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IRB # 1663080: Circadian influence on fear extinction resulting from Prolonged Exposure therapy for PTSD

Funding Agency: NIH/National Institute of Mental Health

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Abstract

Fear extinction learning and memory are the neurocognitive bases of exposure therapies for anxiety- and trauma-related disorders, including prolonged exposure therapy (PE) for posttraumatic stress disorder (PTSD). Proposed research will examine time-of-day effects on extinction produced during PE for PTSD. Using an experimental paradigm in healthy individuals, we reported that extinction is better learned and generalized in the morning than evening. Our team also showed that exposure therapy for panic disorder is more efficacious when provided in the morning, and that higher endogenous cortisol levels mediate this effect. Thus, a possible mechanism underlying this morning advantage is enhanced extinction learning by the morning circadian acrophase of endogenous cortisol. This Exploratory/Developmental mechanistic randomized clinical trial (RCT) will apply these findings to test the hypothesis that PE for PTSD delivered in the morning will show greater effects on fear memory extinction (**target mechanism)** and PTSD symptoms (**clinical outcome**), compared to PE delivered in the late afternoon. PE is an established, efficacious, manualized 10-session treatment. This RCT will compare 26 individuals treated with PE beginning within 2 hours of awakening (i.e., between 07:00-11:00) to 26 treated at 16:00 or later. Participants will complete at-home exposures at the same time of day as PE sessions. Fear memory extinction, the primary mechanistic outcome, will be measured using a validated composite index for psychophysiological reactivity to trauma recall during script-driven imagery (SDI-PR). SDI-PR combines skin conductance, heart rate, and facial electromyography measures. The primary clinical outcome will be PTSD severity on the Clinician-Administered PTSD Scale (CAPS-5). SDI and CAPS-5 will occur at screening and mid-, and post-treatment. Secondary mechanistic (peak subjective units of distress; SUDS) and clinical (PTSD Checklist for DSM-5) measures will be obtained at each PE session. Extinction learning will be operationalized as decreased SDI-PR across the 3 assessment time points and decreased SUDS across the 8 PE sessions that include imaginal exposure. Endogenous salivary cortisol levels, obtained immediately before each PE session and normalized using diurnal cortisol profiles, will be tested as a mechanism contributing to time of day effects on mechanistic and clinical outcome measures. Sleep quality will be assessed using wrist actigraphy and daily sleep diaries throughout treatment. We hypothesize that: (1) Morning, compared to late-afternoon, PE sessions will produce greater declines in mechanistic and clinical outcomes. (2) Higher cortisol levels measured at the previous PE session will be associated with greater session-to-session change in secondary mechanistic and clinical outcomes. (3) Better sleep quality will be associated with greater declines in mechanistic and clinical outcomes. Confirmation of hypotheses would suggest adopting strategic scheduling of PE to maximize clinical outcome, an easily implemented and inexpensive health care strategy.

List of Abbreviations

Provide a list of all abbreviations used in the protocol and their associated meanings.

BAQ– Berlin Apnea Questionnaire [1]
CS+– Reinforced conditioned stimulus
CS- –Unreinforced conditioned stimulus
CS+E– Extinguished reinforced conditioned stimulus
CS+U– Unextinguished reinforced conditioned stimulus
C-SSR-S– Columbia-Suicide Severity Rating Scale [2]
CAPS-5– Clinician Administered PTSD Scale [3]
CAR– Cortisol awakening response
CTQ– Childhood Trauma Questionnaire [4]
Diamond- Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders [5]
ECG– Electrocardiography
EMG– Electromyography
EMSQ– Evening/Morning Sleep Questionnaire
ESS– Epworth Sleepiness Scale [6]
HR– Heart rate
fEMG– Facial electromyography
FIRST– Ford Insomnia Response to Stress Test {Drake, 2004 #25541
GAD-7– General Anxiety Disorder [14]
ISI– Insomnia Severity Index {Bastien, 2001 #11079}
LEC-5– Life Events Checklist for DSM-5
MEQ– Morningness-Eveningness questionnaire [7]
MOSSS– Medical Outcomes Study Social Support Survey
PCL-5– PTSD Checklist for DSM-5 [8]
Demographics– NIMH PhenX Mental Health Research Collection
PE– Prolonged Exposure Therapy
PHQ-9– Patient Health Questionnaire [12]
PR– Psychophysiological reactivity
PSQI– Pittsburgh Sleep Quality Index [9] with PTSD Addendum for PTSD [10]
PTCI– Posttraumatic Cognitions Inventory [11]
PTSD– Posttraumatic Stress Disorder
SCISD–Sleep Disorders Module Clinical Interview for DSM-5 Sleep Disorders Module (SCISD)[13]
SCL– Skin conductance level
SCR– Skin conductance response
SDI– Script driven imagery
SDI-PR– Psychophysiological reactivity to script-driven imagery (index)
SE– Sleep efficiency
SOL– Sleep onset latency
STAI-T– Spielberger State-Trait Anxiety Inventory-Trait [16]
SUDS– Subjective Units of Distress
Substances– Substance-Related and Addictive Disorders, NIMH PhenX Mental Health Research Collection
TST– Total sleep time
WASO– Wake time after sleep onset
WHODAS 2.0– World Health Organization Disability Assessment Schedule [15]

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## Protocol Title:

Circadian influence on fear extinction resulting from Prolonged Exposure therapy for PTSD

VA Boston is the only site recruiting and running study participants. As the Prime site for the NIMH grant, MGH has a separate IRB protocol and BUSM has ceded IRB review to MGH. A single IRB waiver has been granted for this project.

# 1.0 Introduction

The constellation of chronic symptoms diagnosed as posttraumatic stress disorder (PTSD) is a major public health issue that has been brought into sharp focus by recent military conflicts and the COVID-19 pandemic.[17-20] Although Prolonged Exposure (PE) is a well-validated PTSD treatment that consistently produces significantly greater reduction in PTSD symptoms than control treatments, it typically has high dropout rates (23%-38%)[21-26] and most clients suffer from residual PTSD symptoms after completing treatment.[24, 27] The proposed research will investigate whether a putative circadian influence on fear extinction can produce more powerful PE effects when PE is carried out in the morning rather than later in the day. To test this hypothesis, we will examine PE's ability to reduce psychophysiological reactivity (PR) during recollection of the traumatic experience that precipitated an individual's PTSD ("index trauma") using a standardized assessment, script-driven imagery (SDI).[28, 29] Fear conditioning is hypothesized to be an initiating mechanism of PTSD whereby associative memory processes link stimuli that are temporally proximal to a psychological trauma to the trauma itself. These stimuli can later act as cues that evoke symptoms of PTSD such as intrusive memories and disabling avoidance behaviors.[30-32] Similarly, fear extinction is an associative memory process whereby an individual acquires new learning that conditioned cues no longer predict danger.[33, 34] Hence, therapeutic innovations that might augment extinction learning or the consolidation of extinction memory, in the context of exposure therapy, have prompted extensive research efforts.[35-37] Based upon findings from our group and others,[38-41] we predict that the change in reactivity to SDI across a course of PE, and the concomitant decline in PTSD symptom severity, will be greater when PE treatment takes place in the morning than in the late afternoon. The well-documented morning peak (acrophase) of endogenous cortisol[38-40, 42] will be explored as a potential mechanism that produces this advantage. As detailed below, we have reported a morning advantage for experimental extinction learning and memory that may be favored by the circadian acrophase of cortisol.[40, 41] In clinical settings, exposure-based therapy for panic disorder (PD)[38] and spider phobia[39] show greater efficacy when provided in the morning. Moreover, during exposure therapy for PD, levels of endogenous

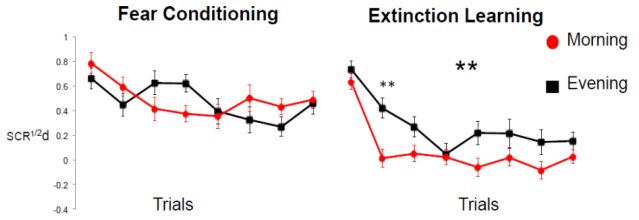


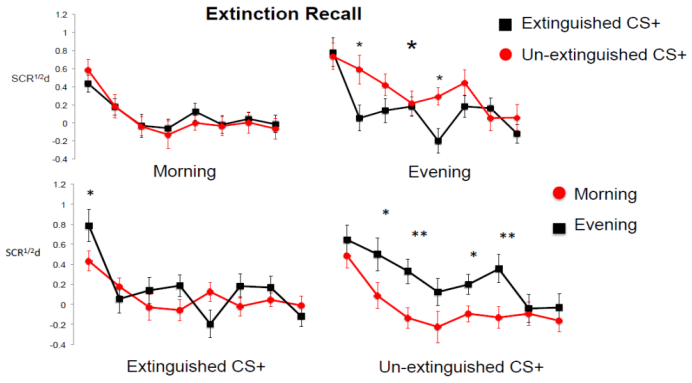

**Figure 1.** Fear conditioning did not differ between morning and evening whereas extinction was significantly better learned in the morning. The starting point of Extinction Learning was equated by examining the upper half of a median split based upon the mean differential SCR of first two trials of Extinction Learning (N=33 evening, 21 morning). Each data point represents the mean differential SCR to two successive CS+. Significance indicated for the Time-of-Day main effect (large asterisks) and trial-by-trial (small asterisks). $SCR^{1/2}d$: differential SCR, ** $p < .01$. Error bars depict SE.

cortisol at treatment sessions mediated the relationship between time of day and session-to-session improvement.[38] Similarly, greater endogenous cortisol levels have been shown to augment exposure

therapy for social anxiety disorder.[43] In our experimental study,[40] as expected from known circadian rhythms,[44] we observed significantly higher morning levels of cortisol.[45] Administration of exogenous glucocorticoids can enhance exposure therapy for various anxiety disorders[46-52] and PTSD.[52-56] Additionally, effects of cortisol on experimental extinction[57, 58] and the neural substrates of extinction[57, 59] have been demonstrated in healthy humans.

**Morning augmentation of experimental extinction:** We used a validated experimental fear conditioning and extinction protocol[40, 41, 60-72] to examine whether fear conditioning, extinction learning and extinction memory might differ between the morning and evening in 109 healthy young men.[40] Six groups completed a 2-session protocol. In Session 1, fear conditioning was immediately followed by extinction learning. During fear conditioning, partial reinforcement (63%) with a mild electric shock produced conditioned skin conductance responses (SCR) to 2 differently colored lamps (CS+), but not a third color (CS-). During extinction learning, one CS+ (CS+E) but not the other (CS+U) was extinguished by un-reinforced presentations. Delay durations of 3 h (within the AM or PM), 12 h (morning-to-evening or evening-to-morning) or 24 h (morning-to-morning or evening-to-evening) followed. In Session 2, extinction recall was tested. Fear conditioning did not differ between morning and evening; however, extinction was better learned in the morning (p=0.002; Fig. 1). Collapsing across CS+ type, there was a smaller morning differential SCR at extinction recall (p=0.003). Morning extinction recall also showed better generalization from the CS+E to CS+U; the response to the CS+U, compared to the CS+E, was larger only in the evening (p=0.028; Fig. 2). Thus, extinction was learned faster and its memory was better generalized in the morning than in the evening.

**Figure 2.** Extinction Recall in the morning showed generalization of extinction memory whereas recall in the evening preserved the differentiation of the extinguished and unextinguished CS+ and favored expression of a greater overall degree of un-extinguished conditioned fear. Significance indicated for the CS+E vs. CS+U main effect (large asterisk) and trial-by-trial (small asterisk). $SCR^{1/2}d$: differential SCR, * p < 05, ** p < .01. Error bars depict SE.




**Morning exposure therapy and higher salivary cortisol promotes therapeutic extinction:** Dr. Meuret, examined the cortisol-related enhancement of extinction after 4 in-vivo exposure sessions in 26 outpatients with PD and agoraphobia.[42] Salivary cortisol from 94 sessions was collected before, during, and after each

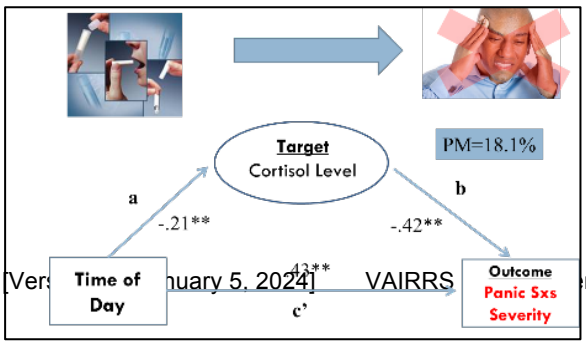



**Figure 4.** Cortisol as a mediator of the effect of time-of-day on outcome on clinical outcomes

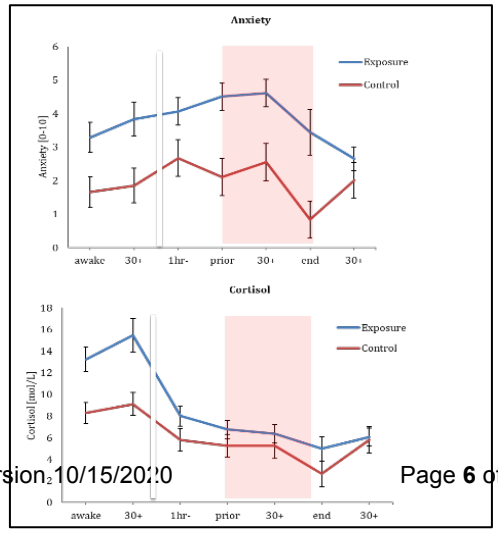



**Figure 3.** Anxiety and cortisol during the exposure and the non-exposure day.

exposure session [0, +30, end, +30], in response to awakening (CAR) [min 0, +30] and 60 min before the start of the first exposure, and during a non-exposure comparison day (Fig. 3). Changes in avoidance, threat appraisal, and perceived control were up to 5x superior for those with high, compared to low, cortisol levels during exposure. Dr. Meuret[38] also examined the potential link between time of the treatment session and treatment gains; if higher cortisol enhances fear extinction and normal diurnal variation in cortisol levels are highest in the morning, then morning sessions should be most advantageous. As expected, individuals whose sessions took place in the morning demonstrated superior reductions in panic symptoms and facilitated fear extinction compared to those who received treatment later in the day (ds>1.05; Fig. 4). Together, higher cortisol levels appear to facilitate processes that are relevant to extinction and contribute to enhanced early-day treatment efficacy. Dr. Meuret also demonstrated this effect in a transdiagnostic sample (including PTSD) undergoing treatment. Higher pre-treatment cortisol reactivity (1 SD > mean) to a stress induction resulted in 2.5x faster symptom improvement.[73]

**Script-driven imagery (SDI) and derivation of SDI-PR:** Individuals with PTSD consistently demonstrate heightened psychophysiological reactivity to trauma-related cues compared to those without PTSD.[74] Indeed, increased psychophysiological reactivity [e.g., heart rate (HR), skin conductance (SC) and frontalis EMG (fEMG)] to trauma-related stimuli in individuals with, compared to without, PTSD is perhaps the most reliable biological association in the PTSD literature.[75-77] Reactivity to trauma-related cues is associated with PTSD severity[29, 78, 79] and, when assessed soon after exposure to a traumatic event, predicts subsequent severity and/or persistence of PTSD symptoms.[80-82] Furthermore, a growing literature demonstrates that successful PTSD treatment leads to decreased physiological arousal and trauma-related psychophysiological reactivity.[76, 77, 83-87] Thus, psychophysiological reactivity to SDI has been discussed as a measure relevant to PTSD in the NIMH PhenX toolkit[88] and has demonstrated utility as an outcome measure in clinical trials of trauma-related psychotherapy.[89] Dr. Orr developed the SDI procedures to be used in the proposed study [79, 90-92] and we have published papers supporting the potential utility of SDI as a measure of PTSD therapy outcome.[28, 29] In trauma-exposed individuals with and without PTSD,[90, 93-96] HR, SC, and fEMG responses during SDI can be combined to derive an optimal discriminant function that best separates PTSD and non-PTSD groups. This PTSD discriminant function, termed “psychophysiological reactivity to script-driven imagery” (SDI-PR), is a canonical variable that reflects the overall magnitude of psychophysiological reactivity during trauma-related imagery.[29, 76, 90, 97] Before creating the composite SDI-PR score, we observed that individuals with PTSD demonstrated significantly greater reactivity for SC, HR, and fEMG, which were moderately inter-correlated. The SDI-PR score has demonstrated strong test-retest reliability over a 6-month period[29] and has accounted for much greater variance in PTSD diagnosis than self-reported emotional distress to the same scripts.[28] Self-reported distress may reflect negative affect, i.e., a distress factor shared by mood, anxiety and trauma-related disorders,[98, 99] whereas heightened psychophysiological reactivity may reflect a specific biological process related to the pathological persistence of conditioned fear.[28]

**INNOVATION:** This will be the first study to prospectively address the hypothesis that the efficacy of exposure-based therapy may be influenced by time of day and its attendant circadian physiology, as suggested by experimental evidence and clinical observations.[38-41] Circadian effects on fear conditioning and extinction have been widely reported in rodents[100-102] and retrospective clinical findings are suggestive of such effects;[38] however, few experimental studies have examined these relationships in humans.[39, 40] Circadian effects are seen in normal emotions[103, 104] and in the symptoms of anxiety disorders[105] and PTSD.[106] Moreover, circadian genes have been associated with both normative[107] and pathological

anxiety[108] and PTSD.[109] The proposed study will take advantage of a therapeutic intervention, PE, that utilizes extinction to effect clinical change in a cohort of individuals with PTSD. Importantly, PE can be easily scheduled, both experimentally and in clinical practice, to accommodate specific circadian phases having distinct endogenous hormonal milieus. If endogenous cortisol is associated with the session-to-session improvement in extinction, clinical trials could be initiated to explore its exogenous administration to augment PE when conducted during times of low endogenous levels. Because sleep quality will be assessed, its associations with improvements in markers of extinction and PTSD symptom change will contribute to evidence from our group and others that improved sleep quality will augment exposure-based therapy.[36, 110-113] Monitoring with diary and actigraphy across an entire course of PTSD treatment enabling session-by-session analysis of both subjective and objective sleep parameters, has rarely been obtained.[114] However, at least one study has done so,[115] and we have also done so over a course of CBT for social anxiety disorder,[116] thus demonstrating both the feasibility and novelty of our proposed approach.

# 2.0 Objectives

**Specific Aim 1: Determine if early-morning versus late-afternoon administration of PE produces greater extinction as measured both by mechanistic (SDI-PR, SUDS) and clinical (CAPS-5, PCL-5) indices.**

*H1A:* Morning PE sessions will produce a greater decline from pre- to mid- to post-treatment in primary mechanistic (SDI-PR) and clinical (CAPS-5) outcome measures.

*H1B:* Morning PE will produce greater session-to-session reductions in secondary mechanistic (peak SUDS ratings during in-session imaginal exposure) and clinical (PCL-5) outcome measures.

**Specific Aim 2: Determine whether the session-to-session change in mechanistic and clinical measures is influenced by endogenous cortisol levels.**

*H2:* The session-to-session change in the mechanistic (SUDS) and/or clinical (PCL-5) outcome variables will be significantly predicted by the cortisol levels measured at the earlier session.

**Exploratory Aim 3: Determine whether longitudinal measures of objective (actigraphy) and subjective (diary) sleep quality across 10 sessions of PE will associated with changes in outcome variables.**

*EH:* Better sleep efficiency, measured by actigraphy and diary, will be associated with a greater decline in primary variables from pre- to mid- to post-PE and in secondary variables across sessions.

# 3.0 Study Design

**Overview:**

This is a randomized clinical trial following the NIMH experimental therapeutics approach. Participants with PTSD will be randomized to receive a full course of Prolonged Exposure (PE) therapy delivered via telehealth at either morning and or late-afternoon times of day. Specifically, we will compare 26 individuals randomized to undergo 10, 90-min sessions of PE with a start time between 07:00 and a time no later than 2 hours past an individual's customary rise time, to 26 individuals who will undergo these sessions beginning at 16:00 or later. The morning-PE group will complete daily at-home imaginal-exposure homework within two hours of awakening, while those in the late-afternoon PE group will complete homework between 16:00 and 2 hours before bedtime.

The primary mechanistic outcome is psychophysiological reactivity to script driven imagery (SDI-PR) of trauma-related scripts; SDI-PR will be measured pre-, mid- and post-treatment. A secondary mechanistic outcome will be session-by-session change in peak subjective units of distress (SUDS) during in-session imaginal exposure. The primary clinical outcome will be change in pre-, mid- and post-treatment severity scores on the Clinician-Administered PTSD scale (CAPS-5).[3] A secondary clinical outcome will be the PTSD Checklist for DSM-5 (PCL-5)[8, 117] obtained at each session. Cortisol awakening response will be investigated as a mechanism contributing to time-of-day effects on mechanistic and clinical outcomes.

**Prolonged Exposure Therapy (PE):** We will use manualized procedures to administer PE.[118] A full course of PE will be administered during 10, 90-minute sessions and participants will work with the same study therapist throughout treatment. PE will be administered via tele-health over HIPAA compliant video platforms (e.g., Webex, Microsoft Teams) Session 1 will focus on psychoeducation, the rationale for in vivo and imaginal exposure, and breathing retraining. Session 2 will involve continued psychoeducation and the collaborative construction of the in vivo exposure hierarchy. Following session 2, participants will begin homework in which they will be instructed to confront situations on their hierarchy. Sessions 3-10 will primarily focus on in-session imaginal exposures to the worst trauma memory for 45-60 min followed by 15-20 min of processing the imaginal exposure. Subjective Units of Distress (SUDS) ratings will be taken throughout imaginal exposure exercises. Throughout the treatment, participants will be instructed to listen to a recording of their imaginal exposure and engage in imaginal exposures daily. Participants will either use their smartphones or borrow an encrypted recording device to record these exposures for use during homework practice.

For participants without a smart phone or who wish to use an encrypted recording device, they will be loaned an encrypted audio recorder to facilitate between-session listening to their in-session exposure exercises. For participants opting to use a loaned encrypted audio recorder, they will be given the option to have a PIN code enabled. This will be set up upon request by study staff. This is a standard component of PE treatment. Before study participation, the device will be checked by a study team member to ensure it is blank. Then, the participant will use the same recorder for the entire study. At the beginning of each session, the therapist will assist the participant in deleting the previous session's recordings (for both loaner recorders or their smart phone) and using the same device to record the current session's recording. For participants who borrowed recorders, the participant will return the loaned recorder after the last PE session. The therapist and a second study team member will double check the recorder to ensure all recordings are deleted from the device.

Participants who have experienced stable remission before completing the 10 PE sessions will not be required to complete the full PE protocol to be considered treatment completers. Stable remission will be defined as a) 2 consecutive sessions in which the participant reports a PCL-5 score below 19, and b) participant and therapist agreeing that early termination is warranted.[119] In these cases, the post-treatment assessment will be scheduled after the last PE session.

PE must be completed in no more than 16 weeks. The maximum number of cancellations/no shows is 5 with no more than 3 cancellations/no shows in a row.

*Training therapists, treatment fidelity and integrity:* The therapists will be naïve to study hypotheses, will be available to provide PE during both time slots and will be assigned to treat an equal number of participants in the morning and late-afternoon. Throughout the study, therapists will have supervision with Dr. Sloan that includes audiorecorded and/or videotaped session review. Dr. Sloan will be blinded to participants' treatment condition.

## 3.1 Recruitment Methods

**Characteristics**
The target population will be adults 18-70 years old with PTSD who are interested in starting a trial of PE (see below for inclusion/exclusion criteria). One hundred fifty participants will be consented with the goal of obtaining at least 52 participants who complete the study.

**Recruitment of subjects**
To reach our goal of 52 participants, we will enroll 2-3 participants/month. Participants will be recruited through: VA Boston primary care and specialty mental health clinics, VINCI-generated patient lists, consult lists, flyers posted on the three VA Boston campuses and CBOCs, and at local hospitals, clinics, college campuses, and public bulletin boards. Announcements of this research opportunity will also be posted on social media.

The PI or a member of the study team will reach out to leadership in primary care behavioral health clinics and specialty mental health clinics, including the Women's Trauma Recovery Team (WTRT), the PTSD Clinical Teams (PCTs), General Mental Health Clinic, and the Center for Returning Veterans to provide information about this study and inquire about the possibility of attending a team meeting. If leadership agrees, we will attend clinic team meetings to briefly describe the goals, methods, and eligibility criteria for the study and leave study recruitment materials with members of the team to distribute to Veterans who may be interested in contacting study staff to learn more about the study. Providers will be given recruitment materials for potential distribution to Veterans for informational purposes only. Providers will also be given copies of the Permission-to-Contact-for-Research forms to allow participants the option to request a member of the research team contact them directly with more information, thus alleviating some burden on potential participants to initiate contact; we will not ask providers to actively ask Veterans to participate in this study or to conduct screening evaluations for this study. In addition to use of the Permission-to-Contact-for-Research forms, Veterans may also provide verbal consent to allow providers to send an encrypted email to the study team, requesting that a member of the study team directly contact the Veteran; this email would include the Veteran's name and contact information. All permission to contact requests sent through encrypted email will be saved on a secure shared drive for documentation purposes.

Similarly, we will reach out to leadership in the Psychiatry Service to ask to attend grand rounds to briefly describe the goals, methods, and eligibility criteria for the study and leave study recruitment materials and the Permission-to-Contact-for-Research forms with staff to provide to Veterans who may be interested in learning more about the study. Flyers will be included in the periodic mailings to all patients who receive primary care through VA Boston and we will contact participants who previously participated in research through the National Center for PTSD participant database.

VINCI will be used to provide Electronic Medical Record (EMR)-driven recruitment support by providing patient data stored in the VA EMR. This service will generate patient lists by searching for patients with relevant diagnoses, in reasonable proximity to the Jamaica Plain VAMC, who meet eligibility criteria for age, medications, and other key parameters. The use of VINCI in this manner will streamline recruitment efforts by ensuring that prospective participants meet eligibility criteria prior to screening.

We also will generate consult reports for any patient for whom a consult was placed within the past week at the time the report was generated. The consult reports to be generated will be for: 1) WOMEN'S TRAUMA RECOVERY TEAM, 2) MH POST TRAUMATIC STRESS DISORDER (JP) OUTPT, 3) MH POST TRAUMATIC STRESS DISORDER (BR) OUTPT, 4) CENTER FOR RETURNING VETERANS (MH) OUTPT, 5) PSYCHIATRY JP OUTPT, 6) PSYCHIATRY BR OUTPT, 7) MENTAL HEALTH CONSULT JP OUTPT, 8) MENTAL HEALTH OUTPT (BR), 9) GMH CASE MANAGEMENT TEAM eCONSULT (BR) OUTPT, and 10) GMH CASE MANAGEMENT TEAM eCONSULT (JP) OUTPT. We submitted a HIPAA waiver to review the medical records of Veterans on these consult lists and VINCI patient lists, for the purpose of recruitment, in order to minimize participant burden and contact only those individuals who meet preliminary inclusion criteria and the consult indicates that the Veteran is seeking treatment for PTSD-related problems. For patients who appear likely to be eligible, we will either a) use UPS to send a letter and previously IRB-approved study brochure asking them to contact study staff if they would like to hear more about this research opportunity or b) use USPS to send them a letter and the previously IRB-approved study brochure. This letter will state that the study staff will contact them in a week to describe the study and discuss their potential interest in the study. There will also be a number for the participant to call if they wish to hear more about the study or would prefer for study staff to not call them. In order to provide double confirmation of the integrity of the mailing process, two independent team members will verify the accuracy of outgoing correspondence.

**Study compensation**

Participants will be paid via direct deposit or debit card for each session completed. Participants will be compensated up to $310 total for the screening, sleep monitoring period, and three assessment appointments totaling approximately 14.5 hours. Participants will not be compensated for engaging in therapy.

The schedule for compensation is: $60 for the screening evaluation visit, $25 for the sleep monitoring period, $75.00 for the pre-treatment assessment, $75 for the mid-treatment assessment, and $75 for the post-treatment assessment.

Additional compensation will be made for on-site visits to offset the cost of travel for both Veterans and non-Veterans. If a participant's home address on file is a distance of 50 miles or greater (round trip) from VABHS, they are eligible to receive $5 for each 10 miles of travel **above** 50 miles, for a maximum of $50 (or 100 miles) per visit. Participants who take a rideshare or taxi to attend in-person appointments will also be eligible to receive additional compensation. They will be compensated for the amount ride fare minus $10. For example, if the rideshare to the appointment was $15 (one way), participants would be compensated an additional $20 – to offset the cost of the $30 roundtrip fare.

For participants who complete the pre-treatment assessment visit more than one month after the screening interview, an additional compensation of $20 may also be provided visit for an additional CAPS-5 and PCL-5 assessment to be conducted during this visit.

## 3.2 Informed Consent Procedures

In order to assess study inclusion/exclusion criteria, we will first use a phone screen. Those who potentially meet study inclusion criteria will be invited to schedule a remote or in-person consenting session. Except for when the facility has policies precluding in-person visits, the participant will have the option to complete this session in-person or remote:

1. Following the phone screen, eligible individuals will be given the option to complete the informed consenting process remotely (via a HIPAA compliant video platform such as Webex or Microsoft Teams) or in-person at the Jamaica Plain VA. Potential participants who choose to complete the informed consent remotely will be mailed and/or emailed the ICF and HIPAA and, if a non-Veteran, then also the Notice of Privacy Practices and a form to create a medical record. For participants who chose mailing as their preferred way to send back forms, a prepaid envelope will also be included in this mailing to allow participants to mail back the informed consent documents (ICDs) to study staff. Participants will be given the option of signing all informed consent documents electronically via DocuSign as well. If participants chose to use DocuSign during the consenting appointment, they will be emailed the DocuSign materials and sign the ICDs electronically.
2. Potential participants who choose to complete the consenting appointment remotely will then schedule a 30-minute consenting call with a study team member. This visit will occur after the potential participant has received the informed consent documents.
3. Potential participants who choose to complete the consenting appointment in person will schedule an in-person appointment with the study team.
4. The content of the informed consent process for both in-person or remote visits is the same. First, the participant will be presented with the ICDs – i.e., a written explanation of the study and the associated risks and benefits to review on his/her/their own. A member of the study team will also verbally explain the purpose of the study and the risks and benefits associated with participation. The participant will be given an opportunity and encouraged to ask questions. The participant will be asked questions to ensure comprehension of the study procedures along with risks and benefits and informed that he/she/they may discontinue participation at any time without personal consequences. The participant will review and sign the consent form if he/she/they agrees to participate. The methods for signing and returning the ICDs differ for remote and in-person.
    a. For participants who choose to complete the informed consent process remotely: Participants who choose the mailing option will then sign the forms and hold the signed forms to the camera, allowing study staff to take a screenshot of the signed document; study staff will only take a screenshot of PHI when logged into a device behind the VA firewall (i.e. while logged into a VA computer or while using CAG/VPN remote access). These screenshots will be saved on the IRB-approved secured shared drive where PHI is stored electronically. Participants will then use the prepaid envelopes provided to them to mail the signed documents back to the study team. No study procedures will be initiated until these signed ICDs are received by study staff.

If participants choose to sign consent forms with DocuSign, screenshots will not be taken and paper versions of the ICDs will not need to be mailed back to the study team.

b. Participants who choose to complete the consenting appointment in person will review the documents with study staff and sign the forms. Participants will receive one copy of all documents to keep for their own records.

Prior to the consenting appointment, participants will be sent the following link from the National Center of PTSD, which provides information on PE therapy for PTSD in the form of reading and brief videos:
https://www.ptsd.va.gov/understand_tx/prolonged_exposure.asp#:~:text=Prolonged%20Exposure%20%28PE%29%20is%20a%20psychotherapy%20for%20PTSD.,challenges%2C%20you%20can%20actually%20decrease%20your%20PTSD%20symptoms.
This information will support the process of informed consent by introducing participants to the risks, benefits, and essential aims of PE prior to enrollment.

## 3.3 Inclusion/Exclusion Criteria

**Inclusion criteria:**

1. a diagnosis of PTSD as defined by DSM-5, in combination with one of the following: a minimum CAPS-5 severity score of 26, a minimum PCL-5 score of 31, or a score of 2 or above on CAPS-5 Item B2 (concerning distressing dreams)
2. interest in starting a course of PE
3. availability for appointments at that will either begin from 07:00 to a time no longer than 2 hours past their customary rise time, or to the last treatment session of the day beginning at 16:00 or later
4. Age range of 18-70
5. A Morningness-Eveningness Questionnaire (MEQ) score above 25.
6. Non-exclusionary psychotropic medications must have been stable for 3 weeks prior to Screening/Assessment with intention to remain stable throughout participation.

**Exclusion criteria:**

1. current unstable bipolar disorder, past or present schizophrenic or other psychotic disorders
2. current organic brain disorder including moderate to severe traumatic brain injury
3. factitious disorder or malingering
4. pregnant or planning to become pregnant in the next four months at time of screening
    a. if a participant does become pregnant during study procedures, the situation will be reviewed on a case-by-case basis and the participant's wishes will be considered in deciding whether the participant will continue with the study or withdraw.
5. current moderate or severe substance use disorder with symptoms present within the past three months
6. diagnosed moderate to severe sleep apnea, narcolepsy, periodic limb movement, or restless legs syndrome that result in daytime sleepiness indicated by Epworth Sleepiness Scale (ESS) above 10
7. active risk of harm to self or others
8. evidence of clinically significant hepatic or renal disease or any other acute or unstable medical condition that might interfere with safe conduct of the study

9. current participation in trauma-focused cognitive-behavioral therapy (e.g., Cognitive Processing Therapy, Written Exposure Therapy, Eye Movement Desensitization and Reprocessing Therapy)
10. prior treatment with an adequate dose of PE (i.e., 8 or more sessions) to the traumatic event that would be the index trauma for treatment in the study
11. having no memory of their traumatic event
12. daily use of benzodiazepines
13. methadone or suboxone maintenance therapy for past opioid addiction
14. diagnosis of Cushing's disease, Addison's disease or use of medications that target cortisol directly such as those used to treat Cushing's disease [ketoconazole, mitotane (Lysodren), metyrapone (Metopirone), and Mifepristone (Korlym, Mifeprex)], those used to treat Addison's disease [Hydrocortisone (Cortef), prednisone or methylprednisolone], as well as cortisone or dexamethasone
15. persons who would habitually awaken so early that more than 2 h would elapse before a morning PE session could occur; or those who engage in habitual shiftwork or transmeridian travel

## 3.4 Study Evaluations

**Screening/Assessment of Inclusion/Exclusion Criteria**

In order to assess study inclusion/exclusion criteria, we will first use a phone screen. Those who potentially meet study inclusion criteria will be invited to schedule a consenting session described above. After completing the consenting session, participants will complete a remote Screening Session:

**Post-consent screening procedures:** During the remote Screening Interview Session, we will administer the LEC, Introductory Screening Questions, Top Problem Assessment, CAPS-5, an abbreviated version of the DIAMOND (*Specifically, we have removed the following: Initial Interview Questions, Separation Anxiety Disorder, Hoarding Disorder, Trichotillomania and Excoriation (Skin Picking) Disorder, Somatic Symptom and Related Disorders, Trauma and Stressor Related Disorders, Avoidant/Restrictive Food Intake Disorder, Neurodevelopmental Disorders, Substance/Medication-Induced Disorder, Disorder Due to Another Medical Condition, Other Specified Disorder, Unspecified Disorder, and Suicide Screen*), SCISD, the CSS-RS, and the interview for constructing the scripts for use in the SDI procedure if required given their experience with the online administration. After these assessments are administered and scored, we will contact participants on the telephone to inform them of their eligibility status.

*Diagnostic interviews*: Structured diagnostic interviews will be completed by study assessors, overseen by Dr. Pineles and Dr. Bovin. All information from these interviews will be identified with participant number only. Data from these interviews will be entered into the database that also contains the questionnaire data and, thus, will be stored in the same secure folder as the questionnaire data. Additionally, these interviews will be audio and/or video recorded in order to determine diagnostic reliability. The recordings will be identified with participant numbers only and stored on a secure folder on a secured server, with access restricted to staff for this specific research study. These data will be stored on a server that is separate from the self-report, diagnostic interview, and electrophysiological data.

As part of this screening session, will also complete a battery of self-report measures (listed below in Table 1). This battery will be completed at home delivered to them via a hard copy of the packet mailed to their home, or an electronic packet emailed via encrypted email. Participants completing hard copies of the measures will either use a prepaid envelope provided to them to return the packet of completed self-report measures or hand deliver the packet to their next appointment.

**Assessment procedures and schedule for participants who meet the inclusion/exclusion criteria assessed during the screening session:**

The assessment schedule will be identical for all participants (Table 1). Participants who meet study inclusion criteria at screening will first begin a 7-day, pre-study sleep-monitoring period with wrist actigraphy, sleep diaries and completion of a diurnal profile of salivary cortisol levels. The sleep diaries, a wrist motion detector, and materials to collect saliva samples will be mailed to participants and there will be a brief phone or video call to show participants how to use these materials. Participants will be asked to wear the actigraph, and keep a sleep diary (i.e., EMSQ) during this initial sleep monitoring period and then throughout the study period. Participants will be asked to keep the saliva samples in their freezer until their next visit to the VA Medical Center. A diurnal profile of cortisol measures will be collected on one day of this initial sleep monitoring period.

Trauma-related fear will be assessed using the standard SDI procedures detailed below[29, 76, 90, 97] at pre-treatment, after 5 PE sessions (mid-treatment), and after all 10 PE sessions (post-treatment). We will invite individuals who elect to dropout of therapy to complete the assessment portion of the study. The assessments for these individuals will be scheduled approximately 5 and 10 weeks after starting PE to align with the mid- and post-treatment time points, respectively. Of note, these individuals who dropout of therapy are distinct from the early-completers described above in section 3.0. The SDI sessions must be completed in-person. For the mid- and post-treatment visits, the CAPS-5 will typically be administered immediately after the SDI, but it would be possible to split this session based on the participant or study staff request and conduct the CAPS-5 remotely within 1 week of the SDI session. [For participants who complete their screening assessment more than 1 month before the pre-treatment assessment appointment, an additional CAPS-5 and PCL-5 will be administered at this visit and participants will be compensated an additional $20 for these measures.] PCL-5 measurements will be obtained at each treatment session and SUDs will be obtained during all treatment sessions that include imaginal exposure (sessions 3-8). PE treatment will be administered remotely at a targeted rate of once per week. At each PE and assessment session, pre-session saliva samples will be obtained for cortisol measurement and normalized using the diurnal profile of cortisol obtained during the sleep-assessment week. Participants will wear the wrist actigraph and complete sleep diaries throughout PE. The diurnal cortisol profile will be repeated at the post-treatment assessment.

We will attempt to have patients who drop out of therapy complete portions of the remaining mid-treatment and post-treatment assessment procedures. Specifically, the instruments that will be administered are the CAPS-5, the SDI, and the mid- and post-treatment PCLs. In addition,

we will ask participants who prematurely dropout of therapy to complete a brief semi-structured interview assessing their reasons for terminating PE therapy. (See Reasons for Treatment Termination Interview Guide.)

We will attempt to contact participants who dropped out of therapy prior to the implementation of the semi-structured interview (Protocol v16) to retroactively complete that brief interview.

**Table 1. Assessment battery and schedule of assessments**

| Assessment | Phone screen | post-consent Screening Interview | Sleep monitoring period | pre-treatment | Session 1 | Session 2 | Session 3 | Session 4 | Session 5 | mid-treatment | Session 6 | Session 7 | Session 8 | Session 9 | Session 10 | post-treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Telephone screen | X | | | | | | | | | | | | | | | |
| Demographics | X | X | | | | | | | | | | | | | | |
| Introductory Questions | | X | | | | | | | | | | | | | | |
| DIAMOND | | X | | | | | | | | | | | | | | |
| Top Problem Assess. | | X | | | | | | | | X | | | | | | X |
| CAPS-5 | | X | | * | | | | | | X | | | | | | X |
| C-CSSR-S | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PCL-5 | | X | | * | X | X | X | X | X | X | X | X | X | X | X | X |
| PTCI | | X | | | | | | | | X | | | | | | X |
| PHQ-9 | | X | | | | | | | | X | | | | | | X |
| WHODAS 2.0 | | X | | | | | | | | X | | | | | | X |
| STAI-T | | X | | | | | | | | X | | | | | | X |
| GAD-7 | | X | | | | | | | | X | | | | | | X |
| DSM-5 Cross-Cutting | | X | | | | | | | | X | | | | | | X |
| MOSSS | | X | | | | | | | | | | | | | | |
| LEC-5 | | X | | | | | | | | | | | | | | |
| CTQ | | X | | | | | | | | | | | | | | |
| SCISD / SDscreen | | X | | | | | | | | | | | | | | |
| MEQ | | X | | | | | | | | | | | | | | |
| BAQ | | X | | | | | | | | | | | | | | |
| PSQI & PTSD addendum | | X | | | | | | | | X | | | | | | X |
| ISI | | X | | | | | | | | X | | | | | | X |
| ESS | | X | | | | | | | | | | | | | | |
| FIRST | | X | | | | | | | | | | | | | | |
| NIDA Quick Screen | | X | | | | | | | | | | | | | | |
| QDS | | X | | | | | | | | | | | | | | |
| SDI | | | | X | | | | | | X | | | | | | X |
| Cortisol | | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Diurnal cortisol profile | | | X | | | | | | | | | | | | | X |
| Sleep diary | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Actigraphy | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

**Script-driven imagery:** SDI procedures[94] will be performed at each assessment session (Table 1). Script preparation and the psychophysiological assessment procedure will follow published procedures.[29, 76, 90, 97] "Scripts" approximately 30 s in length, composed in the second person, present tense, will be created portraying an individual's traumatic event(s). The participants will either complete the script preparation forms independently, or a member of the study team will work with participants to develop these scripts using the standardized instructions. Scripts will then be recorded by a study staff member for use in the actual SDI sessions. These scripts will also be rated by 3 experts for script quality (i.e., level of trauma detail) and trauma severity on 12-point Likert-type scales. During SDI sessions, electrodes will be attached and the participant will first sit quietly for 5 min. HR, SC, and fEMG will be continuously measured using a Biopac MP160 system. The parameters for recording physiological signals will be identical to published procedures.[28] For each script, there will be 4 phases (Baseline, Read, Imagery, Recovery), each of 30-s duration. Participants will be instructed to listen carefully during the playing of each script (Read period) and, upon its conclusion, to continue imagining as vividly as possible the experience that was presented

(Imagery period) until a tone signal is heard. Participants will be instructed to stop imagining the script at the tone and to relax until a second tone is heard (Recovery period). Participants then will make ratings of vividness, valence, arousal, dominance, and of 7 specific emotions on 0-12 Likert-type scales. A rest period will follow. After 1 min, or after HR has returned to within 5% of its value during the previous Baseline period, whichever is longer, the Baseline period for the next script will be initiated. Each SDI session includes three standard neutral scripts and two trauma-related scripts. The order of scripts will be: 1) a neutral script, 2) the first trauma script, 3) the second neutral script 4) the second trauma script, 5) the third neutral script.

**Psychophysiological reactivity:** SC level (SCL), ECG and fEMG level will be continuously monitored using the Biopac MP160 system (Biopac Systems, Inc., Goleta, CA) with AcqKnowledge 5.0.2 data-acquisition software. SCL will be recorded at 37.5 Hz using a 0.5 V constant voltage and an EDA100C transducer with 11-mm, Ag/AgCl sensors filled with isotonic paste attached 14 mm apart on the hypothenar surface of the non-dominant hand. fEMG will be recorded at 2000 Hz using an EMG100C amplifier and two Ag-AgCl 4-mm shielded electrodes filled with CG04 Signa Gel placed over the left lateral frontalis muscle. fEMG electrodes will be placed on abraded skin and located according to published specifications.[120] fEMG will be integrated using a 250-ms time constant. ECG will be recorded at 2000 Hz using an ECG100C amplifier and two Ag/AgCl 11-mm electrodes placed on the right clavicle and left lower rib. The average physiological level during the 30-s pre-script Baseline will be subtracted from the average physiological level during the 30-s Imagery phase for each measure. These difference scores will be square-root transformed to reduce heteroscedasticity, while retaining the negative sign for negative untransformed change scores.[121] As detailed above, HR, SCL and fEMG change scores will be combined to generate the canonical variable SDI-PR which is the standard SDI scoring method.

**Salivary cortisol**: Saliva samples will be obtained a) immediately before each PE and SDI session, and b) twice at home to obtain diurnal profiles, using unstimulated, whole saliva collected by the oral swab technique [122] and using materials provided by Salimetrics, LLC (Carlsbad, CA). A saliva diary will be provided with reminders of all instructions and spaces on which to record whether procedures were followed and to record exact sampling time. Saliva samples will then be frozen and stored at -20 C until shipped on dry ice to Salimetrics. Unbound cortisol will be assayed by Salimetrics using enzyme immunoassay (EIA). To control for individual variability, a diurnal profile of cortisol will be obtained during the sleep assessment week and after the post-treatment assessment to compute an area-under-curve (AUC) baseline[123] with which to normalize values obtained during PE and SDI sessions. To obtain this profile, six samples will be taken: immediately upon waking, 30 min after waking, noon or just before lunch (whichever is first), 5 PM or just before dinner (whichever is first), 8 PM, and bedtime. For the saliva samples taken at home (i.e., those for the diurnal profile and those before each PE session), participants will store samples in their home freezer until their next clinic visit at which point they will bring them to session. If they forget the samples for these in-person session, they may be asked to mail them using materials provided to them by the study team. Participants will be instructed not to eat, smoke, drink caffeinated beverages or exercise, within one hour of providing saliva samples.

**Actigraphy:** The Actiwatch 2 (Philips Respironics, Bend, OR) is a waterproof bracelet worn on the non-dominant wrist 24 h/day.[124, 125] A motion-sensitive monitor counts arm movements in 1-min epochs. Participants will press an event marker when beginning to attempt sleep and upon waking. Within this period, epochs are scored as sleep or wake using a standardized

algorithm. From these values, objective TST, SOL, SE and wake time after sleep onset (WASO) will be computed. Participants will be given a charger and instructed to keep the device charged at home. Periodically, the study team will mail a new device to participants and participants will return the existing device for the purposes of downloading data and ensuring the storage capacity is not exceeded.

**Diagnostic interviews and self-report measures:** These measures are included to assess inclusion/exclusion criteria, monitor safety of participants engaging in the trial, symptom change in response to PE, and to characterize the sample. The schedule of their administration is included in Table 1 above.

BAQ– Berlin Apnea Questionnaire [1] (approximately 3 minutes)
C-SSR-S– Columbia-Suicide Severity Rating Scale [2] (approximately 15 minutes at first administration; approximately 3 minutes subsequently)
CAPS-5– Clinician Administered PTSD Scale [3] (approximately 1 hour at first administration, approximately 45 minutes subsequently)
CTQ– Childhood Trauma Questionnaire [4] (approximately 10 minutes)
Demographics (approximately 10 minutes)
DIAMOND– Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders [5] (approximately 45 minutes)
DSM-5 Cross-Cutting– DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure—Adult [129] (approximately 5 minutes)
ESS– Epworth Sleepiness Scale [6] (approximately 3 minutes)
FIRST– Ford Insomnia Response to Stress Test {Drake, 2004 #25541 (approximately 5 minutes)
GAD-7– General Anxiety Disorder self-report questionnaire [14] (approximately 3 minutes)
Introductory Screening Questions– (approximately 5 minutes)
ISI– Insomnia Severity Index {Bastien, 2001 #11079} (approximately 5 minutes)
LEC-5– Life Events Checklist for DSM-5 [126] (approximately 10 minutes)
MEQ– Morningness-Eveningness questionnaire [7] (approximately 10 minutes)
MOSSS– Medical Outcomes Study Social Support Survey (approximately 7 minutes)
NIDA Quick Screen (approximately 1 minute)
PCL-5– PTSD Checklist for DSM-5 [8] (approximately 7 minutes)
PHQ-9– Patient Health Questionnaire (approximately 5 minutes)
PSQI– Pittsburgh Sleep Quality Index [9] with PTSD Addendum for PTSD [10] (approximately 10 minutes)
PTCI– Posttraumatic Cognitions Inventory [11] (approximately 7 minutes)
SCISD–Sleep Disorders Module Clinical Interview for DSM-5 Sleep Disorders Module (SCISD)[13] (approximately 20 minutes)
SCISD– Sleep Disorders Screener (approximately 20 minutes) [127]
STAI-T– Spielberger State-Trait Anxiety Inventory-Trait [16] (approximately 5 minutes)
QDS-Quick Drink Screen (approximately 2 minutes)
Top Problem Assessment– (approximately 5 minutes)
WHODAS 2.0– World Health Organization Disability Assessment Schedule [15] (approximately 3 minutes)

**Risks**

Potential physical risks to participants include a mild allergic reaction to the electrode paste or adhesive collars used to attach the electrodes for the SDI procedure. We believe the likelihood and seriousness of these risks are low given the steps we have put into place to decrease such risks. Specifically, well-trained study staff will attach electrodes and use tapes and materials specially designed for people's skin.

Potential psychological risks include breach of confidentiality; coercion to participate; and possible emotional distress when discussing their trauma and psychological symptoms during PE, when listening to scripts of their trauma during the SDI procedure, and during diagnostic assessments.

- We believe that the likelihood of a breach of confidentiality and coercion are low given the steps we have put into place to decrease such risks (e.g., numeric coding, informed consent).
- The risk of discomfort from discussing their trauma and other mental health symptoms during diagnostic assessments and completing the SDI procedure are moderate in both severity and likelihood.
- A primary risk for PE is the evocation of uncomfortable levels of anxiety or other emotions during the treatment sessions. Some patients may find sessions or assignments stressful and react to them with anxiety or anger. In addition, imaginal exposures conducted during sessions and exposure-based homework assignments may cause a temporary increase in PTSD symptoms. Recognizing this, the therapists will alert participants to expect a possible increase in symptoms to facilitate management of this should it occur.
- There is a small risk that participants may become pregnant over the course of the study. In clinical practice, PE is routinely delivered to pregnant persons. Although there are not controlled trials testing this, it is believed that untreated PTSD poses a greater risk to the pregnant person and the fetus than trauma-focused treatments. Additionally, for most individuals, imaginal exposure exercises conducted in PE become less distressing over the course of therapy. Thus, prematurely ending PE therapy is contraindicated. If a person becomes pregnant during the course of the study, the study team will defer to the wishes of the participant and would be happy to discuss this decision with them. One consideration is stopping PE prematurely may prevent the participant from getting the full benefit of this treatment.
    - There are data characterizing how the cortisol awakening response (CAR) changes over the course of pregnancy. Over the course of pregnancy, a pregnant participant will still have a CAR that exceeds her evening levels, but her baseline cortisol will likely increase. The increase in baseline cortisol is most notable in the third trimester and participants who become pregnant during the study will likely complete procedures before this time.

All study procedures will be fully explained during the informed consent process such that participants can make an informed decision regarding their level of commitment to the study. Please see the "adequacy of protection from risk section" for a more detailed description of protection of risks.

**Adequacy of Protection from Risks**

(a) Recruitment and Informed Consent.

Prior to completing any study procedures, the participant will undergo the informed consent process. First, the participant will be presented with a written explanation of the study and the associated risks and benefits to review on his/her/their own. A member of the study team will verbally explain the purpose of the study and the risks and benefits associated with participation. The participant will be given an opportunity and encouraged to ask questions. The

participant will be asked questions to ensure comprehension of the study procedures along with risks and benefits and informed that he or she may discontinue participation at any time without personal consequences. The participant will review and sign the consent form if he/she/they agrees to participate. Each participant will receive a copy of his/her/their signed consent form for his/her/their records.

(b) Protection Against Risk.

To ensure confidentiality, questionnaire and interview data will be stored in locked filing cabinets within locked offices. Each participant will have his/ her/their own participant number, which will be the only means that participant information can be identified. Electronic data will be stored on a secure private, password-protected drive that can only be accessed by members of the study team and labeled only with his/ her participant number. One list of names and participant numbers will be kept on a private, password-protected computer account on a separate drive from the de-identified data and accessible only to the study team.

We expect that any issues related to coercion will be very low. First, participants who do not wish to participate in the study or who wish to drop out of the study after enrollment will not experience any negative consequences. Second, a potential human subjects concern is whether the financial compensation offered is too high and therefore coercive to participants. We believe the rate of compensation for the current study is fair due to the length of the study and the potential inconvenience of psychophysiological and sleep measurement. Participants will be compensated up to $310 for the screening and assessment procedures. In addition, participants will not be compensated for engaging in therapy.

We will seek to protect participants from the emotional distress that might be aroused by the screening evaluation and assessments in the following ways: (a) screening evaluation and assessment interviews will be conducted by a Ph.D. level clinical psychologist or advanced doctoral-level graduate student with extensive clinical experience, (b) only a highly trained research assistant will conduct the SDI procedure and a Ph.D. level licensed clinical psychologist will always be available during the administration of these procedures should the participant need psychological assistance, and (c) suicidality will be assessed at every assessment and treatment session and referrals will be made for emergency or other inpatient or outpatient psychiatric services.

Again, we expect a degree of emotional distress during the PE sessions. To mitigate these risks:

a) The risk of an increase in symptoms during this study will be discussed during the informed consent process.

b) We will carefully screen to identify individuals whose risk for potential adverse outcomes is elevated before they begin participation in the proposed research. Such individuals will not be enrolled in the study. As an example, an actively suicidal person would be excluded from study participation and appropriate clinical care and referrals would be provided. The exact nature of "appropriate clinical care" will be determined by the judgment of clinicians and supervisors familiar with the specific participant and that person's access to community resources. This may include cognitive-behavioral treatment, other psychotherapy, referral to inpatient treatment or referral for medication treatment.

c) Clinical staff are trained to cope with any anxiety/distress experienced by participants during the assessments and treatment.

d) Only Ph.D. level clinical psychologists with extensive training in PE will conduct the PE treatment. In addition, study therapists will receive supervision (and additional consultation as needed) with Dr. Sloan.

e) Participants will receive psychoeducation about PE and the fact that feeling distressed is an important part of treatment. This psychoeducation will be provided during the informed consent process, the screening evaluation session, during the first PE session, and at other points during therapy (as appropriate). They will be reminded that this distress will likely be temporary, exposure sessions will be collaborative, and that they have the right to slow down or stop at any point.

f) There will always be a licensed clinical psychologist available to provide assistance; participants who express severe distress will be referred for evaluation and treatment. Suicidality will be assessed at each assessment and treatment session. If the participant expresses significant distress (but no suicidal or homicidal intent), a Ph.D. level clinical psychologist will make a collaborative plan with the participant in order to address their needs (e.g., brief supportive contact with therapist, referral, additional phone check ins). If the participant expresses suicidal or homicidal intent, the therapist will follow standard protocol to assure safety (e.g., arrange for evaluation at a local ER or Urgent Care Clinic). This may result in termination from the research study if the patient would be better served in a clinical care setting.

Risks involved in the SDI procedures (e.g., potential rash from electrodes) will be minimized by using highly trained staff. The study team has received extensive training with the psychophysiological procedures and this will minimize discomfort from the application of the electrodes. Future staff will receive similar training. We will ask subjects if they have any known allergies to adhesive electrodes and will also use hypo-allergenic electrodes to minimize the risk of skin irritation.

There is a small risk that participants may become pregnant over the course of the study. As discussed above, the risks of untreated PTSD are thought to pose a greater risk to the participant and fetus than PE. However, there may be unknown risks to the participant and fetus. To mitigate potential risk:

a) Participants who become pregnant will have a conversation with the PI to address any questions or potential risks. Together the PI and the study participant will weigh the option of whether the participant will continue with the study or withdraw, with the participant's preference being a strong determining factor.

b) Any study related problems requiring further clinical follow up for pregnant participants will be handled similarly as they are for other participants requiring clinical follow up. We encourage participants to communicate any clinical concerns with study staff throughout the study and address adverse events as clinically appropriate. We also work with participants to facilitate referrals for aftercare (when needed).

Finally, we will protect participants from potential inconvenience of study procedures by reminding them that they are free to withdraw from the study at any point.

**Biological Predictors of PTSD and Treatment Data and Specimen Repository (R&D #1592602)** Data collected from participants in this study will be entered into a database for the

purposes of this study. The study database will include birthday and last 4 digits of a subject's social security number to track multiple study enrollment. In addition, data from this study, including the scored physiological and sleep data and scored results of interviews and questionnaires will be entered into the VA Boston R&D-approved database Biological Predictors of PTSD and Treatment Data and Specimen Repository (R&D #1592602). Any future studies that make use of data in the Biological Predictors of PTSD and Treatment Data and Specimen Repository will be reviewed by the Institutional Review Board (IRB) at VA Boston Healthcare System.

**NIMH Data Archive** Data from this study will be submitted to the NIMH Data Archive, an informatics system run by the National Institute of Mental Health that allows researchers to review and use data from this study for their own research. Data entered into the NIMH NDA is linked to a Global Unique Identifier (GUID). NIH assigns the GUID as a unique identifier to use as a longitudinal tracker. In order to establish a unique GUID, VA Boston study team will enter the following PII into the NIH GUID Tool: First Name, Middle Name, Last Name, Sex, Date of Birth, and City/Municipality of Birth.

Specifically, as described on the NIMH Data Archive Website:

1. *"In a local computation, the tool generates a series of one-way hash codes based on the PII entered, without the PII ever leaving your computer.*
2. *The hash codes are encrypted and securely sent to the GUID system at NDA.*
3. *If the hash codes match an existing hash code, the GUID associated with that hash code is sent back to the researcher. The GUID is an alphanumeric code that is randomly and persistently linked to the hash codes within the secure NDA GUID system and cannot be traced back to the PII entered by the research project team member.*
4. *If the hash codes do not match an existing hash code in the NDA GUID system, a new GUID is created and sent back."*

## 3.5 Data Analysis

**Outcome measures:** The primary mechanistic and clinical outcome variables will be SDI-PR and the CAPS-5 score, respectively. As detailed above, SDI-PR is a canonical variable that combines SC, HR and fEMG measures obtained during each SDI session. A secondary mechanistic measure will be peak SUDS ratings obtained during each session's imaginal exposure component (i.e., sessions 3-8). Both SDI-PR and SUDS are negatively related to extinction achieved during prior PE. The primary clinical outcome, CAPS-5, is the "gold standard" clinical interview for assessing PTSD severity and will be administered at each assessment session. In CAPS-5, each of the 20 symptoms of PTSD is rated on a 5-point severity scale ranging from 0 (absent) to 4 (extreme). Total scores range from 0 to 80. Fidelity of administration will be ensured by video and/or audio recordings of interviews to be reviewed during diagnostic consensus meetings. 15% of tapes will be selected for inter-rater reliability. A secondary clinical outcome will be the PTSD Checklist for DSM-5 (PCL-5),[8] a self-report instrument, anchored to the previous week, that will be obtained at every PE session. The PCL-5 includes 20 questions on DSM-5 diagnostic criteria for PTSD self-rated on 5-point scales.
**Data Analysis:** We will assess the equivalence of the treatment groups on key baseline variables (demographics and baseline psychological variables), using t-tests and chi-square tests. Variables on which the groups differ will be used as covariates in subsequent analyses.

We will use intent-to-treat analyses (ITT) and include available assessment data for any participant who was randomized. We will examine missing data patterns, dropout rates, and distributional properties of measures. We will consider normality and variance-stabilizing transformations as appropriate. Data will be analyzed using multilevel, mixed-effects models (MLM). MLMs are intent-to-treat, do not require imputation of missing data, and are the recommended analyses for longitudinal drug use and psychiatric data.[127,128] Significance levels will be set at p<.05 (two-tailed) for all analyses. Alternative within-subject covariance structures will be compared using AIC (Akaike information criterion) and BIC (Bayesian information criterion).[130] In the MLM models, participant will be modeled as a random effect, treatment condition (morning or afternoon) as a categorical fixed effect, and other fixed-effect predictors as appropriate. Response variables in these regression models will include the primary mechanistic endpoint SDI-PR, the primary clinical endpoint CAPS-5, or the corresponding secondary endpoints, SUDS or PCL-5 respectively, depending on the hypotheses being tested. Cortisol levels will also be included as predictors for Aim 2. Theoretically relevant covariates and potential confounders: (chronotype [indexed by MEQ and free-night midpoint], average subjective sleep quality [diary-measured SE] and average objective sleep quality [actigraph-measured SE]) will also be considered as predictors. **H1A** will be supported if the categorical effect, treatment condition, indicates that morning produces significantly greater decline across pre-, mid- and post- treatment in the primary mechanistic (SDI-PR) or clinical (CAPS-5) outcomes. **H1B** will be supported if the categorical effect, treatment condition, indicates that morning produces significantly greater decline across the treatment sessions in the secondary mechanistic (peak SUDS) or clinical (CAPS-5) outcomes. **H2** will be supported if, across all relevant sessions, the session-to-session change in the mechanistic (SUDS) and/or clinical (PCL-5) variables (ΔSUDS or ΔPCL-5; e.g., their session-4 minus session-3 value) is significantly predicted by cortisol levels measured at the earlier session (session 3 in above example). Note that the mechanistic variable (SUDS) will begin to be measured at session 3 (hence a total of 7 ΔSUDS measures), whereas the clinical variable (PCL-5) will be measured at every session (hence a total of 9 ΔPCL-5 measures). In this model, there will also be a treatment condition x session-to-session change interaction term. For the **Exploratory Hypothesis (EH),** similar models will be tested with the addition of sleep efficiency (SE) variables. The EH will be supported if mean objective (actigraphy-based) or subjective (diary-based) SE during the period intervening between measurements (i.e., for H1A, pre to mid and mid to post; for H1B, session-to-session ΔSUDS or ΔPCL-5) is significantly associated with the mechanistic and clinical outcomes.

**Missing Data:** We will use pattern mixture modeling to assess the effect of missing data. We will rerun our analyses coding for various missing data patterns to determine 1) if missingness impacts our findings, and 2) how the differences between treatment conditions depend on the missing data pattern.

**Power Analysis:** With 26 participants in each group, we will have 80% power to detect an effect size of 0.70 for the between-group difference in our primary outcomes, based on a two-sample t-test at $p < 0.05$ (one-tailed).

**In the Event of Pregnancy:** If a participant becomes pregnant during the course of the study, their data may be excluded if the change in diurnal cortisol levels from pre- to post-treatment assessment is determined to be an outlier.

## 3.6 Withdrawal of Subjects

A participant will be withdrawn from the study if they are unable to respond to interview questions (for example, due to significant cognitive or psychological impairment, extreme drowsiness, or due to the immediate effects of substance use) or displays aggressive or

inappropriate behavior towards study staff. We may also discontinue their participation in this study if they are at immediate risk of harming themselves or others. In that event, we will follow all applicable laws and assist them in obtaining appropriate clinical care. If the participant is withdrawn from the study, that will end their involvement in the study and they will be compensated for completed sessions.

# 4.0 Reporting

**Data and Safety Monitoring**

The Principal Investigators (PIs) of the NIMH-funded R21 (Pace-Schott and Pineles), in conjunction with the NIH program officer overseeing this project, have appointed an NIH-approved independent Data Safety Monitoring Board (DSMB). The DSMB will be responsible for monitoring the project, participant safety, and adequacy of data quality. If the DSMB recommends a study change for participant safety or ethical reasons, or if the study is closed early due to slow accrual, the PI will be responsible for implementing the recommendations as expeditiously as possible in compliance with the standard policies of the NIH.

The PIs and DSMB Chair will be responsible for reaching a mutually acceptable decision according to usual practices. The DSMB will consist of 3 members: a psychiatrist, a clinical psychologist, and a statistician. Decisions will be made by a majority vote. The focus of the DSMB will be to monitor study safety. The DSMB will have a start-up meeting and then convene, in person or by conference call, at every 25% of the recruitment goal or at different intervals as needed. The DSMB Chair will receive reports of all serious adverse events throughout the study. The exact procedures for monitoring the study will be finalized during the first year of the study.

DSMB Responsibilities will include the following:

a) Review of the protocol, informed consent documents, and plans for data and safety monitoring

b) Make recommendations regarding the study conduct, enrollment, sample size, and data collection

c) Periodically evaluate progress on the study, including assessing data quality, recruitment and retention, and participant risk

d) The DSMB will be charged with making the decision for termination or continuation of the trial based on the *a priori* rules and the data being obtained and will inform the PIs of its decision. In the event that the study is discontinued, the IRBs and the participants will be informed and intervention-related activities will cease. The PIs will liaise with the DSMB and the NIH Project Office to wind down the study and reconcile the budget.

e) Consider external factors such as scientific or therapeutic developments that may impact the safety of the participants or ethics of the trial

f) Protect the safety and scientific progress of the trial

g) Make recommendations to the PIs regarding the appropriateness of continuation, termination, or other modifications to the trial based on observed beneficial or adverse effects of the intervention in accordance with clearly-defined data-driven algorithms

h) Assure data integrity, confidentiality, and monitoring results

Following each DSMB meeting, the chair will prepare a report to be submitted to the IRBs by the PIs. DSMB reports will be provided to the VABHS IRB when received. All materials, discussions, and proceedings of the DSMB are highly confidential. The meeting minutes will be reported to the NIH funding institute annually.

The PIs will provide to the DSMB a number of reports, including: 1) documentation of any serious adverse events or death within 5 business days of knowledge of event occurrence, 2) bi-annual reports

**Adverse Event/Unanticipated Problems Reporting Plans**
The Principal Investigator at VABHS will report Unanticipated Problems, Adverse Events, and safety monitors' reports to the IRB in accordance with VHA Handbook 1058.01 and VABHS IRB SOP.

# 5.0 Privacy and Confidentiality

To ensure confidentiality, questionnaire and interview data will be stored in locked filing cabinets within locked offices. Each participant will have his/ her/their own participant number, which will be the only means that participant information can be identified. Electronic data will be stored on a secure private, password-protected drive that can only be accessed by members of the study team and labeled only with his/ her/ their participant number. One list of names and participant numbers will be kept on a private, password-protected computer account on a separate drive from the de-identified data and accessible only to the study team. Access may be by the Institutional Review Board and Research & Development Committees of VABHS, the VA, Federal agencies, or national research oversight and accreditation organizations.

Notes regarding study participation will be included in CPRS and, for those who start the PE portion of the trial, limited information will need to be included in the medical record. This will include PTSD diagnosis and initial PCL score, and PE session procedures. Participants will be informed of this during the informed consent process.

For individuals who fail the phone screen, we will store the hard copies of their phone screen data in a locked file drawer in a locked office separate from both the ICFs and the data for participants who enroll in the study (due to identifying information present on the phone screen). In addition, we will add their names, phone numbers, and reason for exclusion to our phone screen log to minimize burden in case the participant calls again (forgetting they previously did a phone screen for this study).

Study staff will be trained in the importance of confidentiality and procedures to protect confidentiality.

Physiological and sleep data labeled with only subject ID will be processed by study collaborators at Massachusetts General Hospital (MGH)/ Harvard Medical School (HMS). Researchers at MGH/ HMS laboratories will not have access to identifying information. We have established a data use agreement with MGH/HMS for their use of the data.

As discussed above, data collected from participants in this study will be entered into the **Biological Predictors of PTSD and Treatment Data and Specimen Repository (R&D #1592602)**. Any future studies that make use of data in the Biological Predictors of PTSD and Treatment Data and Specimen Repository will be reviewed by the Institutional Review Board (IRB) at VA Boston Healthcare System.

Similarly, as discussed above, data will be shared with the NIMH Data Archive.

## 6.0 Communication Plan

All data will be collected at VA Boston. Within the study team, we will maintain study SOPs to ensure compliance with IRB approved protocol. We will also continuously update our study procedure folders to ensure that the most updated HIPAA, protocol, ICF, and recruitment materials are highlighted and used. In addition, the study team will conduct periodic internal audits to ensure adherence to the approved protocol.

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Participant Name: _____ Date:_____

Title of Study: Circadian influence on fear extinction resulting from Prolonged Exposure therapy for PTSD

Principal Investigator: Suzanne Pineles, Ph.D. VA Facility: VA Boston Healthcare System- Jamaica Plain

## KEY SUMMARY INFORMATION ABOUT THIS STUDY

You are being invited to take part in a research study that is being funded by the National Institute of Mental Health. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive. Taking part in this study is completely voluntary.

### WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

By doing this study, we hope to learn how time of day of treatment may impact the effectiveness of Prolonged Exposure (PE) Therapy, a first-line treatment for posttraumatic stress disorder (PTSD). Your participation in this research will last about 29 total hours over 13 weeks.

### WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You might choose to volunteer in the study because you are interested in receiving treatment for symptoms of PTSD. PE, the treatment provided in the study, is a recommended treatment for PTSD. For a complete description of benefits, refer to the Detailed Information section of this informed consent form.

### WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

You may choose not to volunteer to be in the study because the PE treatment and assessment sessions may cause a temporary increase in anxiety or discomfort, you are unavailable to do PE during either the early morning or late afternoon time slots, or the assessment procedures are too burdensome. For a complete description of risks and discomforts, refer to the Detailed Consent and/or Appendix.

Other treatment options available for treatment of PTSD can be psychological or pharmacological or both. For a complete description of alternate treatment/procedures, refer to the Detailed Information section of this consent.

### DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

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## WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of the study is Dr. Suzanne Pineles at the VA Boston Healthcare System, Jamaica Plain Campus. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his/her contact information is: 617-435-8742.

## DETAILED INFORMATION ABOUT THE STUDY

### WHAT IS THE PURPOSE OF THIS STUDY?

By conducting this research project, we hope to learn how the time of day that therapy occurs may affect the degree to which an individual benefits from treatment. PE is a first-line treatment for PTSD that can produce great reductions in PTSD symptoms. However, many individuals do not improve as much as they would like and still have many PTSD symptoms after completing PE. There is laboratory research that suggests that time of day can impact how well people learn and remember what they have learned. Thus, we are interested in how the time of day when PE sessions are scheduled may impact therapy outcomes. In this study, men and women with PTSD who are interested in engaging in PE will participate in 15 sessions including one screening visit, a week of sleep monitoring,10 PE sessions, and three assessment sessions. Before each PE and assessment appointment, we will ask you to provide a saliva sample for measurement of cortisol. During each assessment appointment, we will also measure your body's response (such as heart rate and sweating) to trauma reminders and interview you about your symptoms. You will also be asked to wear an actigraphy watch and keep a sleep diary during this study to track your sleep. You will be in the study for approximately 13 weeks if you decide to stay for the whole study. We expect approximately 150 men and women to enroll in this study.

If you are determined to be ineligible during the screening visit, that will end your involvement in the study and you will be compensated for the screening session, but not for future sessions.

The data collected from the sessions you participate in while enrolled in this study will be entered into a database for the purposes of this study. Coded data (stripped of identifiers) will be shared with off-site IRB-approved collaborators on this study.

This study is funded by the National Institute of Mental Health.

### HOW LONG WILL I BE IN THE STUDY?

This research study is expected to take approximately 2 years. Your individual participation in the project will take around 13 weeks during which you will complete 15 total study sessions.

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**WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?**

If you agree to take part in this study, you will complete a screening session during which we will determine if you are eligible for the rest of the study. If you are determined to be eligible during this appointment, you will be asked to participate in 10 sessions of PE and three additional assessment sessions. These will be scheduled before beginning PE, midway through PE, and shortly after finishing PE.

Your participation in this study is expected to take about 29 hours over 15 separate visits throughout the course of about 13 weeks.

The first visit will focus on determining your eligibility for study participation:

Visit 1 (approximately 4 hours): This session will be conducted remotely. Psychiatric, trauma, and substance abuse histories will be taken through interview and questionnaires; you do not need to answer any questions you do not want to on the questionnaires or during the interview. Questionnaires can be completed electronically (e.g., Qualtrics) or via hard copy. The interview will be audio and/or video recorded for reliability and training purposes; the recordings will only be identified by participant ID. A trained study assessor will conduct the interview, and other procedures will be completed by a trained study staff member. Information you provide during this visit will be used to determine eligibility for the rest of the study. After this session, you will be told if you are eligible to participate in the rest of the study sessions within one week and we will aim to start your participation within two weeks of this session.

Study Procedures for Qualifying Participants: If you qualify, you will be scheduled for the PE study consisting of 10 PE treatment sessions, three assessment sessions, and a week of sleep monitoring. The sleep monitoring phase will start shortly after the screening session and the assessment sessions will be scheduled to begin around a week before starting PE, mid-treatment (within a week of PE session 5), immediately post-treatment (about a week after PE session 10). The assessment sessions will be completed with trained members of the study staff.

Initial week of sleep monitoring: We will arrange with you a time to mail you the study materials and set up a brief phone or video call to show you how to use them. These materials will include sleep diaries, a wrist motion detector and materials to collect saliva samples in your home. The wrist motion detector, called an actigraph, is like a small wristwatch in size and appearance and is completely waterproof. You will be asked to keep a sleep diary and wear and wrist motion detector called an actigraph throughout your treatment to provide information about your sleep patterns. Saliva collection will involve swabbing your mouth at specific times of day,

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storing the swab in a vial, recording this on a saliva diary, and then putting the vial into your freezer until your next visit to the VA Medical Center.

Procedures during the PE treatment sessions: The PE sessions will all be conducted remotely via a secure video platform.

a) PE treatment: PE is a first-line treatment for PTSD and will be administered following standard procedures. It consists of 10, 90-minute sessions during which you will participate in imaginal exposure exercises about your worst trauma memories in session. During this time, you will repeatedly re-tell your worst trauma memory aloud with the clinician in the room for 45-60 minutes. This will be followed by 15-20 minutes of discussion about the exposure exercise. Between sessions, you will engage in exposure exercises to feared situations. These outside of session exposure exercises will be planned with your therapist. In addition, you will be instructed to listen to an audio recording of your in-session imaginal exposure exercise. These sessions will also be recorded for reliability and training purposes; recordings will only be identified by participant ID.

   You will be randomly assigned to the time of day you will engage in PE. Specifically, your PE sessions will be scheduled to begin either within 2 hours of the time you wake up or at 4pm or later. You will also be asked to complete your out of session assignments at the same time of day as your PE sessions are scheduled.

b) Assessments to occur during PE sessions for research purposes: Before each PE session, you will be asked to provide a saliva sample using an at-home saliva kit. You will then bring these samples into the next in-person assessment session. If you forget these samples, you may be asked to mail them to us using pre-paid UPS or USPS envelopes given to you by study staff. You will also be asked questions about your distress throughout the session and you will complete symptom measures after each PE session. These symptom measures will take about 5-10 minutes to complete.

c) Assessments to occur between PE sessions: Throughout the PE portion of this study, we will ask you to provide some information about your sleep. You will be asked to continually wear a recording device that looks and feels like a watch and this device will record information about your sleep. In the morning, you will be asked to fill out some self-report measures about your sleep length and quality. In the evening, you will be asked to fill out different self-report questions about your day. These measures will take about 10 minutes to complete.

Procedures during the assessment sessions (pretreatment, mid-treatment, and post-treatment): The pre-treatment, mid-treatment, and post-treatment sessions will each take about 2.5 hours

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and are mostly identical to each other. These assessment sessions will be conducted in-person. During each of these sessions, you will be fitted with a physiology recording device and your reactivity will be recorded as you listen to brief audiotaped descriptions of your worst traumatic experience that was developed based on the information you provided during the screening session. You will also be interviewed by a clinician about your current psychological symptoms and you will be asked to complete a set of questionnaires. You do not need to answer any questions you do not want to on the questionnaires or during the interview. These interviews will be recorded for reliability and training purposes; recordings will only be identified by participant ID. A trained study assessor will conduct the interview, and other procedures will be completed by a trained study staff member. You will also be asked to provide a saliva sample during each of these visits. If you prefer to split this session into two separate components (one in-person and one conducted remotely), that will be possible as long as the two visits can be scheduled within one week of each other.

We may end your participation in the study early if you are unable to respond to interview questions (for example, due to significant cognitive or psychological impairment, extreme drowsiness, or due to the immediate effects of substance use) or display aggressive or inappropriate behavior towards study staff. We may also discontinue your participation in this study if you are at immediate risk of harming yourself or others. In that event, we will follow all applicable laws and assist you in obtaining appropriate clinical care.

PE must be completed in no more than 16 weeks. To remain in this study, you cannot cancel or miss a total of 5 or more PE appointments and you cannot cancel or miss 3 appointments in a row.

You may choose to stop the PE treatment. If you do, you will have the option of completing the remaining assessment (mid-treatment, post-treatment) visits and receive full compensation for these visits if you are able to attend these appointments within the required timeframe for these assessments.

**Schedule of study visits**

| Visit # | Approximate Duration of Session | Weeks Since Enrollment |
|---|---|---|
| 1. Screening session 1 | 4 hours remote | |
| 2. Sleep monitoring phase | 1 week at home | |
| 3. Pre-treatment assessment | 2.5 hours in person | Around Week 2 |
| 4. PE session 1 | 100 minutes remote (90 minutes PE) | Around Week 3 |

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|---|---|---|
| 5. PE session 2 | 100 minutes remote (90 minutes PE) | Around Week 4 |
| 6. PE session 3 | 100 minutes remote (90 minutes PE) | Around Week 5 |
| 7. PE session 4 | 100 minutes remote (90 minutes PE) | Around Week 6 |
| 8. PE session 5 | 100 minutes remote (90 minutes PE) | Around Week 7 |
| 9. Mid-treatment assessment | 2.5 hours in person | Around Week 6 or 7 |
| 10. PE session 6 | 100 minutes remote (90 minutes PE) | Around Week 7 |
| 11. PE session 7 | 100 minutes remote (90 minutes PE) | Around Week 8 |
| 12. PE session 8 | 100 minutes remote (90 minutes PE) | Around Week 9 |
| 13. PE session 9 | 100 minutes remote (90 minutes PE) | Around Week 10 |
| 14. PE session 10 | 100 minutes remote (90 minutes PE) | Around Week 11 |
| 15. Post-treatment assessment | 2.5 hours in person | Around Week 12 or 13 |

**WHAT IS EXPECTED OF ME IF I TAKE PART IN THIS STUDY?**

- *Below is a list of responsibilities and expectations for all study participants:* .
    - Keep your study appointments. If you miss an appointment, please contact the investigator or research staff to reschedule as soon as you know you will miss the appointment.
    - Tell the investigator or research staff if you believe you might be pregnant.
    - Complete your sleep diaries as instructed and wear your actigraph during the course of the study.
    - Complete your questionnaires as instructed.
    - Complete the at home saliva collection kits and mail them to the study staff with the included prepaid envelopes or bring them in-person as instructed.
    - Ask questions as you think of them.
    - While participating in this research study, do not take part in any other research project without approval from the investigators. This is to protect you from possible injury from things such as conflicting advice from different treatment

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approaches. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other studies.

- If the study team needs to communicate with your doctors that are not at the VA, a VA Form Letter 10-212 will need to be filled out and signed for each non-VA facility.

**WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?**

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur.

Risks during Prolonged Exposure:
Because PE involves decreasing avoidance behaviors and discussing your traumatic experiences, you will likely experience emotional distress and possibly physical symptoms associated with distress (e.g., headaches, upset stomach) during the PE sessions.

Risks during assessment sessions:
Similarly, during the assessment procedures, you will listen to an audio recorded script of your worst traumatic experience and be interviewed about your symptoms. Therefore, you will likely experience some emotional distress during these sessions as well. In addition, some of the questions that you will be asked are of a personal nature (e.g., questions about medications and diagnoses), and you may experience some discomfort in answering them. There will be questions asked specifically about your trauma experience that may be emotionally upsetting. These risks are no different than if you were to participate in PE outside of a research study. If you become extremely distressed during the study, you will be asked to meet with Dr. Suzanne Pineles, the Principal Investigator, or another study clinician, to discuss your feelings.

Risks from psychophysiological recording procedures:
There may be some discomfort from the placement of the recording electrodes attached to the physiological recording device. This involves the use of mild abrasion and alcohol to cleanse the surface of the skin. The electrodes might feel uncomfortable or awkward at first, but after a few seconds, they should be mostly unnoticeable. The conductive gel that is used on the electrodes may cause an allergic reaction. You may also experience some discomfort during saliva collection or while wearing the actigraphy watch.

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There is the risk of a breach of your confidential information. For details about measures taken to reduce this risk, see section 9 below: Use of research results and confidentiality.

There is always a chance that any procedure can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect.

If you become pregnant during the course of the study, we will consider your wishes as to whether you would like to continue participating. The study PI will have a conversation with you about this decision. There is a small chancewe will not use some of your cortisol data if you become pregnant during the study procedures. In addition to the risks described above, your fetus may experience a previously unknown risk.

Risks of the usual care you receive are not risks of this study. Those risks are not included in this research consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

**WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?**

There are no direct/personal benefits to you from your taking part in this research study. However, the information we get from this study might help others with your condition(s).

**WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS STUDY?**

Other treatment to that described above may include different psychological treatments for PTSD, such as cognitive processing therapy, pharmacological treatments (medication), or both, and will be under the supervision of your doctor or caregiver.

**HOW WILL MY PRIVATE INFORMATION BE PROTECTED?**

Information collected for the purpose of this research study will be kept confidential as required by law. The results of this study may be published for scientific purposes, but your records or identity will not be revealed unless required by law.

**Information about you is protected in the following way:** Only the research team will have access to the information collected from you for this study. The paper data collected from this study will be kept in a locked cabinet in a locked office, while the electronic data will be coded

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and stored without personal identifiers on a secure drive that is only accessible to IRB-approved study staff. Any personally identifiable information will be kept on a separate drive of the computer with password protection or in a locked cabinet in a different locked office from the other information collected in this study.

Your physiological and sleep data labeled with only your subject code may be processed by study investigators at Massachusetts General Hospital (MGH)/ Harvard Medical School (HMS). Researchers at MGH/ HMS laboratories will not have access to your identity. We have established a data use agreement with MGH/HMS for their use of the data.

***Typical PE treatment involves listening between sessions to recordings of the imaginal exposure exercises. You will have the option of recording these exposure exercises on your own device such as a smart phone. If you decide to use your own device, we encourage you to use a password to protect that recording, if possible. Alternatively, if you prefer, we will lend you an encrypted audio recorder that will be password protected.***

***Please initial if you agree to record exposure exercises on your personal device.***

_____ ***I agree to recording exposure exercises on my personal device.***

Identifiers might be removed from the identifiable private information or identifiable biospecimens that are collected. After that removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

We will store your saliva samples until they are sent to a lab for processing. Saliva samples labeled with only your subject code will be stored in the freezers located within VA Boston. The saliva samples will then be sent for measurement of stress hormones to VA or non-VA laboratories. These samples will be labeled only with your research code. Researchers at these laboratories will not have access to your identity or any individual private, protected health information. Saliva samples, as well as general data from the study also may be sent to other, not yet selected, non-VA laboratories or researchers for analysis. Again, these samples and data will carry only your research code and will not carry any personally identifying information. Samples will be kept at these laboratories for up to 3 months, after which they will be destroyed.

While this study is being conducted, you will not have access to your research related health records. This will not affect your VA healthcare including your doctor's ability to see your records as part of your normal care.

Clinical interviews and PE sessions will be audiotaped or videotaped for training and reliability purposes, and to help clinicians make accurate psychiatric diagnoses and to ensure that

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treatment is being delivered correctly. Your voice and/or image will be identifiable in the recordings. These audio or video files will be saved on a limited access folder on a secure VA server with only your subject number as a label. Only members of the research team will have access to the audio or video recordings. Any personally identifiable information (e.g., this signed Informed Consent Form) will be kept in a locked cabinet in a different locked office from the other information collected in this study. Digital audio recordings will be deleted from the recording device.

*Your research records will be kept indefinitely or until the law allows their destruction per the VA Record Control Schedule.*

Your data collected as part of this study may be sent to a repository. A repository is a large database containing data from many studies. Your data will only be sent to a repository after being de-identified. This means that any information that could be used to identify you will be removed before any data are shared. In order to do this, you will be assigned a Global Unique Identifier (GUID). The GUID is a code consisting of letters and numbers created by software maintained by the National Institute of Mental Health. This GUID will be unique to you but will not contain any identifying information about you. The GUID will help make sure that your data are not repeated within a repository.

Your data will also be entered into a local data repository and may be used for future studies approved by an IRB. This data repository is called the Biological Predictors of PTSD and Treatment Data and Specimen Repository. Dr. Suzanne Pineles is the Principal Investigator of this repository, and it is located at VA Boston Healthcare System. Only authorized personnel on the Biological Predictors of PTSD and Treatment Data and Specimen Repository (R&D #1592602) will have access to the data in this data repository. Additional projects and analyses may be conducted with the data stored in the data repository; additional informed consent is not required for the use of your data in these studies and/ or analyses. All data shared for additional projects and analyses will be de-identified any data so participants cannot be identified.

To comply with state laws and regulations, we may need to share safety-related information such as that relating to child abuse or neglect; elder or disabled person abuse; specific reportable diseases; harm to self or others.

We have obtained a Certificate of Confidentiality from the Federal Government. This helps protect your privacy by allowing us to refuse to release your name or other information outside of the research study, even by a court order. The Certificate of Confidentiality will not be used to prevent disclosures to local authorities of child or elder abuse or neglect as defined by the Commonwealth of Massachusetts; or if you are deemed at immediate risk of suicide; or if you are deemed to be at risk of doing bodily harm to a specifically identifiable individual. The

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Certificate does not prevent you or a member of your family from releasing data about yourself or your involvement in this study.

We will include information about your study participation in your medical record. If you do not currently have a VA Boston medical record, one will be created for you.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

**WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?**

You will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

You will be compensated up to $310 for your time and effort taking part in this study if you complete all study visits. Based on where you live, you may be eligible for additional travel compensation or compensation for an additional assessment if there is a time delay between screening and starting the study assessments (detailed below).

You will be paid $60 for the screening evaluation visit.

For individuals who qualify and choose to participate in the remaining visits, you will receive $25 for the sleep monitoring period, $75 for the pre-treatment assessment, $75 for the mid-treatment assessment, and $75 for the post-treatment assessment. Because the PE sessions are primarily for the purpose of PTSD treatment, you will not be compensated for these visits. Thus, you will be compensated $310 if you attend all study assessment visits.
If your home address on file is a distance of 50 miles or greater (round trip) from VABHS, you are eligible to receive $5 for each 10 miles of travel above 50 miles, for a maximum of $50 (or 100 miles) per visit. If you choose to pay for a rideshare or taxi to attend in-person appointments, you are eligible to receive additional compensation; you would be compensated for the amount ride fare minus $10. For example, if the rideshare to the appointment was $15 (one way), you would be compensated an additional $20 – to offset the cost of the $30 roundtrip fare. If you choose to attend the consenting appointment in person, you will be paid $10 (or more depending on travel compensation rules listed above) to compensate for your travel.

If the time between your screening interview and your first in-person assessment session is more than 1 month apart, you will be asked to do some additional interviews and self-report measures about your symptoms. If this occurs, you will be compensated with an additional $20.

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If you are excluded from the study because you don't meet study inclusion criteria, if you withdraw from the study, or if we terminate your participation, you will be compensated only for the sessions you have participated in, but not for future sessions.

If payments are made by a VA-issued debit card, you consent to the release of personally identifying information about you including your name, address, and social security number to the VA so that we may provide compensation to you. You can expect to receive a debit card within 2-6 weeks.

If payments are made by direct deposit, you consent to the release of personally identifying information about you including your name, address, social security number and bank information (bank name, routing number, and account number) to the VA so that we may provide compensation to you. You will receive payment within 7 to 10 days.

If payment is made to you by the VA (whether by direct deposit or a VA issued debit card), an IRS Form 1099 will be generated regardless of the amount you are paid. The government may garnish the compensation against outstanding debts a veteran has to the federal government.

**WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?**

If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you unless the injury is due to non-compliance by a study participant with study procedures or if the research is conducted for VA under contract with an individual or non-VA institution.

If you should have a medical concern or get hurt or sick as a result of taking part in this study, call:

DURING THE DAY:

Dr. Suzanne Pineles at 617-435-8742, and

AFTER HOURS:

The Medical Center operator at 617-232-9500 and ask for the fellow on call for the Psychiatry Service.

**DO I HAVE TO TAKE PART IN THE STUDY?**

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Participation is voluntary. Refusal to take part in the study will involve no penalty or loss of benefits to which you are otherwise entitled. You are free to withdraw from this study at any time. If you are a VA employee or student, refusal to take part in the study will in no way influence your employment, ratings, subsequent recommendations, or academic progress as applicable. You may withdraw and still receive the same standard of care that you would have otherwise received.

Should you choose to withdraw from the study, the study investigators may continue to review the data already collected for the study and information from public records, such as survival data. Saliva samples collected up until the point you withdrew from the study cannot be withdrawn.

If you decide you would like to withdraw from the study, you may inform any member of the study staff of your decision.

If you wish to discontinue the therapy portion of the study, you will have the option to continue participating in study assessments.

**RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION**

We may end your participation in the study early if you are unable to respond to interview questions (for example, due to substantial cognitive or psychological impairment, extreme drowsiness, or due to the immediate effects of substance use) or display aggressive or inappropriate behavior towards study staff. We may also discontinue your participation in this study if you are at immediate risk of harming yourself or others. In that event, we will follow all applicable laws and assist you in obtaining appropriate clinical care.

If you miss over a certain amount of study PE sessions, are not willing to complete key components of the treatment (for example, if you are not willing to do any exposure exercises) or if you are unable to attend weekly sessions, the study investigator may ask you discontinue participation in the therapy component of the study. You may still be invited to participate in the study assessments if it is feasible for you to attend these visits within the required timeframe for these assessments.

**WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?**

I understand that if I have any medical questions about this research study, I can call **Dr. Suzanne Pineles** at ***617-435-8742*** during normal working hours.

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I understand that if I have any general questions about this research study, I can call **Dr. Suzanne Pineles** at ***617-435-8742*** or another study staff member at ***617-390-3397*** during normal working hours.

I understand that if I have any medical problems that might be related to this study that **during the day** I can call **Dr. Suzanne Pineles** at ***617-435-8742*** and **after hours** I can call ***the Medical Center operator*** at ***617-232-9500*** and ask for the fellow on call for Psychiatry service.

If you have questions about your rights as a study participant or any complaints, concerns or suggestions about this study, you may contact the Institutional Review Board at (617) 637-3794. The Institutional Review Board is responsible for overseeing the safety of human participants in this study.

**WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?**

You will be told of any significant new findings that come to light during the course of this study and that may relate to your wanting to stay in the study.

**WHO COULD PROFIT FROM THE STUDY RESULTS?**

The samples collected in this study may not be used for commercial profit. If any commercial product is developed related to the findings from this study, participants will not share in the profit.

**FUTURE USE OF DATA AND RE-CONTACT**

As mentioned above, your data will be entered into the Biological Predictors of PTSD and Treatment Data and Specimen Repository and may be used for future studies approved by an IRB. Data that is stored in the repository will include your birthday and the last 4 digits of your social security number. In addition, data from this study, including the scored physiological and sleep data and scored results of interviews and questionnaires will also be included in the data repository. Dr. Suzanne Pineles is the Principal Investigator of this repository and it is located at VA Boston Healthcare System. Only authorized personnel on the Biological Predictors of PTSD and Treatment Data and Specimen Repository (R&D #1592602) will have access to the data in this data repository. Additional projects and analyses may be conducted with the data stored in the data repository; additional informed consent is not required for the use of your data in these studies and/ or analyses. The data in the data repository will be both identified and de-identified. All data shared for additional projects and analyses will be de-identified any data so participants cannot be identified.

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Similarly, your data will be entered in the NIMH Data Archive and may be used for future studies. Data that is stored will not include personal identifiable information beyond the unique subject number assigned to you. Additional projects and analyses may be conducted with the data stored in the data repository; additional informed consent is not required for the use of your data in these studies and/ or analyses. All data shared for additional projects and analyses will be de-identified any data so participants cannot be identified.

**AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY**

An appropriately trained study staff member has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study and authorize the use and disclosure of your health information to this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it.

| **I agree to participate in this research study as has been explained in this form.** | | |
|---|---|---|
| _____ Participant's Name | _____ Participant's Signature | _____ Date |

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