PROTOCOL TITLE:

Intelligent Biometrics to Optimize Prolonged Exposure Treatment for PTSD-Clinical Trial

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

Posttraumatic stress disorder (PTSD) is a debilitating mental health condition that increases suicide risk and affects up to 20% of military veterans and 8% of the general population. Prolonged Exposure (PE) is a highly efficacious, evidence-based, cognitive-behavioral therapy for PTSD. However, dropout rates are high (25-30%) and an estimated one-third of patients who complete PE remain symptomatic. The primary objective of this study is to test a technology-based system that will (1) enable clinicians and clinical support staff to virtually accompany patients during in vivo exposures (IVEs) exercises to enhance engagement and successful completion of the exercises, and (2) provide clinicians and clinical support staff with real-time streaming of physiological biomarkers of affective engagement--galvanic skin response (GSR) and heart rate (HR)--and subjective units of distress (SUDS). This *actionable data* will be used in real-time by clinicians to modify the exercises and avoid under- and over-engagement, thereby minimizing inefficiencies and maximizing therapeutic value of IVEs. Secondary objectives are to use *passive data* collection to characterize IVEs, identify predictors of change, and inform next steps. To accomplish this, Zeriscope, a local small business with experience developing cutting-edge mobile technology platforms for health care, has partnered with clinical researchers at the Medical University of South Carolina (MUSC) to (1) develop a technology-based system to use intelligent biometrics (IB) to optimize PE ("IB-PE"), and (2) compare the guided IVE intervention to a passive data record-only version which will collect and store biometric and behavioral data for offline analyses. The following Specific Aim is proposed:

Specific Aim: Conduct a 10-session randomized clinical trial (N=40 treatment-seeking veterans/civilians with current PTSD) to evaluate the acceptability and preliminary efficacy of IB-PE and investigate predictors of outcome. *Milestones*: (1a) Evaluate ability of IB-PE (guided vs. record only) in reducing PTSD severity from baseline to session 10; and (2b) Use GSR, HR and SUDS to characterize IVEs and identify how each of these indicators predicts treatment response.

2.0 Background

Posttraumatic Stress Disorder (PTSD). PTSD is the most common mental health diagnosis among veterans seeking treatment at VA hospitals (Ramsey et al., 2017). Up to 20% of military veterans and approximately 8% of the general population meet criteria for PTSD during their lifetime (Kessler, Chiu, Demler, & Walters, 2005; Medicine, 2012). PTSD develops following exposure to traumatic events, such as combat, rape, serious accidents (e.g., motor vehicle accidents), or natural disasters. *Hallmark symptoms of PTSD include:* (1) intrusive symptoms (e.g., distressing memories, nightmares); (2) avoidance (e.g., avoiding places or situations that serve as reminders of the event); (3) negative cognitions and mood (e.g., guilt, anger); and (4) alterations in arousal (e.g., sleep impairment, hypervigilance) (American Psychiatric Association, 2013). If left untreated, PTSD increases risk of other psychiatric disorders (e.g., substance use disorders, depression), medical problems, impairment in social/family functioning, employment problems, and suicide (Chan, Cheadle, Reiber, Unützer, & Chaney, 2009; Fang et al., 2015; Kaier, Possemato, Lantinga, Maisto, & Ouimette, 2014; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Ouimette, Read, Wade, & Tirone, 2010). Data on U.S. Army soldiers reveals that service members with, as compared to without, PTSD are 6 times or more likely to commit suicide (Bachynski et al., 2012; Black, Gallaway, Bell, & Ritchie, 2011; Conner et al., 2014). PTSD is a chronic condition and almost half (45.7%) of individuals with PTSD remain symptomatic three years later (Kessler et al., 1995). Finally, the economic costs associated with PTSD are substantial and estimated to be $4 billion per year (Haviland, Banta, Sonne, & Przekop, 2016; Agency for Healthcare Research and Quality, 2014).

Prolonged Exposure (PE) Therapy for PTSD. PE is one of the most highly effective treatments for PTSD, with response rates ranging from 65-80% (McLean & Foa, 2011; Mouilso, Tuerk, Schnurr, & Rauch, 2016; Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010). PE is recommended as a first-line treatment by the

VA/Department of Defense Clinical Practice Guidelines (The Management of Posttraumatic Stress Disorder Work Group, 2017) and other professional organizations, (Forbes et al., 2010; Agency for Healthcare Research and Quality, 2014) and is widely disseminated throughout the VA healthcare system. Key components of PE are *imaginal exposure* (revisiting the trauma memory during therapy sessions) and *in vivo exposure (IVE)* (approaching avoided but objectively safe stimuli in the "real world" such as crowded stores that serve as reminders of the trauma). Both imaginal and in vivo exposures are designed to activate pathological fear structures and provide corrective information in order to alter maladaptive behaviors and thoughts (Foa & Kozak, 1986; Foa & McLean, 2016). *Physiological indicators of distress (e.g., heart rate, skin conductance) are objective indices of activation and extinction learning, and numerous studies show that greater activation and reactivity before and during PE therapy is associated with improved treatment outcomes* (Foa, 1997; Jaycox, Foa, & Morral, 1998; Norrholm et al., 2016; Rauch et al., 2015; Rothbaum et al., 2014; Wangelin & Tuerk, 2015). The new system to be developed in the proposed study will monitor physiological activation so that if a patient is under-engaged, adjustments can be made in real-time to increase activation and enhance extinction learning.

IVE is crucial to exposure therapy in order to ensure the new knowledge and behaviors learned in the office are successfully transferred to patients' "real world" environments. Although IVE is a fundamental component of exposure therapy for PTSD (and anxiety disorders), surprisingly little research has addressed this critical aspect of treatment. Substantial gaps exist in our understanding of what occurs during IVE, and which psychophysiological, behavioral, or contextual factors are predictive of treatment response. This critical gap of knowledge is due, in large part, to the fact that IVEs are conducted outside the office and are "invisible" to the provider. In rare cases, therapists leave the office and literally go to exposure sites with patients, an inefficient and unsustainable practice. More commonly, patients are given in vivo assignments to complete in-between therapy sessions (e.g., visit Walmart twice next week during lunchtime) and report back to the therapist at the next session (Foa, Hembree, & Rothbaum, 2007). This approach has numerous shortcomings; some patients fail to attempt the exercises (e.g., given high avoidance symptoms) and other patients attempt the exercises but are under- or over-engaged, both of which confer suboptimal treatment response. At present, providers are reliant upon patient self-report, which is subject to inaccuracies due to retrospective memory or survey bias (National Advisory Mental Health Council, 2019). This study leverages recent advances in mobile technology to mitigate these shortcomings by enabling the clinical team to virtually monitor and modify, in real-time, IVEs based on patient-specific physiological and subjective data to optimize treatment engagement and maximize the therapeutic value of IVEs.

Current Use of Technology to Enhance PTSD Treatment. Over the last decade, there has been a notable increase in the use of digital technologies to address PTSD. For example, telehealth delivery of PE overcomes access barriers to care (e.g., transportation problems, travel costs) with comparable efficacy and patient satisfaction (Acierno et al., 2017; Frueh et al., 2007; Gros, Lancaster, López, & Acierno, 2016; Tuerk, Yoder, Ruggiero, Gros, & Acierno, 2010; Yuen et al., 2015). The advent of Health applications (e.g., PE Coach; Reger et al., 2013) provides psychoeducation, self-management tools, and homework tracking. Clinicians and patients rate these applications as feasible, acceptable, and highly promising (Botella, Serrano, Banos, & Garcia-Palacios, 2015; Erbes et al., 2014; Gilmore, Wilson, Skopp, Osenbach, & Reger, 2016; Gould et al., 2018; Wenze & Miller, 2010). Rothbaum and colleagues pioneered Virtual Reality (VR) for PTSD, which uses computer-generated, simulated environments presented to patients via head-mounted displays (Beidel et al., 2019; Difede & Hoffman, 2002; Gerardi, Cukor, Difede, Rizzo, & Rothbaum, 2010; Gerardi, Rothbaum, Ressler, Heekin, & Rizzo, 2008; Maples-Keller, Bunnell, Kim, & Rothbaum, 2017; McLay et al., 2011; Rothbaum et al., 1999). Importantly, research consistently shows that digital interventions are as effective as face-to-face interventions when coupled with human support.(Andersson, Nordgren, Buhrman, & Carlbring, 2014; Baumeister, Reichler, Munzinger, & Lin, 2014; Cuijpers, Donker, van Straten, Li, & Andersson, 2010; Fairburn & Patel, 2017) The recent National Advisory Mental Health Council's report (2019) on technology states, "while there may be some people

who can fully benefit from standalone digital interventions, the vast majority require human support or coaching to obtain more consistent engagement and outcomes." Taken together, this growing body of literature suggests patients are open to and can benefit substantially from technology-enhanced, supported services. Clearly, however, further advancements in the use of technology to treat PTSD are needed.

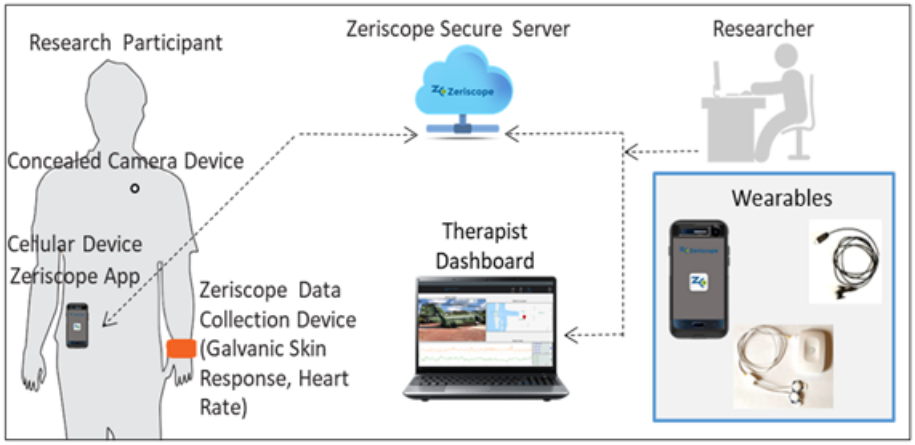


Figure 1. Patient interface consisting of wearables and a software application on a mobile phone that is transmitted to a secure server and can be viewed by the therapist.

How the New Technology-Based System is Distinct from Existing Technologies. In contrast to VR, which uses a computer-generated simulation and targets imaginal exposures in the office setting, the new system will be the first to target IVEs in the patient's real-world environment, bringing biometric and behavioral data "from the field" into the clinician's office and treatment planning in ways that have not previously been possible. Clinicians can now use *intelligent biometrics (IB)* to evaluate and optimize IVEs in real-time to maximize their therapeutic potential. This new technology-based system ("IB-PE") may increase patients' willingness, confidence, and ability to attempt and complete exposures effectively (e.g., attain optimal activation and remain in the situation long enough). In turn, this may improve the efficiency of PE, reduce attrition, and decrease the number of therapy sessions required to treat PTSD, thereby lowering costs and improving access.

3.0 Intervention to be studied

PE will be delivered to all participants based on Foa's therapy manual (Foa et al., 2019). Therapy sessions will be delivered once or twice per week up to 10 weeks. All participants will wear the IB-PE system, affording maximum data collection during IVEs and thorough evaluation of the new system. Using a 3 to 1 randomization scheme (3 guided: 1 record only), the participants will be randomly assigned to either IB-PE (guided) or to IB-PE (record only). A description and images that describe the system are provided below:

The Zeriscope system includes a customized (1) patient interface, (2) clinician interface, and (3) cloud-based system specifically designed for IB-PE (**Figure 1**). The *patient interface* consists of (a) wearables that enable continuous collection of quantitative (e.g., heart rate) and qualitative data (e.g., video) with as little burden as possible to the patient, and (b) software application on a mobile phone. All participants will be provided a mobile phone to use during the study. The prototype tested in the prior feasibility pilot study will be enhanced to include: (a) local (phone) session storage when no cellular or WiFi service is available to prevent loss of connection, (b) keypad for self-report of SUDS, (c) application login and authentication, and (d) intuitive user control and notification features. The wearables will be comfortable and designed to be

Figure 2. Clinician Dashboard. (A) dashboard controls, (B) live video feed from patient, (C) geolocation, and (D) real-time streaming of heart rate and skin conductance.

inconspicuous. The *clinician interface* will include a "dashboard" or display (see **Figure 2**) to enable live video of the patient's environment; real-time streaming of heart rate (HR) and galvanic skin response (GSR); SUDS ratings; and a secure system to store and review completed IVEs offline. New capability will be designed to allow clinicians to demarcate moments of interest during IVEs (e.g., with a time stamp or event marker) which may be "hot spots" (similar to hot spots in imaginal exposures) when the patient's physiological and/or subjective levels are high; those will be stored and can be replayed and/or reviewed in the future to help instruct patients on what to do (or not do) in subsequent IVEs to optimize engagement and efficiency. The dashboard will include summary statistics for each IVE, such as the total number of minutes spent in the exercise, as well as mean and peak HR, GSR, and SUDS ratings. The *cloud-based system* is HIPAA-compliant and designed to rapidly store quantitative and qualitative data from IVEs. Summary reports for individual patient in vivo assignments will be stored and allow for comparisons across multiple IVEs within each person and across treatment conditions. These reports will access data from the session database as well as the system usage logs. The database will be secure and backed up daily.

4.0 Study Endpoints

Feasibility and acceptability of IB-PE. Will assess if participant can turn on/off the equipment in ≤5 minutes; will examine perceptions toward IB-PE via self-report assessments (see assessment below).

Reductions in PTSD severity. Will assess pre- to post-treatment reductions in PTSD severity, as assessed by the PCL-5 and CAPS-5, by treatment group.

5.0 Inclusion and Exclusion Criteria/ Study Population

Initial eligibility screening will be conducted by the PI, Co-Is, Coordinator, or a trained Research Assistant by telephone or in person. If preliminary inclusion and exclusion criteria are met, staff will schedule an assessment appointment for the participant.

Inclusion criteria:

1) Male or female; any race or ethnicity; aged 18-75 years.
2) Participants must be able to comprehend English.
3) Participants must meet DSM-5 diagnostic criteria for current (i.e., past 6 months) PTSD (assessed via the Clinician Administered PTSD Scale for DSM-5). Subjects may also meet criteria for a mood disorder (except bipolar affective disorder, see Exclusion Criteria) or anxiety disorders (panic disorder, agoraphobia, social phobia, generalized anxiety disorder, or obsessive-compulsive disorder). The inclusion of subjects with affective and other anxiety disorders is essential because of the marked frequency of the co-existence of mood and other anxiety disorders among patients with PTSD.
4) Participants taking psychotropic medications will be required to be maintained on a stable dose for at least four weeks before study initiation.

Exclusion criteria:

1) Participants meeting DSM-5 criteria for current and unstable psychotic or bipolar affective disorders. Those participants will be referred clinically to ensure they have appropriate level of clinical care.
2) Participants meeting DSM-5 criteria for a current (past 6 months) moderate to severe substance use disorder. Those participants will be referred to addiction treatment centers at the VA, MUSC and in the local community. Individuals with mild SUD will be included.
3) Participants considered an immediate suicidal or homicidal risk or who are likely to require hospitalization during the course of the study for suicidality. Those participants will be referred clinically for care.
4) Participants on maintenance anxiolytic, antidepressant, or mood stabilizing medications, which have been initiated during the past 4 weeks.

5) Participants enrolled in ongoing evidence-based behavioral therapy for PTSD who are not willing to discontinue these therapies for the duration of the trial. Attendance at therapeutic activities other than study sessions will be closely monitored using the Treatment Services Review.
6) Participants with implanted electronic devices of any kind, including pacemakers, electronic infusion pumps, stimulators, defibrillators or similar.

Women and members of minority groups will be eligible for participation. Children under age 18 will not be eligible for participation. The rationale for this is that different current treatment recommendations differ for children versus adults with PTSD. No special classes of subjects, such as, pregnant women, prisoners, institutional individuals, or others will be recruited for this study.

6.0 Number of Subjects

40 participants will be enrolled.

7.0 Setting

All procedures will be conducted on the MUSC campus or at the Ralph H. Johnson VA Medical Center (RHJVAMC). Subjects recruited through VA will complete research procedures at the VA or through VA-approved telehealth interface (consent, baseline appointment, weekly assessments, prolonged exposure therapy). VA subjects will be consented via telehealth only if and when consent via telehealth is approved at VA. Subjects recruited through outside of the VA - or subjects who are not receiving care at the VA will complete research procedures at MUSC or through telehealth (consent, baseline appointment, weekly assessments, prolonged exposure therapy). Out-of-office IVE locations will vary based on subject's needs and will take place at the designated location decided on by the subject and study team. No research procedures will take place at Zeriscope.

8.0 Recruitment Methods

The primary recruitment site will be the Ralph H. Johnson VAMC PTSD Clinic Team (PCT) in Charleston, SC and affiliated community-based outpatient clinics. The National Crime Victims Research and Treatment Center (NCVC) at MUSC and the Wounded Warriors Program will serve as a secondary recruitment source. We will also place IRB-approved study flyers in prominent locations in MUSC and local mental health clinics, as well as advertisements on social networking sites (e.g., Facebook, Craigslist). Direct mailing in the form of EPIC or VA VINCI letters/calls will also be used. As a result of seeing an advertisement or talking with someone involved in their clinical care, prospective subjects will be encouraged to reach out to the study team to learn more about the study or complete an online or phone screener. In addition, the study team may reach out to prospective subjects if participants from other trials have agreed to contact for future research. In addition, the research team may reach out to participants in VA support groups or contact a potential participant (with their consent).

HIPAA Waiver for Authorization for Research may be used. We will be using the waiver to enhance the efficiency of participant enrollment once a patient is referred to us or contacts us for screening. This waiver will allow us to prevent and avoid creating patient burden and prevents the patient from unnecessary time and effort that could be used for other appointments. We are requesting a HIPAA waiver to have the approval to view their medical record to ensure no obvious exclusionary criteria exist *before* we bring them in for a baseline visit (recent suicidality, homicidally, psychiatric inpatient stays or psychosis). This would be beneficial to the patient because we could determine quickly if the patient would not be a good fit for research and make a proper referral. This would also eliminate the burden of a 3-hour baseline visit where the patient would otherwise be asked to discuss trauma history at length.

9.0 Consent Process

Prospective participants will either contact the study team to learn more about the trial and/or to complete an initial screening process. Alternately, the study team may contact prospective participants directly for screening. If prospective participants complete the initial pre-screen process, they will be invited to come to our research office for a baseline visit or complete the visit via telehealth. Potential participants will be given a full description of the study procedures and asked to read and sign (or electronically sign) an IRB-approved informed consent form before any study procedures or assessments are conducted. Informed consent will take place on the MUSC or VA campus, or via telehealth. Initial eligibility screening will be conducted by the PI, Co-Is, Coordinator, or a trained Research Assistant by telephone or in person. If preliminary inclusion and exclusion criteria are met, staff will schedule an assessment appointment for the participant. In a private room, participants will be provided with a description of the nature and requirements of study participation and asked to read and sign an IRB-approved consent form prior to beginning any study procedures. eConsent will be conducted through an IRB-approved platform, such as Doxy.Me or RedCap.

VA eConsent: in the case of VA eConsent study staff will send the paper consent document to the study participant via email or snail mail prior to the consent and baseline appointment. Study staff will arrange to have a call with the study participant where the study participant will sign the consent and then hold to camera for screenshot by study staff (using government furnished equipment). This screenshot image would then be saved by the study staff as documentation.

10.0 Study Design / Methods

General Procedures. Interested individuals will be screened by telephone or in person. Individuals who meet inclusion/exclusion criteria will be invited to come into the office or will schedule a telehealth appointment for a baseline assessment. Potential participants will be given a full description of the study and asked to read and sign an Institutional Review Board (IRB) approved informed consent form before any study procedures occur. All eligible and interested participants will then receive 10, 90-minute sessions of PE therapy (described below).

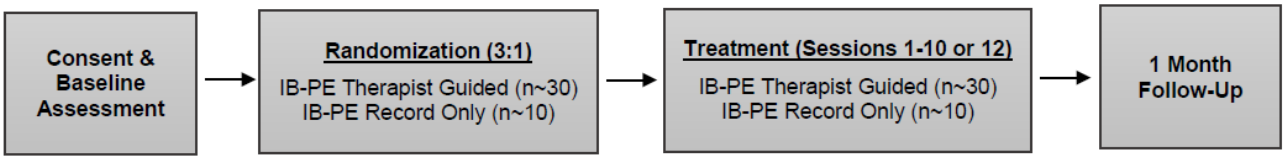
Virtual In-Service Appointment. All eligible participants will be provided with a technology package (either at the office or via mail) that includes a cell phone, electronic tablet (for telehealth participants), complete Zeriscope technology system, training materials, device cleaning supplies and masks. After receipt of the technology package, an in-service call will be scheduled with Zeriscope to review the use and comfort of the equipment.

Prolonged Exposure (PE) Therapy. PE will be delivered based on Foa's therapy manual (Foa et al., 2019). Specific to this study, participants will be asked to wear the apparatus during therapy sessions. During session 1, the Study Therapist will provide the rationale for PE, review trauma history, conduct breathing retraining, and orient the patient to the apparatus. Session 2 will include review of common reactions to trauma, introduction of SUDS, in vivo hierarchy development, instructions on how to use the IB-PE system, and a brief in-session practice. During the in vivo hierarchy development, participants will work with the study therapist to identify stressful triggers, listing these from most stressful to least stressful. The most stressful situation will be listed at the top of the hierarchy. A large part of PE therapy is safely exposing the participant to these individualized stressful situations (for example, going to a mall, walking in a crowded grocery store, visiting a park or engaging in a stressful activity, such as watching a suspenseful video clip). Part of the PE therapy includes going to these stressful situations as "homework" each week. That is, participants will be asked to expose themselves to their identified stressful scenarios outside of the office. Specific to this study, participants will be asked to wear the apparatus during these exercises. The exercises will be audio and video recorded. Sessions 3-9 include in vivo "homework" review

and planning for next in vivo assignments, imaginal exposure, and processing. During session 10, the therapist and patient review treatment progress and discuss potential next steps depending on each patient's needs (e.g., couple's therapy, vocational counseling). A participant may be offered the option of two additional sessions of PE (for a total of 12 sessions) if he or she does not demonstrate sufficient improvement of PTSD symptoms as determined by a decrease of 10+ points in PCL-5 score from Baseline to Session 9. All Study Therapists will have a master's or doctoral degree, complete a PE training, and attend weekly supervision during the trial. Sessions checklists will be used for fidelity to the manual (Carroll et al., 2007).

As shown in **Figure 3**, 10 sessions of PE will be delivered, with the possibility for participants to complete two sessions per week. Prior to using the IB-PE system, participants will use the system to develop an 'in-office' baseline that will be used for reference throughout the IVEs. Another 'in-office' baseline will be recorded at final session to assess physiological and subjective changes that have occurred throughout the course of the treatment. All participants will wear the IB-PE system, affording maximum data collection during IVEs and thorough evaluation of the new system. The in vivo exercises will be guided by either the Study Therapist or a clinical support team member. This role will be referred to as the 'IVE Coach.' The participants will be randomly assigned to either IB-PE (guided) or to IB-PE (record only) based on a 3 to 1 randomization scheme (3 guided: 1 record only). In the guided group, the IVE Coach will lead the participant in the in vivo exercises. The IVE Coach will use actionable data during IVEs (e.g., HR, GSR) to modify the assignments in real time. The IVE Coach will virtually accompany patients to at least three IVEs. After that the IVE Coach will start out the session by guiding the participant for the first several minutes, then will leave the session once the participant demonstrates competency in finishing the exercise on his or her own. The IVE Coach will be in close communication with the rest of the clinical support team regarding the participant's IVE completion. Study Therapists will receive a system notification each time a patient completes an IVE, along with a summary report from that assignment (e.g., total time, $\bar{x}$ and peak GSR). These data may be used to objectively monitor treatment progress and discussed with the patient in the office (e.g., to highlight habituation within or between IVEs) (Rauch et al., 2018). In the record-only group, passive data collection will be utilized to collect and store biometric and behavioral data for future offline analyses to investigate predictors of outcome. Wifi availability will be considered in the selection of the therapist-guided locations for IVEs. In the rare event that wifi signal is not present during a therapist-guided IVE, the participant and IVE Coach would work together to find an alternate solution (complete the IVE without wifi, and/or complete an additional therapist-guided IVE at another time and location, and/or reevaluate the in vivo hierarchy and make modifications to include locations with wifi. If equipment malfunctions at any point throughout the study, a replacement system will be provided to the participant. Zeriscope will be notified of equipment malfunctions.

Figure 3. Overview of the randomized clinical trial. Participants (N=40) randomized to 10 sessions of PE (once or twice weekly visits) and either a) PE with guided IVEs using Intelligent Biometrics (IB-PE Guided) or b) PE alone (IB-PE Non-guided).



How the IVE Coach will guide the patient through IVEs: While there will be some variability based on individual patients and specific in vivo activities, the patient and IVE Coach will use synchronous audio/video to communicate, and will provide a brief (3 min) review of the instructions before the patient begins the IVE. In addition, a baseline for each IVE will be established prior to beginning the IVE exercise. If the patient is optimally engaged in the exercise, as demonstrated by increasing physiological (e.g. skin conductance, heart rate) and subjective (increase in SUDS scores) indices, the IVE Coach will provide

encouragement to continue but will not interrupt the patient. If the patient is not engaged (e.g., showing low/no increase in physiological and subjective indices of engagement, not following instructions, engaging in distraction behaviors), the IVE Coach will intervene and review the instructions, provide specific guidance to help the patient engage, and provide feedback until the patient is optimally engaged to maximize benefits. After the IVE, a brief (5 min) processing will occur. The IVE Coach will ask the patient how he/she thinks the exercise went, what was learned, and plan the next IVE. The IVE Coach will complete a check-out form documenting how the exercise went and will communicate this with the clinical support team.

Telehealth: Participants in this research study may choose to complete informed consent/baseline appointment, study visits and therapy sessions via home-based telehealth (HBT) care (i.e., service delivery to patients in their homes using consumer-friendly, video-conferencing technology) which may likely enhance retention by directly circumventing financial and transportation barriers associated with traveling to MUSC/VA for in-person sessions. HBT sessions will be delivered via standard desk, laptop computer, tablet, or smartphone running MUSC/VA approved applications.

Assessments. The instruments to be used were selected because many are standardized, have good psychometric properties, are widely used, and have been used by our research group. The primary outcome measures are described in this section. Information regarding additional measures can be found in Table 1.

Primary clinical outcomes include: the CAPS-5 for clinician-rated and PCL-5 for self-reported PTSD symptoms. The CAPS-5 is a 30-item structured diagnostic interview and gold standard for assessing PTSD (Weathers, Blake, et al., 2013). Independent evaluators blind to treatment condition will conduct the CAPS-5 at baseline, end of treatment, and follow up. The PCL-5 is a 20-item self-report measure that assesses PTSD severity each week and has excellent psychometric characteristics (Weathers, Litz, et al., 2013). IVE assessments include: psychophysiological reactivity (HR and GSR), which will be measured passively and continuously during IVEs using the patient worn data acquisition system (Zeriscope Inc.). Consistent with imaginal exposures, Subjective Units of Distress (SUDS; 0=no anxiety to 100=extreme anxiety) will be collected at 5-minute intervals during IVEs. A tone will signal patients to enter their SUDS using the device. Self-report questionnaires employed in our pilot feasibility study and other studies will assess comfort, acceptability, willingness to use, utility, and client satisfaction (Attkisson & Greenfield, 2004; Rizzo et al., 2010).

Table 1. Assessment Instruments and Timeline

Instrument Name	Purpose/Domain	BSL	Session 1-9	Post TX	1 Mth F/U
Informed Consent	Obtain informed consent	X			
Demographics Form	Characterize sample	X			
MINI International Neuropsychiatric Interview	Assess DSM-5 psychiatric disorders	X			
Adverse Events	Monitor AEs and safety		X	X	X
Life Events Checklist: LEC	Assess trauma exposure	X			
Clinician Administered PTSD Scale: CAPS-5	PTSD symptom severity (clinician-rated)	X		X	X
C-SSRS	Assess suicidality	X		X	X
PTSD Checklist: PCL-5	PTSD symptom severity (self-report)	X	X	X	X
Beck Depression Inventory-II: BDI-II	Measure depression	X	X	X	X
Race Related Events Scale	Assess Race Related Trauma	X		X	X
Trauma Symptoms of Discrimination	Assess Race Related Trauma	X		X	X
Distress Tolerance Scale: DTS	Measure distress tolerance skills	X		X	X
Client Satisfaction Questionnaire-8: CSQ	Satisfaction with treatment			X	
Posttraumatic Cognitions Inventory PTCI	Assess trauma-related thoughts and beliefs	X	1, 5	X	X
COVID 19 Survey	Assess impact of COVID-19	X	5	X	X
Helping Alliance Questionnaire: HAQ-II	Assess therapeutic alliance			X	
Treatment Services Review: TSR	Monitor services utilization	X	5	X	X
In Vivo Exposures: IVEs	Assess biological and self-report indices of engagement (HR, GSR, SUDS), and evaluate feasibility and acceptability		3-9	X	
System Usability Scale: SUS	Assess usability and comfort		3,5	X	
SUS-Therapist	Assess usability and comfort		5	X	
Wangelin survey	Acceptability and comfort		3,5	X	
Turn on/off system in <5 min	Feasibility		2	X	
How often attempted to use and completed IVEs using the system	Feasibility		3,5	X	
Exit Feedback Survey	Collect general feedback on study treatment			X	

Note. BSL = baseline, TX = treatment, F/U = follow-up, HR = heart rate, GSR = galvanic skin response, SUDS = Subjective Units of Distress Scale

Subject Compensation. Subjects will receive $50 for the baseline appointment, $30 for each of the 10 visits and $50 for the one-month follow up. The total compensation available is $400. Payment will be provided in Visa gift card or pre-paid debit card, called a ClinCard. Subjects will be compensated at the end of each visit by IRB-approved study personnel.

The ClinCard works like a bank debit card and you may use the card to purchase goods or services everywhere Debit MasterCard is accepted as long as you do not exceed the balance available on the card. Participants will be given a ClinCard at the beginning of the study. Each

time they receive payment for participation in this study, the money will be added to the card, as outlined in the payment schedule above. The ClinCard will come with information on how to use the card, a phone number to call to set a PIN and a phone number to call to check the card balance as well as the study staff contact information in the case that the ClinCard is lost or stolen.

11.0 Data Management

Overview. Research materials obtained from participants include self-report surveys and structured clinical interviews, and physiological and behavioral observation data. All data collection described in this protocol is collected specifically for the purposes of the proposed research project. To maintain confidentiality, all digital and paper data collected will be numerically coded. Paper data will be kept in locked filing cabinets and digital files will be kept on password-protected computers within MUSC/RHJVA encrypted data server. No parties shall have access to these data aside from the PI and necessary research staff. A master list of participant names, study ID numbers, and contact information will be kept in a location separate from study materials within MUSC/RHJVA encrypted data server. VA data will be stored in dedicated research offices of the Study Coordinator and Research Assistant within the RHJVA Research Building. Access to research records (paper and computerized) will be restricted to the project staff. The data will be kept in a locked file cabinet within a locked office at the RHJVA. Names will not be used on specimens, assessments, or be available in the research laboratory. The investigators and all study personnel will sign a confidentiality agreement that no identifying information of specific individuals will appear in any internal reports or external documents (e.g., peer-reviewed publications, presentations). Research subjects' data will be entered in a computer database with only number codes for identifiers and will not identify study subjects by name. Custody and disposition of VA Federal Records are maintained in accordance with RCS 10-1

General Statistical Analyses. All analyses will be performed on the intent-to-treat sample consisting of all randomized subjects. Baseline clinical and demographic characteristics will be collected and t-tests, chi-square tests, or their non-parametric equivalents will test for group differences, as appropriate, in SAS v9.4 (SAS Institute, Cary, NC, USA). Baseline characteristics that are associated with the primary outcome measures will be included as covariates in subsequent analyses. For all analyses, alpha will be set at 0.05. Urn randomization will be stratified by PTSD severity (CAP-5 total score at baseline). Based on our sample size and assuming 20% attrition (N=32), we have 80% power to detect a large effect (Cohen's d = 1.02) for treatment outcome at a probability level of 0.05 for a two-tailed test (Cohen, 1988).

Hypothesis 1: IB-PE will be feasible and acceptable, as evidenced by at least 80% of participants (a) being able to turn on/off the equipment in ≤5 minutes; (b) reporting positive perceptions toward IB-PE via self-report assessments (Sekhon, Cartwright, & Francis, 2017). Hypothesis 2: Participants in the IB-PE guided group will evidence significantly greater pre- to post-treatment reductions in PTSD severity as compared to the record-only group. To test this hypothesis, independent generalized linear mixed effects models will be used to examine PCL-5 and CAPS-5 scores at final session by group. Models will be adjusted, respectively, for baseline PCL-5 and CAPS-5. Group will be entered as the predictor variable. Hypothesis 3: Higher levels of physiological and subjective engagement will predict greater treatment response. To test this hypothesis, mean HR, GSR, and SUDS responses during IVEs will be calculated according to previously published methods (Norrholm et al., 2016; Rauch et al., 2018; Rothbaum et al., 2014) and multilevel modeling (MLM) will be used to analyze these variables as predictors of CAPS-5 at final session within and between treatment groups.

Exploratory analyses will examine group differences in the number of sessions required to attain significant symptom improvement on the PCL-5 from baseline (Rothbaum et al., 2014) and durability of effects at 1-month follow up. Data from both groups will be harnessed to explore the development of patient-specific algorithms predicting optimal engagement during IVE.

Data Management and Capture. We plan to use REDCap (Research Electronic Data Capture) for data capture and management for self-report surveys and clinical interviews. REDCap is a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap provides secure, web-based flexible applications, including real time validation rules with automated data type and range checks at the time of entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R and Microsoft Excel. The system allows the research team to create and engage respondents using a variety of notification methods.

REDCap data dictionaries can be distributed for reuse at multiple institutions. The underlying database is hosted in a secure data center at MUSC/VA, 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. Data that will be collected during IVEs (i.e., physiological data, self-reported SUDs, and video-recorded behavioral observation data), will be stored on Zeriscope's secure cloud-based system, which is HIPAA-compliant and designed to rapidly store quantitative and qualitative data from IVEs. The database will be secure and backed up daily.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

This Data and Safety Monitoring Plan (DSMP) has been developed in accordance with the National Institutes of Health (NIH) Office of Human Research Protection (OHRP) to assure the appropriate clinical safety monitoring of study subjects participating in this project.

Summary of the Protocol. The proposed Phase I project will develop and test a mobile technological system to be integrated into Prolonged Exposure (PE) treatment for posttraumatic stress disorder (PTSD). The investigative team will evaluate the usability, acceptability, feasibility, and preliminary efficacy of the system in civilians and US veterans or military personnel with PTSD. The primary outcomes of interest include self-report and clinician-administered PTSD severity scales.

Trial Management. The study will be managed from the Addiction Sciences Division within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina (MUSC), College of Medicine, Charleston, SC.

Responsible Party. Dr. Back (PI) will be responsible for distinguishing between serious adverse events (SAEs) and non-serious adverse events (AEs), and determining initial study relatedness.

Data and Safety Monitoring Board (DSMB). We will create a DSMB to monitor overall participant safety, the rate and severity of adverse events, and the validity and integrity of the data. The panel will include 2 researchers with experience in treating patients with PTSD and a biostatistician. The board may be called at any point if needed for unexpected AEs, etc. Modifications will be made in the procedures and/or the protocol if necessary, based on the recommendations of the board. Confidentiality will be maintained during all phases of the study.

Adverse Events. An *Adverse Event (AE)* is defined as any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the study that may or may not be related to study participation. All AEs will be reviewed weekly by the PI, and annually by the DSMB, MUSC IRB, and VA Research and Development. A *Serious Adverse Event (SAE)* is defined as an adverse event that has one of the following outcomes: results in death, is life-threatening, requires inpatient hospitalization

or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, OR requires intervention to prevent one of the above outcomes.

AE/Unanticipated Problem Follow-up. Unanticipated problems, potential AEs and SAEs will be identified during the study via self-report data, as well as weekly assessments and interviews. All unexpected AEs and SAEs will be monitored until resolved. A detailed summary of all AEs will be prepared weekly by the research staff and reviewed by the PI at the weekly study team meeting.

Risks of Study Participation. Risks of participation related to inconvenience, psychological discomfort and boredom, physical discomfort, and confidentiality are outlined in the Human Subjects Section. Well-established strategies to protect participants against risks are also outlined.

Safety Reporting. AEs are reportable to the local IRB if the AE is unexpected AND related or possibly related AND are serious or more prevalent than expected. The IRB definition of *unexpected* is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of *related* is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. SAEs will be reported within 48 hours of knowledge of the SAE. In accordance with the MUSC IRB, any deaths that occur during the study or 30 days post termination from the study will be reported within 24 hours, regardless of whether it is expected or unrelated. Follow-up of all unexpected and serious AEs will also be reported to the appropriate agencies. All AEs are reviewed weekly by the PI, and annually by the DSMB and IRB. Any significant actions taken by the local IRB and protocol changes will be reported to NIMH. An annual report summarizing all AEs will be provided to the NIMH project officer. This report will include 1) confirmation of adherence to the DSMP, 2) a summary of any data and safety monitoring issues that have arisen since the previous report, 3) a description of any changes in the study protocol or DSMP that might possibly affect risk, and 4) all new and continuing IRB approvals.

AEs and SAEs occurring during the course of study will be collected, documented, and reported in accordance with protocol and IRB reporting requirements. All research staff involved with AE reporting will receive training including identification, evaluation, documentation and reporting. All research staff will identify any potential AEs during the course of the study from self-report data and administration of assessments and interviews. This information will be provided to the PI, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

When a reportable SAE is identified, research staff will initiate an SAE form, and the following individuals will be notified within 48 hours of knowledge of the SAE: study co-investigators, the MUSC IRB, the NIMH project officer, and members of the DSMB, as appropriate. If complete information is not available when the initial 48-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research staff will attach copies of source documents to the SAE report for review by the PI and for forwarding to the NIMH project officer as appropriate.

Study Safety. Protocols for reported AEs and SAEs are outlined above. All unexpected AEs and SAEs will be monitored until resolved. A detailed summary of all AEs will be prepared weekly by the research staff. At the weekly team meetings (or before if urgent), the research staff will report any premonitory symptoms of clinical deterioration. Study procedures will follow the FDA's Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). Any outside requests for information or any breaches in confidentiality will be reported to Dr. Back. All requests by participant's physicians and other medical providers will be

referred directly to Dr. Back.

Follow-Up Phase. All participants will be provided with a list of community resources upon study completion. Individuals presenting at any time with serious mental or physical health symptoms will be referred clinically for treatment. In the unlikely event that a participant demonstrates clinical deterioration, he/she will be referred clinically consistent with the procedures outlined in the Human Subjects section. In the event that emergency evaluation or intervention is necessary, the participant will be escorted by a study staff member to the psychiatric walk-in clinic or emergency room. Psychiatric hospitalization is available for emergencies at any point in the study.

Data Management and Analysis. A data analytic plan is outlined in the Statistical Analysis section. This study is powered to examine the efficacy of intelligent biometrics to optimize PE on the primary outcomes of interest. The main outcome variables include the severity of self-report and clinician-rated PTSD measures. Analyses will be guided by the specific hypotheses of the study and conducted by the study biostatistician. Post-hoc exploratory analyses will be conducted with two-tailed tests and more conservative statistical procedures which guard against Type I error (e.g., Tukey tests). All primary hypotheses will be tested at level of significance $\alpha=0.05$. We will also estimate the effect sizes of interest and provide 95% confidence intervals. Please see the Statistical Analysis and Power section for more details.

Quality Assurance and Confidentiality. Data quality will be monitored by random inspection of the completed forms by research staff and any irregularities or problems detected will be discussed with the PI. Project therapists will receive standardized training from the PI and Co-Is. Adherence to the manual will be monitored using session checklists and weekly supervision. If therapy drift is observed the therapists will be re-trained.

DSM Plan Administration. The PI will be primarily responsible for monitoring the study. The PI and a statistician will examine the outcomes database for missing data, unexpected distributions or responses, and outliers. A DSMB report will be filed with the IRB on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs and SAEs. We will report main outcome results at the end of the trial. An annual report of all AEs will be submitted to the NIMH project officer. In addition, all AEs will be reviewed weekly by Dr. Back, and annually by the DSMB, local IRB and VA Research and Development. Any significant actions taken by the local IRB and protocol changes will be reported to NIMH.

For any SAE, the appropriate IRB-approved SAE protocol specific reporting forms will be completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. If complete information is not available when the initial SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. Follow-up of all unexpected and serious AEs will be reported to all regulatory entities including the local IRB, DSMB, and NIMH, as appropriate. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization, or until the subject is no longer in the study.

Stopping Rules for Clinical Trials. The trial will be stopped under any of the following conditions: 1) there is clear evidence of harm; 2) there is no likelihood of demonstrating treatment benefit, or 3) there is overwhelming evidence of the benefit of treatment.

ClinicalTrials.gov Requirements: In accordance with Public Law 110-85, the proposed trial will be registered with ClinicalTrials.gov. Applicable requirements regarding results reporting will be adhered to.

14.0 Withdrawal of Subjects

All participants will be screened thoroughly for eligibility following informed consent. The PI may discontinue participation at any time if a participant demonstrates or reports significant distress, presents a risk of harm to self or others, or is otherwise unable to complete the study. Participants may withdraw from participation at any time during the study procedure. Clinical referrals to community resources will be made available to all study participants.

15.0 Risks to Subjects

Inconvenience, Discomfort, and Boredom: Some participants may experience distress by questions pertaining to their trauma or their emotional functioning. All participants will be informed at the outset that the study is voluntary, and they may terminate participation at any point. Our past and ongoing research suggests that data collection using many of these measures can be conducted without undue psychological distress or exacerbation of symptoms. This experience includes substantial research with younger and older adults, active duty service members, military Veterans, rape victims, victims of other forms of violence (e.g., natural disasters, car accidents), and work on large-scale studies asking questions about similar topics with general population samples. Legal risks arise if individuals are homicidal or suicidal and make these intentions known to project staff, who may then be required to notify authorities and the target of homicidal intent. These risks are outlined in the informed consent documents.

Some participants may experience a temporary increase in PTSD symptoms during the Prolonged Exposure (PE) treatment. This is normal, not unexpected, and not associated with negative treatment outcomes. Research by our group and others shows that the majority of patients undergoing PE treatment do not experience an increase in symptoms, and that any increases in symptoms that do occur are mild-moderate, temporary, and not related to retention or end of treatment PTSD symptoms.

In the event that subjects experience psychological distress secondary to participation, they will be encouraged to contact the Principal Investigators. Dr. Back (PI) is a licensed clinical psychologist and Staff Psychologist at the VA. Participants will be given contact information for Dr. Back at the time of consent, as well as resources for local and national 24-hour hotline numbers. In addition, participants will have access to urgent care services at MUSC and the VA. The research team is comprised of licensed clinical psychologists with extensive experience working with adults who have experienced significant life stressors and PTSD. If assessors or project staff believe that a participant is significantly distressed by participation, the PI will be notified and will contact the participant immediately to assess distress and assure participant safety. If called by a participant, the PI will attempt to address all participant concerns and will set up an alternate referral for clinical services outside the project if desired.

Physical Discomfort: Participants may experience some physical discomfort from wearing the device. The foam electrode gel may cause mild irritation though the electrodes being used have a unique, patented pre-gelled adhesive side with non-irritation gel especially developed to prevent allergic reactions. The foam electrode is latex free and therefor suitable for every skin type. We will instruct participants how to appropriately wear the device and have them practice wearing it. We will also provide written and illustrated instructions for how to wear and use the device during in vivo exercises to ensure it is as comfortable as possible.

Confidentiality: All possible efforts to protect participants' privacy and confidentially will be made throughout the course of the study. Participants will be provided with a written informed consent document which specifies the risks and confidentiality protections and limits of study procedures.

Sources of Materials: Data will be in the form of structured clinical interviews, self-reported questionnaires and subjective units of distress scale (SUDS) ratings, and physiological data that will be obtained specifically for research purposes. Access to research records will be limited, as they will be maintained in a locked cabinet in the project coordinator's locked office within MUSC or VA. Only researchers working

on this project will have access to the participants' data. The material will be specifically obtained for research purposes. Telehealth sessions will be conducted using only approved MUSC/VA applications to maintain confidentiality. Data will be collected by trained study personnel under the direct supervision of Dr. Back (PI). Participants will be permitted all the time they need to ask questions and/or consult with family members. Participant will be fully informed of all aspects of the study before signing the informed consent and beginning any study procedures.

Adequacy of Protection against Risks

Recruitment and Informed Consent Procedures: Participants will be primarily recruited from the Ralph H. Johnson VA Medical Center (VAMC) and the Medical University of South Carolina (MUSC). IRB-approved flyers and brochures describing the study and providing contact information will be placed in the PTSD and mental health clinics at both hospitals. We will also post IRB-approved recruitment flyers in prominent locations in other VA and MUSC hospital clinics (e.g., internal medicine, women's health, emergency department). We will additionally recruit from the general community via online and local media advertisements. The research team has used these methods successfully in previous and ongoing research studies to recruit veterans and civilians with PTSD and other psychiatric conditions.

The research team and all of the study staff have completed (or will complete upon hiring) the Miami Collaborative IRB Training Initiative (CITI) course and its associated tests in research ethics. Informed consent (IC) will be collected at the study research offices, in a private, interruption-free environment. The PIs, Co-Is, or a Study Coordinator will obtain IC. The IC form will outline: a) the sponsorship of the study; b) the nature, purpose and procedures of the study; c) the voluntary nature of participation (i.e., participation is not required; participation can be discontinued at any time); d) the duration of the study; e) potential risks and discomforts, as well as benefits of participation; f) that all information will be kept confidential subject to the provisions of the state and federal law; g) compensation; and h) alternative treatments. The IC form will specifically review the potential for psychological distress, and the risks associated with treatment that may occur as a result of study participation. The IC form will be explained to participants in easy-to-understand language, and participants will be instructed to read the form carefully prior to signing it. The IC form will include emergency contact information for the PIs. Any questions pertaining to the study or consent process will be answered fully. Potential participants will not be required to make a decision to participate at the initial contact, though that possibility will be available. If participants wish to discuss study participation with their family and/or significant others, they will be encouraged to do so. Participants will be informed that they can discontinue their participation in the study at any time and that this decision will not influence the care they receive at MUSC or the VAMC. Consent will be documented by the signature of the participant on the IC form, accompanied by the signature of the individual obtaining the consent. Participants will be given a copy of the informed consent to keep. Research staff will document the informed consent process in the medical record of the participant.

Confidentiality: Risks to confidentiality will be minimized by using initials and code identifiers. There will be no linkage between a participant's identity and their responses. There will be only one master list of participants (not linked to any participant responses) which will be kept locked separate from all data and will be available only to the PI, Co-Is and approved study personnel. All data will be stored in a confidential manner (i.e., in locked files or on encrypted computers in the Study Coordinator's office) so as to protect the confidentiality of participant information. Access to research records (paper and computerized) will be restricted to the project staff. Our research staff are well trained in the confidential nature of research subjects' records. Research staff complete annual courses on confidentiality protection and most recently on HIPAA regulations. These procedures are highly effective in protecting confidentiality issues. Names will not be used on specimens, assessments or be available in the research laboratory. The investigators and all study personnel will sign a confidentiality agreement that no identifying information of specific individuals will appear in any internal reports or external documents (e.g., peer-reviewed publications, presentations). Participants' data will be entered in a computer database with only number codes for

identifiers and will not identify study subjects by name or other identifiers (e.g., birth date). These procedures have proved highly effective in preventing breaches of confidentiality in our current and previous research studies.

Assessment Procedures: Risks associated with assessment and treatment include the possibility that participants might be upset by questions pertaining to trauma or their emotional functioning or talking about their trauma. The research team will closely monitor participants for any increase in distress at every treatment visit. PTSD and depression symptoms will be monitored weekly using standardized measures (PCL-5, BDI-II) in order to detect any symptom worsening requiring further evaluation. Additionally, participants will be advised to observe any signs of worsening PTSD, depression, and other symptoms, and to discuss these with the research team. All participants will be informed at the outset that they may terminate participation at any point. If a participant becomes upset in-between visits, he or she will be encouraged to contact the Study Coordinator, their Study Therapist, and/or Dr. Back. If a participant needs or desires immediate attention, arrangements will be made for an appointment with an experienced mental health provider. The informed consent document provides direction to contact the study staff during office hours and/or the Emergency Room at any time for worsening of symptoms.

Our previous and ongoing PTSD research suggests that data collection using many of these measures can be conducted without undue psychological distress or exacerbation of symptoms among participants. This experience includes substantial research with younger and older adults, military service members, rape victims, victims of other forms of violence, and work on large-scale studies asking questions about similar topics with general population samples. In addition, it includes Veterans with military-related PTSD. In the event that participants experience extreme psychological distress secondary to participation, they will be encouraged to telephone the PIs. In addition, they will have access to urgent care services at MUSC and the Ralph H. Johnson VAMC. The research team is comprised of licensed clinical psychologists with extensive experience working with adults who have experienced significant life stressors and addiction. If project staff believes that a participant is significantly distressed by participation, Dr. Back will be notified and will contact the participant immediately to assess distress and assure participant safety. If called by a participant, Dr. Back will attempt to address all participant concerns and will set up an alternate referral for counseling for those who desire it from outside the project. All participants will review, at the initiation of participation, an informed consent document which specifically reviews potential psychological distress from the assessments or PE therapy as a potential outcome of participation. If necessary, they will be asked to complete a safety plan and agree to call the project staff or 911. However, if safety is in question in the minds of any project staff, the Mobile Crisis unit of Charleston County, which involves a team of police and psychiatric workers, or the EMS unit will be dispatched to the participant's home to assure safety. In our NIH-, VA- and DoD-funded clinical trials of PTSD treatment provision, we have not had any problems related to participation that could not be safely resolved with these methods.

16.0 Potential Benefits to Subjects or Others

While there is no guarantee of specific benefit to participants in this study, the potential benefits include a thorough psychological assessment, referral to appropriate treatment services and community resources, and remuneration. Participants may also benefit from receiving access to an evidence-based behavioral treatment which may result in a reduction in aversive PTSD symptom severity and symptoms of other mental health problems (e.g., depression, anxiety) and improvements in other areas of functioning (e.g., sleep, quality of life). Other study benefits include regular contact with research staff, access to assessment information pertaining to PTSD, and referral to treatments for associated problems such as substance use disorders. While these benefits may be considered minimal, we believe that they outweigh the minimal risk and burden incurred by participants. Participants will also enroll in a study that has the potential to enhance treatment for other patients with PTSD.

17.0 Sharing of Results with Subjects

Study data will not be shared with participants to maintain confidentiality.

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