either PE+Exposure Workout Buddy or PE+Peer General Support).*

Analysis Plan for Exploratory Objective 3 The analytic requirements of the exploratory objective to detect initial signal of differential effect of the PE+Exposure Workout Buddy program for those receiving treatment via telehealth vs. in person mirror those of Objective 1 with respect to 'dose' and '% completing treatment', and Objective 2 with respect to clinical outcomes. As such, the logistic regression analyses conducted for Objective 1 will be repeated, this time including treatment delivery medium (in person vs. telehealth) as an independent predictor variable. Likewise, the analytic plan for Objective 2 will also be repeated, including treatment delivery medium as an independent variable for continuous clinical outcome analyses. In this way, the hypothesized advantage of the PE+Exposure Workout Buddy program for telehealth will receive initial study.

As is typical in most treatment outcome studies, we will also supplement exploratory analyses by examining the possible mediating effect of the process variables on clinical outcomes. These analyses address the question of whether process outcomes such as satisfaction with the intervention, treatment credibility, and session attendance explain the relationship between the outcome variable (PTSD severity) and intervention group (primary independent variable). For example, these analyses will explore whether a more positive outcome in one group may be explained by greater session attendance and higher satisfaction ratings in that group, or as hypothesized here, social support. Specifically, in mediator analyses, it is posited that variation in the primary independent variable (intervention group) accounts for variation in the mediators (e.g., social support, session attendance), and variations in the mediators account for variations in outcome (PTSD severity). For these analyses, we will use the GLMM modeling approach described above coupled with the method of Baron and Kenney (1986) and Holmbeck (1997) for evaluating putative mediators.

7.7. Confidentiality. Some in-person therapy sessions and interview assessments will be delivered in private offices located at the Ralph H Johnson VAMC 109 Bee Street, Charleston, SC 29401 or an associated Community Outpatient Clinics (CBOCs). Those addresses are: Beaufort VA Outpatient Clinic 1 Pinckney Road Beaufort, SC 29902; Goose Creek Clinic 2418 NNPTC Circle Goose Creek,

SC 29445; Hinesville VA Outpatient Clinic 500 East Oglethorpe Highway Hinesville, GA 31313; Myrtle Beach VA Outpatient Clinic 3381 Phillis Boulevard Myrtle Beach, SC 29577; Savannah VA Outpatient Clinic 1170 Shawnee Street Savannah, GA 31419; Trident VA Outpatient Clinic 9237 University Boulevard North Charleston, SC 29406. Some in-person therapy sessions and interview assessments will be delivered at MUSC leased space at 740 East General Stewart Way, Suite 202 Office E, Hinesville, GA 31313. Secure offices may be rented in the community to ensure there is private space to see participants. The location of these rented facilities will be determined pending final agreements. Digital audio recordings of assessments and video recordings of treatment sessions will be labeled with the participant's study id number and saved on a secure password protected server. Those recordings are to be reviewed for fidelity to ensure that the treatment is being delivered in accordance with the treatment manual will be viewed on a secure password protected server. Every member of the research team will be trained and monitored about how to handle and protect both medical and research records. Only authorized study staff will have access to either the raw data or electronic study data.

7.7.1. Certificate of Confidentiality. We are not seeking a Certificate of Confidentiality.

7.7.2. Data Protection. Data will be coded using an assigned number. Data collected on paper during treatment will be placed into locked cabinets at the respective clinics where the data is collected. 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.

8.0 RISKS/BENEFITS ASSESSMENT

8.1. Foreseeable Risks. Potential psychological risk of the treatment includes exacerbations of distress during the assessment or treatment sessions. Measures to avoid this include constructing an intervention that has as one of its primary aims, reduction of distress and depression through increased activity. Additional measures include informing participants that they are free to terminate treatment sessions at any time. Risks associated with follow-up assessment include the possibility that participants might be upset by questions pertaining to their emotional functioning. Again, all participants will be informed at the outset that they may terminate participation at any point. Our past research suggests that data collection using many of these measures can be conducted without undue psychological distress or exacerbation of symptoms among adult participants. This experience includes substantial research with younger and older adults, rape victims, victims of other forms of violence, and work on large-scale studies asking questions about similar topics with general population samples. Alternative treatments generally include group treatment, treatment by antidepressant medication, or by relatively invalidated psychotherapeutic techniques.

Another, albeit unlikely risk is to peer support specialists if patients have some negative outcome and the peer blames themselves for this outcome. For example, if a patient is very distressed during an exposure therapy assignment and subsequently drinks alcohol and drives and is arrested or has a

crash, the peer may blame him or herself for this negative outcome. To address this, the PI stresses in his training of peers that their responsibility is limited to themselves with respect to showing up at exposure assignments as a workout buddy, and that any negative behaviors on the part of the peer would very likely have occurred, and occurred with greater severity had they not been involved and helping.

Social risks are present if another person or parties observe participants attending treatment clinics or learn by other means of participants receiving treatment. Participants will not be overtly identified as research candidates or candidates for psychological intervention. Participants in mental health research at the VAMC are NOT required to 'check in' at the mental health front desk, and instead report directly to treatment areas in order to reduce any potential for stigma.

Legal risks arise if individuals are homicidal or suicidal and make these intentions known to project staff, which are then required to notify authorities and the target of homicidal intent. These risks are outlined in the informed consent documents.

Risk Management and Emergency Response. In the event respondents experience extreme psychological distress secondary to participation, they will be encouraged to telephone the Principal Investigator (PI) or the Co-Investigators. In addition, they will have access to the VA's urgent care services. Any adverse effects noted by any project personnel in response, or in potential response to any project intervention, assessment protocol, or study involvement will be immediately reported to the PI and Project Co-Is, who will then report these serious adverse effects in writing to the University/VA IRB within 24 hours of the initial report. The research team is comprised of licensed clinical psychologists with extensive experience working with adults who have experienced significant life stressors. Participants will be requested at the beginning and the end of the initial interview session to write down the PI's name and telephone number. Moreover, if assessors or project staff believe that a participant is significantly distressed by participation, the PI will be notified and will contact the participant to assess distress and assure participant safety. If called by participants, the PI will attempt to address all subject concerns and set up an alternate referral for counseling for those who desire it from outside the project.

In any study of mental health problems or symptoms, risk of suicide is amplified relative to most other medical disorders. Therefore, specific precautions will be taken to prevent harm to participants and potential participants. All assessors will be specifically trained to assess suicide risk (e.g., suicide verbalizations, extreme sadness, etc.) associated with major depressive disorder, and the structured clinical interview will specifically query for both suicidal ideation and intent. In initial screening procedures, participants identified by clinical interview with both suicidal ideation and acute intent will be excluded from the study, but will be offered emergency psychiatric care immediately. This care is available 24 hours per day at the Charleston VAMC emergency room. In any instance where ideation or intent is identified, a Project Investigator will be immediately notified and will contact the participant for further evaluation. If both ideation and intent are present, the aforementioned hospital intervention will be provided.

Thus, all assessment points represent suicide risk identification, assessment, and intervention opportunities. In addition, all project therapists will be specifically trained regarding the increased risk

of suicide in depressed persons and will receive specific instruction of suicide risk assessment by Project Investigators.

In any instance (either during assessments or during treatment sessions) where suicide risk is identified: (1) a Project Investigator will immediately contact the participant and determine suicide risk. (a) If suicidal ideation, but not intent is present, the individual will be retained in the study and assessed for suicide risk by one of the Investigators in one week. (b) In cases of acute suicidal intent, state law requires immediate hospitalization and we will follow these guidelines. Note, as mentioned, suicidal ideation is not grounds for study exclusion or mandatory hospitalization, whereas clear intent to commit suicide requires hospitalization.

Potential Benefits. The benefit to the volunteer is a potential reduction in aversive psychological symptoms of anxiety and depression, as well as the cognitive realization that, through their volunteer efforts, they are helping to advance the state of knowledge as it applies to positive mental health for Veterans. The benefit is (1) reducing attrition from the military due to mental health causes and (2) reducing eventual mental health costs for the VAMC system, thereby benefiting individuals and the VA. Another benefit is to the peer support specialist, who may be particularly happy to 'give back' to other Veterans.

8.2. Alternatives. Mental health treatment is available, including various forms of psychotherapy and drug treatments. Military personnel may be eligible for care at one of the Veterans Healthcare System facilities or clinics. If not, they will be instructed that they can request treatment for PTSD through Army One-Source. Not participating in the study is also an alternative.

9.0. ADVERSE EVENTS, UNANTICIPATED PROBLEMS, AND DEVIATIONS

9.1. Adverse Events. All adverse events will be assessed and monitored according to the established SOP and the IRB of record's policies and procedures.

9.2. Reporting Adverse Events, Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), and Deviations to the Office of the IRB. All adverse events, unanticipated problems involving risk to participants or others, and deviations will be reported to the Institutional Review Board (IRB) in accordance with current IRB policy. UPIRSOs and recurrent non-compliance with study procedures will be reported promptly to the IRB. All adverse events that do not meet the UPIRSO criteria and deviations that are not non-compliance will be summarized at Continuing Review per the IRB of record's policy.

9.3. Research Monitor. Tataina Davidson, Ph.D.

Responsibilities of the Research Monitor. The research monitor is required to review all unanticipated problems involving risk to volunteers or others, serious adverse events and all volunteer deaths associated with the protocol and provide an unbiased written report of the event to the USAMRMC Office of Research Protections (ORP) Human Research Protection Office (HRPO). At a minimum the research monitor should comment on the outcomes of the event or problem and in the case of a serious adverse event or death comment on the relationship to participation in the study. The

medical monitor should also indicate whether he/she concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death should be promptly forwarded to the HRPO. Additional responsibilities include:

- observe recruitment and enrollment procedures and the consent process for individuals, groups or units;
- oversee study interventions and interactions;
- may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research;
- reviewing monitoring plans and UPIRTSO reports;
- overseeing data matching, data collection, and analysis
- shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report;
- shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

10.0. WITHDRAWAL FROM STUDY PARTICIPATION

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 PE sessions or to receive a full course of PE 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.

11.0. USAMRMC VOLUNTEER REGISTRY DATABASE

We do not anticipate that this will be a greater than minimal risk study necessitating the use of the Volunteer Registry Database will be necessary.

12.0. REFERENCES

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