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PROTOCOL TITLE:

Telehealth-delivered Massed Imaginal Exposure for PTSD: Toward Increasing Access to Alternative, Evidence-based Treatment Schedules for Virtual Care

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

The goal of this project is to establish the safety, feasibility, and acceptability of abbreviating and accelerating telehealth-delivered imaginal exposure therapy for post-traumatic stress disorder (PTSD). Importantly, conventional telehealth-delivered Prolonged Exposure (PE) therapy is non-inferior to the conventional, gold standard in-person PE for PTSD (Acierno et al., 2017). Intensive or massed schedules of in-person exposure- based trauma-focused treatments have likewise recently been shown, in a nascent but promising literature, to produce comparable treatment outcomes to conventional once or twice weekly schedules, but importantly, with lower levels of premature dropout (Sciarrino et al., 2020; Zoellner et al., 2017).

AIM 1: Establish the safety of VVC-delivered massed imaginal exposure for PTSD. We hypothesize that VVC-delivered, massed imaginal exposure will be safe as indexed by no significant adverse events.

AIM 2: Establish the feasibility, tolerability, and acceptability of VVC-delivered massed imaginal exposure for PTSD. We hypothesize that 1) veterans will consider the treatment acceptable and tolerable and that 2) recruitment and retention will be feasible (> 80% retention).

EXPLORATORY AIM 1: Establish acceptability among stakeholder providers of VVC-delivered massed imaginal exposure for PTSD. We hypothesize that 1) telemental healthcare providers will consider the treatment acceptable and tolerable and that 2) will be willing to receive training and/or refer patients to such services.

EXPLORATORY AIM 2: Establish the preliminary efficacy of VVC-delivered massed imaginal exposure for PTSD. We hypothesize that 1) veterans will demonstrate moderate reductions in posttraumatic stress and associated symptoms and impairment from intake to the end of treatment that will in turn, 2) be maintained or extended at the 1-month post-treatment follow-up.

2.0 Background

The need for enhancing PTSD treatment. PTSD is a chronic, impairing condition with variable rates of recovery. PE, which consists primarily of imaginal and in vivo forms of exposure to trauma reminders, is an effective first-line intervention (Power et al., 2010), with wide acceptance among evidence-based practitioners. However, many PTSD patients show non- remittance (~25-50%; Rosellini e al., 2018), poor treatment responses (~60%); Loerinc et al., 2015) and dropout (~18-68%; Imel et al. 2013). Thus, there are well-defined needs to improve the efficacy, effectiveness, efficiency, and tolerability of this challenging, but potent form of intervention, and an equally pressing need to develop and deploy technologies that enhance access to treatment.

Accelerated protocols for enhancing treatment efficacy and efficiency. In response to calls to enhance the efficiency of exposure-based treatments, accelerated protocols have been demonstrated to be non-inferior to the standard PE protocol. This includes a previous trial by Col Dr. Cobbs and colleagues that implemented a daily 6-session protocol (Zoellner et al., 2017), resulting in comparable efficacy and much lower dropout (6.3%) compared to standard bi-

weekly 10-session PE. This is consistent with a small, but growing number of studies of massed evidence-based treatments for PTSD, which have revealed large effects (d = 1.15–2.93) and low attrition across studies (5.1%; Sciarrino et al., 2020). Thus, by reducing burden by enhancing efficiency, accelerated protocols may especially be indicated for those at high risk of dropout, such as Veterans (28.1%; Eftekhari et al., 2013).

Telehealth delivery of exposure-based interventions. Enhancing access is another critical aspect of improving interventions. The VA system has served as a guidepost for deployment of empirically-supported telehealth interventions for PTSD, and our PTSD Clinical Team (PCT) completed 1,800+ telehealth therapy visits using VA video connect (VVC) in the last year. Further, recent seminal work from Ralph H. Johnson VAMC (RHJVAMC) investigators has demonstrated equivalence of telehealth-delivered versus standard in- person PE for reducing trauma-related symptoms (Acierno et al., 2017). Additionally, CoI Dr. Sciarrino and colleagues (2020) have recently summarized the emerging literature showing the equivalence of intensive trauma-focused treatment (e.g., daily sessions) in comparison to standard weekly, or bi-weekly protocols (Sciarrino et al., 2020). The present pilot study reflects an extension of these efforts, by evaluating a telehealth- delivered accelerated treatment consisting of the core imaginal exposure component of PE.

Remote affective and physiological measures. Theoretical and empirical support suggests emotional and physiological engagement with feared, dreaded, and avoided targets is requisite for therapeutic change to occur in exposure-based interventions (Foa & Kozak, 1986; Lang, 1979). While it is customary in PE to assess engagement based on self-reported distress, there is a need to integrate more objective measures of emotional and physiological activation. For instance, there is relatively low correspondence between subjectively-reported and objectively-measured engagement, and whereas heightened physiological activation predicts better outcomes, blunted physiological activation predicts poorer outcomes in exposure-based treatments (Wangelin & Tuerk, 2015). Of course, telehealth delivery presents challenges to physiological monitoring. However, recent technological advancements, including in areas of machine learning, afford the ability to monitor physiological activation and other affective markers entirely remotely. This is achieved by extracting affective and physiological signals, such as heart rate, respiratory rate, and facial and vocal affective markers based solely on visual and acoustic features of ordinary webcam footage (e.g., van der Kooij & Naber, 2019).

Impact and innovation. The goal of this proposal is in line with the priorities of the VHA and HSR&D priorities as well as the priorities of the Charleston HEROIC RIVR Pilot Project Program. Specifically, this proposal aligns with the mission stipulated in the HEROIC RFA to focus on “novel applications of telemental healthcare delivery including feasibility and/or preliminary efficacy/effectiveness trials”.

We propose that there is strong potential for broader implementation of intensive or massed exposure-based, trauma-focused treatments, and that such implementation could be even greater if virtual deployment is feasible and acceptable to patient and provider alike. Furthermore, an alternative VVC-delivered trauma- focused treatment with shorter demands on total duration

could broaden VA providers' arsenal of evidence- based interventions. This would enable greater tailoring of treatment plans to individual veteran preferences for frequency and duration of sessions as well as more flexible accommodation to daily life demands and related scheduling barriers. Taken together, we propose that establishing the safety, feasibility, and acceptability of massed exposure-based therapy delivered via VA Video Connect is a productive first step toward advancing telemental health treatment options and furthering personalized care for our veterans.

Importantly, in regards to the likelihood of impact from an implementation standpoint, all proposed VVC and therapeutic methods (imaginal exposure) in this proposal are already widely adopted across the VA system. This includes an extensive IT infrastructure for supporting VVC and the nation's largest cadre of evidence- based, trauma-focused therapists. As such, if findings from this pilot and follow up RCTs indicate safety, acceptability and efficacy, VVC-delivered massed trauma-focused therapy could be readily implemented in the VA system.

Our proposal includes unique and important contributions to veteran mental healthcare through the following innovations:

- For the first time, we will establish the safety, feasibility, tolerability, and acceptability of VVC-delivered, massed imaginal exposure for PTSD. While these aspects have been established for in-person imaginal exposure, the remote nature of VVC presents unique challenges.
- For the first time, we will establish the preliminary efficacy of VVC-delivered, massed imaginal exposure for PTSD. While these findings will be preliminary as the study is not powered for efficacy, it will provide preliminary estimates of pre- to post- effect sizes and variance in outcomes that will aid in planning well-crafted and properly statistically powered follow up RCTs.
- COVID-19 has fundamentally altered the delivery landscape for clinical and research practice. The methods proposed here further advance the VA's capacity to promote evidence-based care and research amidst unforeseen disruptions to in-person procedures.
- For the first time, we will establish acceptability among stakeholder providers, of VVC-delivered, massed imaginal exposure for PTSD. While in-person, massed imaginal exposure has been effective in RCTs, the perceptions of evidence-based clinical providers at the forefront of treating veterans have not been assessed. In order to assess implementation likelihood, as well as to assess the need to disseminate findings and techniques, input from provider stakeholders is essential.

3.0 Intervention to be studied.

Study Overview. In this open-label pilot, we will recruit 25 veterans with PTSD from the Ralph H. Johnson VAMC PTSD Clinical Team (PCT), as overseen by CoI, licensed clinical psychologist, and Section Chief, Dr. Wangelin. Massed imaginal exposure will be delivered via VVC or any other VA approved telehealth platform, modeled after the in-person protocol of Zoellner et al., (2017). Following the initial assessment of PTSD and related symptoms and impairment, all veterans will receive six daily 60-minute telehealth sessions focusing on imaginal exposure therapy (details below). The initial assessment will

be repeated at 1-week post-treatment and 1-month post-treatment completion. As an open-label, feasibility pilot study, there is no control arm.

Intervention: VVC-delivered Massed Imaginal Exposure. Consistent with Zoellner et al., (2017), six, 60- minute daily sessions of imaginal exposure will be conducted based on the PE manual (Foa et al., 2007). Session 1 will include rationale for imaginal exposure and common reactions to trauma. Sessions 2-6 will focus on imaginal exposure (45 minutes) and processing (15 minutes), with later sessions focused on the most distressing aspect of the trauma memory. The final session will include relapse prevention. Between-session assignments will include listening to audio recordings of sessions at least once. All sessions will be delivered within a 10-day window. If participants do not respond, they will be offered additional services at no additional cost or loss of benefits for which they would otherwise be entitled.

4.0 Inclusion and Exclusion Criteria/ Study Population

Veterans who are aged 18-65 (inclusive), who meet full DSM-5 criteria for current PTSD will be recruited from all racial, ethnic and gender categories. The rationale regarding a cutoff of 65 years was for correspondence to prior massed in-person protocols (e.g., Zoellner et al, 2017). Planned follow up studies will include a broader age range and will be powered to analyze age effects on outcomes. To contend with dropout, we propose to enroll 25 veterans, with the aim of completing assessments and treatment for 20 participants. In-person investigations have shown a dropout rate of 5% (Sciarrino et al. 2020), thus a 20% allowance will ensure adequate recruitment to meet study aims.

Exclusion Criteria. Participants will be excluded for the following: 1. clinically unstable physical illness; 2. bipolar Type I disorder; 3. dementia; 4. repeated abuse or dependence upon drugs within 3 months; 5. unstable psychotropic regimen within 6-weeks; and finally, 6. active suicidal ideation or a suicide attempt within the past year.

Table 1. Eligibility Criteria

Inclusion Criteria:
1. Age 18-65. 2. Ability to speak, read, and write English. 3. Diagnosis of PTSD based on CAPS-5 (> 3 mo. post-trauma). 4. Seeking treatment for PTSD at the Charleston VA. 5. Willingness and ability to engage in assessment and treatment visits through VVC, or another VA-approved telehealth videoconferencing platform.
Exclusion Criteria:
1. Currently receiving psychotherapy for another anxiety- or stress-related condition. 2. Current substance use disorder diagnosis with repeated abuse or dependence within 3 months of study entry and unwillingness to abstain for 24 hours prior to study visits.

3. Unstable dose of psychotropic medications within 6 weeks prior to baseline assessment (based on the DMSC; see measures).
4. Medical condition that would contraindicate participation in treatment or assessment activities (e.g., severe cardiovascular problems; based on MINI, DMSC, and chart review; see measures).
5. Current, or history of bipolar I disorder (based on MINI; see measures).
6. Current, or history of psychotic symptoms (based on MINI; see measures).
7. Serious suicidal risk or a suicide attempt in the past year, as determined by self-report (PHQ-9) and clinical interview (C-SSRS; see measures).
8. Active neurological conditions, e.g., seizures, stroke, loss of consciousness or concussion (based on MINI, DMSC, and chart review; see measures)

5.0 Number of Subjects

Targeted / planned enrollment. We will enroll a total of ***N* = 25** participants, 18-65 years of age (inclusive), who meet full DSM-5 criteria for PTSD. Participants will be recruited from all racial, ethnic, and gender categories. Women and minorities will be included in the study. In FY 2014, the PCT averaged 25.3 new referrals per week (11% female, 36% Black, 4% Hispanic / Latino). The consistency of PTSD referrals will greatly facilitate recruitment for the proposed research.

Table 2. Targeted/Planned Enrollment
Total Planned Enrollment: N = 25

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	3	21	24
Ethnic Category: Total of All Subjects*	25		
Racial Categories	**Sex/Gender**		
	Females	**Males**	**Total**
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	1	8	9
White	2	14	16
Racial Categories: Total of All Subjects*	3	22	25

6.0 Setting

Outcome assessment visits. All participants will be assessed using a standard battery of clinician-administered and self-report outcome assessments at pre-treatment, post-treatment (1-week after completing treatment), and at a 1-month follow-up visit. These outcome assessments will be conducted entirely remotely via VVC or a comparable VA-approved videoconferencing platform (e.g., VVC Now, WebEx, Microsoft Teams, etc.).

Remote telehealth treatment visits. All treatment visits, which consist of 60 min. sessions including imaginal exposure (45 min.) followed by emotional processing (~15 min.) will take place entirely through telehealth using VVC, or if needed, a comparable VA-approved videoconferencing platform (e.g., WebEx). Note that telehealth delivery of trauma-focused therapy is already standard practice in the Charleston PCT, and our group has consistently demonstrated high-fidelity delivery in standard care, with robust clinical gains on par with carefully designed and executed RCTs, as documented in several peer-reviewed reports (e.g., Tuerk et al, 2018).

7.0 Recruitment Methods

As part of standard clinic procedures, all referrals receive a diagnostic assessment and are asked if they would like to hear about opportunities to participate in research. If Veterans respond that they are interested in being contacted about research opportunities and if they choose to begin evidence-based therapy (the modal treatment choice in the PCT), then study staff will make contact regarding potential enrollment prior to the Veteran's first therapy session. Communication between clinic and study staff will be facilitated by the PI. Research recruitment is well-integrated with the standard clinic operating procedures and similar recruitment strategies in this environment have supported successful recruitment goals of multiple studies in recent years. In support of a high likelihood of expeditious attainment of recruitment goals, in FY20, the PCT completed nearly 600 assessments for trauma-focused therapy, and triaged over 1500 consults for PTSD and related conditions via VVC. Further, the PCT has a longstanding history of supporting successful recruitment for numerous studies targeting treatment innovations.

8.0 Consent Process

All participants will be referred on the basis of a routine intake assessment in the PCT or another VA behavioral health clinic prior to study entry. As indicated above in the eligibility criteria, those who report clinical symptoms that suggest trauma-focused therapy for PTSD is not in their best interests will be excluded from the study and directed to alternate care as recommended by the PCT and their clinical care team. Participants who appear to meet criteria for entry into the study will be informed of the study and if they express interest, they will review

study consent, and HIPAA Authorization with study personnel (PI, study coordinator, or study evaluator).

The consent process and HIPPA authorization procedures will be completed electronically through VVC or another VA-approved videoconferencing platform, following all VA institutional guidelines pertaining to the consent and authorization procedures. Consent documents will be provided by mail, or through secure messaging, then subsequently reviewed with study personnel at the first study visit (i.e., the pre-treatment or baseline assessment). During review of consent, study staff will detail study procedures and ensure that patients understand what components are part of the study procedures and what is part of standard treatment for PTSD. Study staff will ensure that potential participants understand the study and are interested and able to complete study procedures prior to providing signed informed consent. Participants will receive in the consent document emergency contact information for use in case of acute exacerbation of symptoms. Participants will be informed that they can withdraw from the study at any time and receive alternate care outside of the study. Participants will also be informed that if they report imminent suicidality or intolerance for study procedures at any point during the protocol, they may be withdrawn from the study and receive alternate care as appropriate (i.e., inpatient hospitalization, treatment in outpatient psychiatry, etc.).

Following review of the consent documents and verbal expression of understanding and agreement by the participant, participants will be instructed to indicate their consent and authorization on the forms with their signatures. The attending study personnel will then take screen shots of the signature pages, save them on a secure, access-controlled, and encrypted VA server, and note the consent and authorization in CPRS to document study involvement.

Participants have the option to indicate they would like to be contacted for future research studies that they may qualify for on the consent documents. For participants who provide this consent, their contact information only will be stored in a separate secure data repository that will not expire upon study completion. The PI, Dr. Lisa McTeague will serve as the repository administrator. The standard operating procedures for administering this repository have been outlined in the SOP associated with this protocol. Note that there will be no attempt to identify directly or indirectly any participant in their research data.

9.0 Study Design / Methods

Overview.

This pilot project will implement an open-label single-arm design to address our specific aims to establish the safety, feasibility, tolerability and acceptability of massed imaginal exposure therapy for PTSD delivered via telehealth to Veterans with PTSD, and to obtain a preliminary estimate of efficacy (i.e., to support adequately powered follow-up studies employing group-randomized designs). All participants **(*N* = 25)** will receive a total of six-60 min. therapy sessions, delivered via VVC or a comparable VA-approved platform. Outcome assessments consisting of clinician-administered interview measures, self-report measures, and collection of remote affective and physiological indices derived from webcam footage will occur at pre-treatment, and at 1-week and 1-month following

treatment completion. Assessment instruments and procedures are detailed in the following sections.

Assessment Procedures

Baseline Demographic, Clinical Characteristics, and Diagnostic Measures

This study will implement a standard battery of clinician-administered and self-report measures to capture important baseline differences and changes over the course of treatment. These measures are detailed in the following sections, and the assessment schedule is provided in **Table 1** below.

Table 1. Schedule of Assessments

Measure	Pre-tx	Tx	Post-tx	1-mo. follow-up
Trauma Interview	x		x	x
CAPS-5	x		x	x
MINI	x			
C-SSRS	x		x	x
CGI	x		x	x
DMSC	x			
LEC-5	x			
PCL-5	x	x	x	x
PTCI-9	x	x	x	x
PHQ-9	x	x	x	x
PSBQ	x		x	x
MASQ	x		x	x
SDS	x		x	x
ERNS	x			
STTS-R			x	x
TTSQ			x	
SUDS		x		
PETQ		x		

Note. Trauma interview = remote affective and physiological measures based on video of a standardized trauma interview; CAPS-5 = Clinician Administered PTSD Scale for DSM-5; MINI = MINI Neuropsychiatric Interview Schedule; C-SSRS = Columbia-Suicide Severity Rating Scale; CGI = Clinical Global Impressions; DMSC = Demographics and Military Service characteristics Form; LEC-5 = Life Events Checklist for DSM-5; PCL-5 = PTSD Symptom Checklist for DSM-5; PTCI-9 = Posttraumatic Cognitions Inventory, 9-Item Version; PHQ-9 = Patient Health Questionnaire; PSBQ = PTSD Safety Behaviors Questionnaire; MASQ = Mood and Anxiety Symptom Questionnaire; SDS = Sheehan Disability Scale; ERNS = Emotional Reactivity and Numbing Scale; STTS-R = Satisfaction with Therapy and Therapist Scale; TTSQ = Technology and Treatment Satisfaction Questionnaire; SUDS = Subject Units of Distress Scale. PETQ = Prolonged Exposure Therapist Questionnaire.

Demographics and Military Service Characteristics Form (DMSC). The DMSC collects information regarding standard demographics (race, gender, age) and military service information (e.g., rank), and will be administered at the pre-treatment assessment visit.

Life Events Checklist for DSM-5 (LEC-5). The LEC-5 is a 17-item self-report measure that assesses prior extent of exposure to traumatic events, as defined by DSM-5 criteria (Blake et al., 1995; F. W. Weathers et al., 2018). This measure will be administered at the pre-treatment assessment to capture baseline differences in lifetime history of trauma exposure.

MINI Neuropsychiatric Interview Schedule (MINI, version 7.0.2). The MINI is a widely-used brief structured interview that assesses common mental health diagnoses based on DSM-5 criteria (Pinninti, Madison, Musser, & Rissmiller, 2003). This instrument will be administered at the pre-treatment assessment visit to capture common diagnostic comorbidities.

Primary Outcome Measures

Treatment Dropout/Completion. We will collect data on treatment completion, to include the number of treatment sessions and assessment visits attended, via chart review from CPRS.

Treatment Non-Compliance. We will collect data on treatment compliance, including completion of in-session and between-session assignments, as determined by chart review and self-report.

Satisfaction with Therapy and Therapist Scale - Revised (STTS-R). The STTS-R is a 13-item Likert-type self-report scale designed to assess patient satisfaction with therapeutic services and providers (Oei & Green, 2008). This instrument will be administered at the post-treatment and 1-month follow-up time-points.

Technology and Treatment Satisfaction Questionnaire (TTSQ). The TTSQ is a 14-item self-report measure developed by the investigators. Items assess satisfaction, acceptance, tolerability, perceived utility and treatment outcome-related expectancies related to incorporating the remote affective physiology procedures into the assessment procedures (see below), as well as opinions about incorporating such measures into routine care. Both patients and

providers will complete slightly different versions of this measure, addressing the same items, but adapted appropriately for wording. This instrument will be administered at the post-treatment time-point.

Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). The CAPS-5 is a structured interview for diagnosis of PTSD and is widely considered the gold-standard assessment (Blake et al., 1995; F. W. Weathers et al., 2018). The CAPS-5 will be administered at pre-treatment, post-treatment, and the 1-month follow-up visits, and will be used to evaluate inclusion criteria and as a comparative criterion to assess relations between our objective measurements and severity of trauma-related symptoms and functional impairments.

PTSD Symptom Checklist for DSM-5 (PCL-5). The PCL-5 is a 20-item self-report measure of PTSD symptom severity based on the DSM–5 (Wortmann et al., 2016). This measure will be administered at pre-treatment, post-treatment, and the 1-month follow-up, serving as a primary self-report outcome measure. It will also be administered at the beginning of each treatment session, to index trajectories of change over the course of treatment.

Patient Health Questionnaire (PHQ-9). The PHQ-9 is a 9-item widely used self-report instrument that assesses core symptoms of major depression (Kroenke, Spitzer, & Williams, 2001) As with the PCL-5, the PHQ-9 will serve as a primary outcome measure administered at pre-treatment, post-treatment, and the 1-month follow-up, and just prior to each treatment session.

Secondary Outcome Measures

Posttraumatic Cognitions Inventory, 9-Item Version (PTCI-9). The PTCI-9 is a 9-item well-validated self-report measure of maladaptive beliefs that commonly manifest in PTSD (Wells et al., 2019) This measure will be administered at pre-treatment, post-treatment, and the 1-month follow-up, and at the beginning of each session to index change in problematic trauma-related beliefs.

Mood and Anxiety Symptom Questionnaire (MASQ). The MASQ is a brief 26-item questionnaire with three separate subscales including general distress, anxious arousal, and anhedonic depression (Casillas & Clark, 2000). This measure will be administered at pre-treatment, post-treatment, and the 1-month follow-up.

PTSD Safety Behaviors Questionnaire (PSBQ). The PSBQ is a 10-item validated measure of unnecessary protective actions, including avoidant behaviors, that are common in cases of PTSD, and are widely believed to serve to maintain and exacerbate trauma-related symptoms (Foulser & Telch, 2019) This measure will be administered at pre-treatment, post-treatment, and the 1-month follow-up.

Emotional Reactivity and Numbing Scale (ERNS). The ERNS is a 62-item self-report measure that assesses tendencies to experience a restricted range of emotions, or emotional numbing, including in response to emotionally arousing situations (Orsillo, Theodore-Oklota, Luterek, & Plumb, 2007) This instrument will be administered at the pre-treatment assessment visit.

Sheehan Disability Scale (SDS). The SDS is a 5-item measure that assesses disability and functional impact associated with symptoms (Leon, Shear, Portera,

& Klerman, 1992). This instrument will be administered at the pre-treatment, post-treatment and 1-month follow-up assessment visits.

Clinical Global Impressions (CGI). The CGI is a 5-item, clinician-rated measure that provides a global assessment of severity, functioning, and improvement over the course of treatment (Kadouri, Corruble, & Falissard, 2007) This measure will be administered at the pre-treatment, post-treatment, and 1-month follow-up assessment time-points.

Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS is a widely used standard assessment of lifetime and follow-up suicidality, including thoughts of intent, methods, plans, and preparatory efforts, as well as suicidal and self-harm behaviors (Posner et al., 2011). This instrument will be administered at the pre-treatment, post-treatment, and 1-month follow-up time-points.

Treatment Process Measures

Pre-session Self-Report Measures. Prior to each session, participants will complete a number of self-report measures, which will be reviewed with the participant at the beginning of each session. The pre-session measures are indicated in **Table 1**, and described in the sections above, and include: the PCL-5, PTCI-9, and PHQ-9.

Subject Units of Distress Scale (SUDS). The SUDS is a simple visual analogue scale reflecting anticipated, peak, and/or current distress levels, rated from 0 = “No distress” to 100 = “Extreme distress.” This scale is commonly used as part of standard PE to assess the level of emotional arousal, engagement, and response to in-session and between-session exposure practices (Wolpe, 1973).

Prolonged Exposure Therapist Questionnaire (PETQ). Our group developed the PETQ, which is an 8-item Likert-type scale, as a means to capture therapists’ assessments of session-by-session trauma-memory engagement, recovery of significant details, meaning making, and change in trauma-related beliefs. This instrument will be completed by study therapists immediately following each treatment visit that involves imaginal exposure and processing components (i.e., sessions 2-6).

Remote Affective and Physiological Measures.

As implemented in our ongoing VA study (PI: Wangelin), participants will undergo standardized trauma interview procedures at pre-treatment, post-treatment, and the 1-month follow-up that will be audio and video recorded. This will involve capturing reactivity to (1) 1-min. standardized neutral imagery (e.g., describing and recounting a mundane morning routine); (2) a 5-min. standard trauma interview designed to elicit emotional, cognitive, and sensorial details related to the traumatic event; followed by (3) very brief, 1-min. imaginal “hot-spot” revisiting, in which participants will be guided in verbally recounting and vividly imagining the worst part of their index traumatic event. Additional details regarding these procedures can be found in the appendix (see standard trauma interview form in the appendix). Video and audio streams will be analyzed using open-source software to extract affective and physiological signals based solely on visual and acoustic properties of webcam footage. The specific markers to be extracted are described in the following sections.

Remote photoplethysmography (rPPG). We will apply state-of-the-art procedures for extracting high fidelity heart rate data from video (van der Kooij & Naber, 2019) acquired via commercial-grade webcams already in use within our clinic, and comparable to that used nationwide in the delivery of VA telemental health. Video quality will be consistent across assessment sessions (1080p, 60 frames per second). Default settings for video recordings will be used, and any automated corrections (e.g., dynamic adjustments for variations in brightness) will be turned off. Open-source MATLAB-based software (https://github.com/marnixnaber/rPPG/) will be used to extract heart rate from video recordings. This will involve a series of automated steps, as described by van der Kooij and Naber (2019), including: (a) spatiotemporal cropping; (b) facial detection and selection of target pixels on the skin surface; (c) averaging/filtering signals based on dynamic color variations; (d) independent component analysis; (e) fast Fourier transformations; (d) power spectra filtering; and (f) corrections for respiration and movement artifacts. Previously validated parameters will be used to extract the final rPPG heart rate, which will be defined as the tallest power peak across components. Heart rate variability will also be calculated, based on the root mean square of successive differences in beat-to-beat intervals (RMSSD). Finally, in addition to heart rate indices, respiratory rate will be similarly derived from the rPPG signal using validated acquisition, processing, and analytic steps, including applying MATLAB-based algorithms for spatiotemporal filtering, motion correction, and signal pruning to produce contactless, high-quality respiratory rate signals (Chen et al., 2019).

Facial emotion expressivity. Whereas coding of emotional facial expressions by independent raters is a well-established practice in the affective sciences, advanced algorithms based on artificial intelligence can now be applied to visual signals from video to allow for automatic and continuous detection of emotional facial features, providing a more objective means of measuring expressivity in comparison to subjective and observer-based assessments (Samadiani, Huang, Cai, Luo, Chi, Xiang, & He, 2019). Following a similar approach as with the rPPG data, MATLAB-based algorithms will be applied to the video recordings to extract continuous measures of affective valence, arousal, and intensity, and emotion classification based on empirically-derived facial features associated with each primary emotion (i.e., joy, sadness, fear, anger, and disgust), as well as affective displays associated with physical pain.

Affective vocal features. In addition to the metrics above that rely on visual features, affective vocal features will be extracted from auditory streams of the video recordings by applying established acquisition, processing and analytic pipelines, utilizing MATLAB-based scripts to automatically isolate the patient's voice, and subsequently extract and quantify vocal prosodic and spectral features characteristic of emotional states (e.g., Gunawan, Alghifari & Kartiwi, 2018).

Treatment Procedures.

Telehealth-delivered massed imaginal exposure therapy. Within 1-week of completing the initial pretreatment assessment visit and eligibility determination, enrolled participants will receive a total of six 60-minute treatment sessions, with sessions 2-6 scheduled daily, following the manualized procedures developed for use by Zoellner et al., (2017), as previously implemented by Co-I Dr. Cobb. This

protocol closely follows core elements of PE, which is a gold standard intervention widely disseminated throughout the VA. In addition to in-session components, participants will also complete between-session assignments involving listening to the entire session recording for session 1, and listening to their imaginal exposures for sessions 2-6. Additionally, the treatment provider will conduct a brief (~5-10 min.) nightly check-in with participants via Doxy.me, VVC-now, or another VA-approved videoconferencing or secure messaging platform. More details regarding in-session components are provided in the following sections.

Session 1 primarily consists of psychoeducation delivered in an interactive (rather than purely didactic) manner to promote understanding of participants' trauma-related reactions, symptoms, and functional impairment. A brief rationale for treatment is also provided in this initial visit to support understanding and engagement with subsequent exposure-based visits.

Session 2 begins with a more detailed, but still brief rationale for treatment, followed by 30 to 40 min. of imaginal exposure and approximately 15 min. of discussion (i.e., emotional processing) aimed at promoting elaboration on thoughts and feelings associated with participants' index trauma.

Sessions 3-5 consist of ~30-40 min. of imaginal exposure, and ~15 min. of processing trauma-related thoughts and feelings. As treatment progresses, participants' will be encouraged to focus on "hot-spots", reflecting the most distressing parts of their index trauma.

Session 6 is the final treatment visit, including 30 min. of imaginal exposure, 15 min. of processing, and 15 min. of reviewing treatment progress, promoting maintenance of treatment gains, discussing treatment termination, and planning follow-up assessments.

The procedural flow is illustrated in **Figure 1** below.

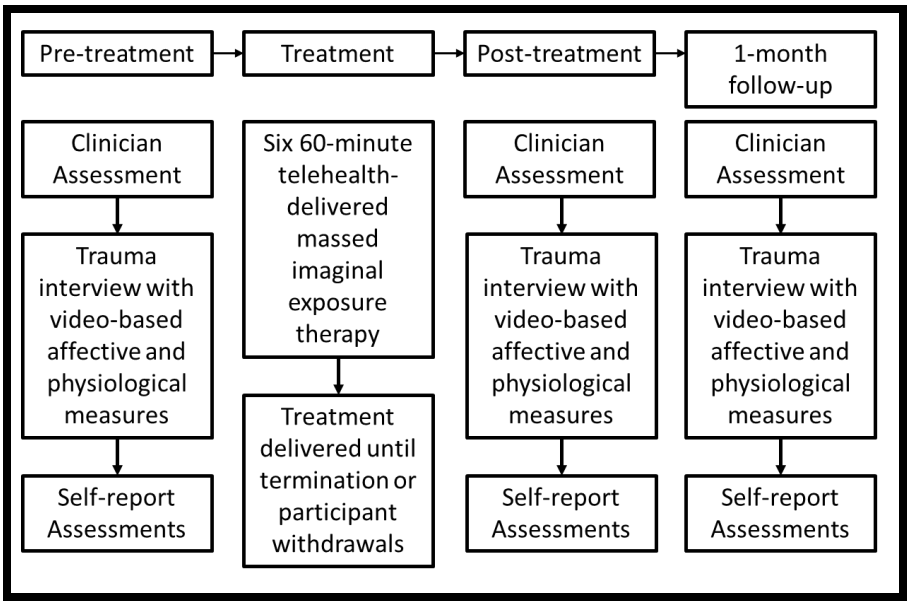

Figure 1. Study procedures. Outcome assessments will take place at pre-treatment, and at 1-week, and 1-month after treatment. At each assessment, remote photoplethysmography (rPPG) will be utilized to extract heart rate data from videos of a standard trauma-focused interview administered at pre-treatment, post- treatment, and 1-month follow-up, in addition to other video-based measures of affective reactivity, a clinical diagnostic interview, and self-report measures. Tolerability, acceptance, and perceived utility of the procedures based on the providers' and participants' self-reports will also be collected. Treatment process measures based on patient self-report will be collected before and just after each of 6-daily treatment sessions. Provider ratings of engagement and emotional processing will also be collected immediately following each treatment session that includes imaginal exposure and processing components (i.e., sessions 2-6).

Participant Compensation

For their time and effort, participants will be compensated a total of $100.00 for completion of the three assessment visits, including the 2-hour pre-treatment assessment and the 1 ½ hour post-treatment and 1-month follow-up assessments. The rates below are based on standard participant compensation in our ongoing VA clinical trials and were selected to enhance generalizability of feasibility and acceptability findings to our routine treatment-seeking Veterans, with due consideration of the need to minimize coercion.

Participant Compensation Schedule

Completed Visit:	Amount to be Paid:
Pre-treatment Assessment Visit	$25.00
1-Week Post-treatment Assessment Visit	$25.00
1-Month Follow-up Assessment Visit	$50.00
All Study Visits (3) Completed (Total):	**$100.00**

10.0 Data Management

Data Acquisition. If (and only if) ultimately approved by the VA, we propose the use of VA Qualtrics, which is a secure, FedRAMP-authorized online data capture system that is widely used as a HIPPA-compliant web-based means to collect sensitive research data. Moreover, if approved, in addition to remotely collecting validated self-report questionnaire data from participants using this platform, we also request leveraging Qualtrics' functionality to integrate java script, which would enable us to directly capture audio and visual data from the participant's side from their webcam and microphone. This is an excellent alternative to our initially proposed procedures, which involve collecting streamed, then captured (i.e., on the clinician's side) footage. This is problematic due to significant temporal distortion and low sampling rate for screen-captured footage on currently deployed telehealth platforms approved by the VA (i.e., Teams, Webex, and VVC). As mentioned, the use of Qualtrics will be entirely contingent on obtaining full MUSC IRB and VA R&D approval for our proposed use. If ultimately not approved, we will continue to implement our procedures that involve capturing questionnaire data with hard copies, by mail.

Data Preparation. Pre-processing of data as the study progresses will allow for more expedient dissemination of study findings. As appropriate, pre-processing will follow standard best practices to ensure excellent data quality and security. Prior to analyses, data will be visually and statistically inspected for the presence of aberrant data points, which will be omitted prior to analyses.

Analytical Plan. Descriptive statistics will be reported for safety, feasibility, tolerability, and acceptability. Linear mixed-effects models will be used to characterize trajectories of change in symptoms and impairment, while controlling for potential confounders, such as baseline severity.

Following standard pre-processing steps, analyses will be conducted using generalized linear models, and will proceed in a bottom-up manner involving selection of the best fitting fixed and random growth terms, followed by adding predictors of interest. Factors (e.g., sex) will be dichotomously coded, whereas all continuous predictors will be scaled and centered as a function of baseline values to allow for meaningful interpretation of effects as indicative of reliable change.

Additionally, all models will control for baseline levels of the outcome to control for individual differences at pre-treatment in estimating effects. Model refinement will be guided by theory, evaluating standard fit statistics (e.g. Log Likelihood, AIC, BIC, etc.) and whether modeling assumptions are sufficiently met.

11.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Safety will be monitored by reports of adverse events at all study visits throughout all phases of the project. This will include formal assessment of psychiatric symptoms (including suicidality and homicidality) as well as invitation at each study visit to speak to a therapist regarding any suicidal or homicidal thoughts and a reminder about the Veterans' Crisis Line. Formal assessment of suicidality will be conducted using the C-SSRS, and suicidality will also be monitored throughout study participation based on item 9 on the PHQ-9. Should a Veteran endorse suicidality on this question, or otherwise report to study staff any thoughts of wanting to hurt him/herself or others, the veteran will be fully evaluated for safety, and steps to ensure safety will be followed. Suicidal or homicidal plan or intent will be immediately reported to the PI.

All research participants will be assigned a numeric code (Subject ID) that is based on the chronological order in which they were enrolled in the study. This number accompanies all de-identified data. The participant's identifying information and numeric code will be stored in the password-protected database on a protected VA virtual drive previously described. Password to participant data will be updated quarterly as an additional security measure. All identifying information (e.g., signed consent forms and contact information) will be maintained separately from the rest of the study data collected. The Subject ID will not contain any identifiers or protected health information (PHI) as defined by HIPAA. All data on separate VA data analysis computers (that are also password protected) are stripped of potential identifiers, with special attention paid to the problem of "cell size." VA research data will be retained according to RCS 10-1 and VA Information Security policies. Moreover, if the proposed use of Qualtrics is ultimately approved, all procedures described above to de-identify

data will apply. Specifically, data will only be connected to a numeric code (i.e., Subject ID, last name initial, and last four of SS#).

Upon study completion, all links between identifiers and clinical research data will be deleted. The process for de-identifying data will be completed by a qualified biostatistician with an extensive background in statistics, mathematics, clinical science, and knowledge of and experience with generally accepted statistical and scientific principles and methods for de-identification applying generally accepted principles and methods, as outlined in VHA DIRECTIVE 1605.01, Appendix A.

In addition, for participants who express willingness to be contacted for future research opportunities on their informed consent document, we will retain their contact information (i.e., name, address, and phone number) in a repository consisting of a password-protected spreadsheet, with the password updated quarterly. These data will likewise be stored on a secure VA server.

Data and Safety Monitoring Plan (DSMP). The PI, Dr. McTeague will be in charge of (1) providing scientific oversight; (2) reviewing all adverse effects or complications related to the study; (3) monitoring enrollment; (4) reviewing summary reports relating to compliance with protocol requirements; and (5) providing advice on resource allocation. Dr. McTeague will meet every 6-months in-person and as necessary with the CoI-s as an internal Data Safety Monitoring Committee (DSMC) to review progress. The recommendations of the DSMC will be reviewed and the PI will take appropriate corrective actions as needed. At each meeting the DSMC will:

- Review the research protocol and plans for data and safety monitoring.
- Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, enrollment, and retention, participant risk versus benefit, integrity of the intervention, and other factors that can affect study outcome.
- Consider factors external to the study when interpreting the data, such as scientific developments that may impact the safety of study participants or the ethics of the study.
- Make recommendations to the IRB for continuation or termination of the study.
- Protect the confidentiality of study data and monitoring.

DSMC reviews and reports will occur on a semi-annual basis and will be organized and prepared by the PI. Planned interim analysis will occur once 50% of the target study enrollment is reached (N = 13).

On a daily basis, Dr. McTeague will be responsible for data and safety monitoring and will provide continuous, close data monitoring. Dr. McTeague will promptly report serious adverse events to the MUSC Institutional Review Board (IRB). A report of all non- serious adverse events will be provided to the IRB yearly.

12.0 Withdrawal of Subjects (if applicable)

If it is determined that it is not in the subject's best interest to continue participating in the study, he or she will be withdrawn from the study without their consent. Examples of such circumstances include emergence of symptoms or

behavior that meet study exclusion criteria, consistent non-compliance with study assessment instructions, or if treatment of other acute health/mental health symptoms becomes a priority over study participation. In such cases, the PI will meet directly with the subject to explain the reasons for withdrawal from the study, and to assess whether any further action is required, including additional mental health intervention or modification of the current treatment plan. The treating therapist will be included in this discussion as appropriate.

13.0 Risks to Subjects

Clinical interviews and questionnaires administered include questions about exposure to stressors and other topics that might produce transitory distress in some individuals. There is also the potential for participants experiencing embarrassment or other negative consequences if some of the experiences were disclosed via a security breach, particularly if their identity were linked to their interview data. These risks appear minimal given the protections in place to maintain confidentiality and to respond to participants who experience distress.

We will use several procedures to protect against the risks that were previously identified. The first risk is that some participants might experience transitory distress when asked about stressor events in the interviews or during treatment. Based on our research teams' previous experience in asking similar questions to more than 2,400 combat exposed veterans, we think that this risk is low if questions are phrased sensitively and interviewers are trained properly. Therefore, we will provide special training and supervision to the research interviewers and treatment providers. Only the best, most experienced clinicians will be used, many of whom will have had experience with other clinical and research interviews with trauma exposure populations, and are well-versed in each of the gold-standard treatments for PTSD. Interviewers and treatment providers are supervised on a weekly basis to ensure they are conducting the study procedures effectively, appropriately, and with high fidelity to our established protocols.

Study staff will report any potentially dangerous suicidal or homicidal ideation, or evidence of child abuse, to the appropriate individuals as required by law. The possibility of such reporting is included in the informed consent process. If the participant expresses a wish to talk to a team member, Dr. Lisa McTeague (PI of the current study proposal) or Dr. Bethany Wangelin (director, staff clinician on the PCT and co-I), both with extensive experience in the assessment and treatment of PTSD, will be notified by the interviewer. Drs. McTeague and Wangelin are committed to being available via instant messaging, email, text, and phone during the time that the research interviewer is conducting interviews. Drs. McTeague or Wangelin will contact or greet the participant and determine whether any further action is required. If it is decided that some type of mental health intervention is needed, or modification of the Veteran's current treatment plan, arrangements will be made.

Based on our prior experience, it is extremely unlikely that a participant will experience significant sustained distress. These procedures for addressing participant distress are similar to those that have been successfully used in several prior studies directed by members of this research team. Specifically, with respect to assessment of suicide risk, all investigators complete VA training

on the recognition and management of suicide risk. They will assess and document acute and chronic risk factors. Any individuals deemed to be at an elevated risk for suicide, will be reevaluated and treated as clinically indicated by Drs. McTeague (PI) and Wangelin (Co-I), and their clinical care team.

We will follow all standard operating procedures for the conduct of secure videoconferencing for remote study participation and receipt of therapeutic services, as is approved and routinely implemented by the VA. For example, with respect to ensuring participant safety, each study and treatment visit will commence with confirming the participants' location, inquiring whether responsible others are available on-site in the event of an emergency, and procuring other local emergency contact information in the event that intervening is clinically required (e.g., for individuals expressing suicidal risk).

As mentioned, some participants might experience embarrassment or other negative consequences if the confidentiality of their interview responses regarding sensitive topics was breached. Some of these topics involve victimization experiences and mental health problems. If confidentiality of this material were breached, the potential harm to participants is clear. Our research team has considerable experience conducting interviews on sensitive topics and has never had a breach of confidentiality. In addition to stressing the need for confidentiality in training and supervision, our research team has developed successful procedures to keep interview data confidential. The risk of loss of confidentiality is extremely small given the measures that we have in place. All information will be stored in locked files in a locked research area (i.e., behind two locks) specifically designated for research personnel. Computer data will only be stored on password-protected computers and using the VA virtual drives, with the exception of the potential use of Qualtrics for collecting data, as described above. No names or identifying information will be used in publications that result from this research. Under no circumstances will identifying information be released to any outside party (beyond those immediately connected with the study) without written consent from the subject.

14.0 Potential Benefits to Subjects or Others

We believe that the potential risks to participants are minimal and are minimized further given the steps we will take to reduce and respond to participants' distress and to maintain confidentiality. Further, participants may benefit from receiving imaginal exposure, which is a core component of Prolonged Exposure (PE) therapy – a gold-standard evidence-based treatment for PTSD. However, while our group's prior work has suggested comparable efficacy of massed imaginal exposure relative to the full PE protocol (Zoellner et al., 2017; Sciarrino et al., 2020), it is unknown whether these effects will generalize to a telehealth modality, and thus these potential benefits cannot be guaranteed. Should participants fail to respond, additional treatment will be offered.

Benefits to others are potentially substantial. If successful, this pilot study may provide support for developing alternative treatment schedules to afford flexibility and accommodate preferences, reduce burden on patients, providers, and clinic resources, and provide support for more developing more efficacious, efficient, and accessible treatments for PTSD.

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