Human Protocol (Version 1.44)

General Information

***Please enter the full title of your study::**

Cannabidiol as an Adjunctive to Prolonged Exposure for the Treatment of PTSD

***Please enter the Study Number you would like to use to reference the study:**

CBD-PE
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

Add departments

and Specify Research Location:

Is Primary?	Department Name
◉	**VASDHS** - VASDHS

Assign key study personnel(KSP) access to the study

***Please add a Principal Investigator for the study:**

Ayers, Catherine R., PhD

3.1 If applicable, please select the Research Staff personnel

A) Additional Investigators

Angkaw, Abigail Candare, PhD
Co-Investigator
Davis, Brittany C
Co-Investigator
Martis, Brian, MD
Co-Investigator
Matthews, Scott Christian, MD
Co-Investigator
Mayes, Tina Louise, PhD
Co-Investigator
Norman, Sonya B., PhD
Co-Investigator
Stein, Murray B., MD
Co-Investigator

B) Research Support Staff

Abirgas, Kira Renee
Research Associate
Blanco, Brian H., MSW
Clinical Research Associate
Brody, Arthur L., MD
Participating Clinician
Carty-Campbell, Alexis
Research Associate
Gonzalez, Alan R
Clinical Research Associate
Holcomb, Julie M.
Study Coordinator
Huege, Steven F., MD
Participating Clinician
Park, Jae Eun
Clinical Research Associate
Pittman, James O. E., PhD
Clinical Research Associate
Vacco, Chad
Clinical Research Associate
Wilhite, Emily R., PhD
Participating Clinician

***Please add a Study Contact**

Ayers, Catherine R., PhD
Holcomb, Julie M.

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

VASDHS IRB
Human Subjects Protocol
v20190121

Section 1 - Preliminaries

Principal Investigator:

Catherine R. Ayers, PhD

Protocol Title:

Cannabidiol as an Adjunctive to Prolonged Exposure for the Treatment of PTSD

IRB Protocol Number:

H180062

Protocol Nickname:

CBD-PE

Form Template Version:

v20150115

Date Prepared:

11/06/2023

Please be advised that this protocol application form has changed as a result of the 2018 Common Rule. There are new questions and sections, and you may be required to provide additional information to previous sections.

1a) Is this study considered human research?

- (●) Yes
- ( ) No
- ( ) I don't know

1b) Please select:

- ( ) This is an application for a NEW human subject research protocol
- (●) This is a revision of an existing protocol

Was this study initially approved prior to January 21, 2019?

(●) Yes ( ) No

Were you instructed to convert to the 2018 Common Rule Requirements?

(●) Yes ( ) No

Section 2 - Research Subjects

2a) What is the total planned number of VA-consented subjects?

Include the total number of subjects who will prospectively agree to participate in the study (e.g., documented consent, oral consent, or other).

300

2b) What is the total number of VA subjects who WILL NOT be consented?

Include the total number of subjects that will be included without consent (e.g., chart review). *Note: Data about people are still considered "human subjects" by the IRB, so even if you do not intend to contact the patients whose charts you will review, you still should enter the number of charts as your "planned subjects."*

0

Section 2.1 Consented Subject Groups

2.1) For each of the subject categories listed below, indicate whether or not these subject groups will participate in the study:

2.1a) Children under the age of 18
Note: If neonates or children will be involved in this study, certification by the Medical Center Director will be required. Only minimal risk research may be performed with children. Only non-invasive monitoring and/or prospective observational and retrospective record review studies that are minimal risk can be conducted in VA involving neonates.

( ) Yes (●) No

2.1b) Pregnant women

( ) Yes (●) No

2.1c) Individuals with cognitive/decisional impairment

( ) Yes (●) No

2.1d) Non-English-speaking individuals

○ Yes ◉ No

2.1e) Prisoners of War (explicitly targeting this group)

○ Yes ◉ No

2.1f) Non-Veterans (Note: Justification for inclusion of non-Veterans will be required)

○ Yes ◉ No

2.1g) Incarcerated individuals (Note: VA CRADO approval will be required)

○ Yes ◉ No

2.1h) VA employees - including VA paid, IPA, or WOC (Note: Union review and authorization may be required)

○ Yes ◉ No

2.1i) Students of the institution (e.g., resident trainees) or of the investigator

○ Yes ◉ No

2.1j) Patients with cancer (or high cancer risk) [explicitly targeting this group]

○ Yes ◉ No

Section 3 - Study Features (these items default to "No" for convenience)

3) This section consists of several Yes/No questions addressing protocol characteristics. Click on *Save and Continue*.

Section 3.1 Protocol Basics

Select all that apply

3.1a) The research **intends to change** the participant.

◉ Yes ○ No

3.1b) **Interactions** with living participants to collect data or specimens with no intent to change them.

○ Yes ◉ No

3.1c) This is a study that **never** has any **subject contact and does not collect subject identifiers**

○ Yes ◉ No

3.1d) This is a **chart review** study involving retrospective or prospective medical records.

○ Yes ◉ No

3.1e) This is a **multi-site** study occurring in-part or in-full at other locations.

○ Yes ◉ No

3.1f) There is an **international** component to this research. *International research includes sending or receiving human derived data or specimens (identifiable, limited data set, coded, or deidentified) to or from an international source. International research does not include studies in which VA is only one of multiple participating sites where the overall study-wide PI is not a VA investigator.*

○ Yes ◉ No

3.1g) This study includes **off-station activity** (not including VA-leased space or CBOC clinics) conducted under VASDHS IRB approval. *Note: this does not include research conducted by a collaborator at their home institution under their institutional approval.*

(•) Yes ( ) No

3.1h) VA subjects will **participate** in part or in full **at other locations** (not including VA-leased space or clinics) under VASDHS IRB approval. *Note: if this study involves remote participation of subjects, please indicate "no" and describe their remote participation in section 9 of the application. This question is intended to understand whether participants must physically go to a non-VA location to participate in this VA research study.*

( ) Yes (•) No

Section 3.2 Specimen Use and Data Repository

Indicate whether or not each of the following applies to this protocol

3.2a) Involves specimens that are left over from pathological or diagnostic testing (**non-research specimens**)

( ) Yes (•) No

3.2b) Involves **specimens collected for research** purposes **only**

(•) Yes ( ) No

3.2c) This study includes **specimen banking** (specimens are retained for use outside of the purposes of this protocol)

( ) Yes (•) No

3.2d) The study involves **DNA** genotyping or other **genetic analysis**

( ) Yes (•) No

3.2e) Biological **specimens/material** will be sent outside of the VA.

( ) Yes (•) No

3.2f) A **data repository** is maintained (data are retained after completion of the protocol for other uses, IMPORTANT: see **?** before checking "yes")

( ) Yes (•) No

3.2g) **Data will be shared outside** of the VA (identifiable, coded, limited data set, or deidentified)

( ) Yes (•) No

Section 3.3 Treatment and Clinical Trials

Indicate whether or not each of the following applies to this protocol

3.3a) Includes a **treatment** component (a research treatment)

(•) Yes ( ) No

3.3b) Study is a **clinical trial.** *Note: A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.*

(•) Yes ( ) No

3.3c) Has a data safety monitoring board (**DSMB)** or data safety monitoring committee.

( ) Yes (•) No

3.3d) Has a **data safety monitoring plan** (but not a DSMB) (this is not the data security plan, it is a safety plan).

(•) Yes ( ) No

Section 3.4 Drugs and Devices

Indicate whether or not each of the following applies to this protocol

3.4a) **Drugs** that require **FDA** action such as an Investigational New Drug (IND) approval or exemption or 510 (k) approval.

(•) Yes ( ) No

3.4b) Other drugs, supplement, etc. that **do not require FDA** action for inclusion in the study.

( ) Yes (•) No

3.4c) Medical **devices requiring FDA** IDE approval or waiver

( ) Yes (•) No

3.4d) **Other** medical **devices**

( ) Yes (•) No

Section 3.5 Risk and Hazards

Indicate whether or not each of the following applies to this protocol

3.5a) Study places subjects at **greater than minimal risk** (do not include risks that are due to standard care)

(•) Yes ( ) No

3.5b) Human subjects are exposed to **radioisotopes** (do not include standard care).

( ) Yes (•) No

3.5c) Subjects have other **radiation exposure** (e.g., x-rays) (do not include standard clinical use).

( ) Yes (•) No

3.5d) Target population has psychiatric diagnosis, behavioral complaint, or chronic pain.

(•) Yes ( ) No

Section 3.6 Clinical Facilities and Standard Care

Indicate whether or not each of the following applies to this protocol

3.6a) Study **uses VA clinical services** (e.g., adds required tests run in the VA lab for study purposes; research procedures concurrent with clinical care)

(•) Yes ( ) No

3.6b) Includes procedures or drugs that will be considered **part of standard care.**

(•) Yes ( ) No

3.6c) Involves **lab tests done for research** purposes.

( ) Yes (•) No

Section 3.7 Subject Expenses and Compensation

Indicate whether or not each of the following applies to this protocol

3.7a) There may be expense or added **costs to the subject** or the subject's insurance.

○ Yes ◉ No

3.7b) This is a **qualifying cancer treatment trial** and subjects may be billed for study drugs or procedures.

○ Yes ◉ No

3.7c) This is a cancer treatment trial but **subjects will not be billed** for study drugs or procedures.

○ Yes ◉ No

3.7d) Subjects will be **compensated** (either in cash or other means such as a gift certificate).

◉ Yes ○ No

Section 3.8 Subject Activities

Indicate whether or not each of the following applies to this protocol

3.8a) Involves **surveys or questionnaires** completed by subjects

◉ Yes ○ No

3.8b) Includes the use of **recruitment materials** such as flyers, advertisements, or letters

◉ Yes ○ No

3.8c) Involves facial **photographs** or audio or video **recordings** of **patients**

◉ Yes ○ No

Section 3.9 Sponsors and Collaboration

Indicate whether or not each of the following applies to this protocol

3.9a) This research is a funded research project **(commercial (industry) sponsor, NIH, VA, other).**

○ Yes ◉ No

3.9b) Other **commercial (industry) non-financial support** is provided (e.g., drugs or supplies).

○ Yes ◉ No

3.9d) The protocol has **Department of Defense** involvement (e.g., subjects or funding).

○ Yes ◉ No

3.9c) The PI or other study staff member has a financial interest or other **real or potential conflict** related to this study.

○ Yes ◉ No

3.9e) This study involves **collaborative** research activities (research conducted at other institutions under the authorities or approvals of the other institution/s). *Note: this may include other VA and/or non-VA institutions, but does not include off-site VA research.*

◉ Yes ○ No

Section 4 - Estimated Duration

4) What is the estimated duration of the entire study? (From IRB approval to IRB closure)

5 years

Section 5 - Lay Language Summary

5) Provide a summary or synopsis of the proposed study using non-technical language (not more than 1 paragraph)

The study will include a randomized control trial to evaluate the efficacy of using Cannabidiol (CBD), a non-intoxicating phytocannabinoid, as an adjunctive to prolonged exposure therapy (PE). The trial will compare PE + CBD to PE + placebo (cellulose pill) in a sample of Veterans with PTSD at the VASDHS.

Section 6 - Specific Aims

6) Provide a statement of specific aims and hypotheses that serve as the basis for this protocol. Emphasize those aspects that justify the use of human subjects.

Prolonged exposure therapy (PE) is among the most efficacious treatments for PTSD (Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010) and is designated as a VA/DoD frontline treatment (Management of Post-Traumatic Stress Working Group, 2017). However, PE does not always lead to clinically meaningful symptom reductions in Veterans with PTSD (Steenkamp, Litz, Hoge, & Marmar, 2015). Successful PE treatment relies on extinction learning (VanElzakker, Kathryn Dahlgren, Caroline Davis, Dubois, & Shin, 2014), which is often impaired in patients with PTSD (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007). Cannabidiol (CBD) is a non-intoxicating phytocannabinoid. Administration of phytocannabinoids, like CBD, increase extinction learning in patients with PTSD (Rabinak, Peters, Elrahal, Milad, Rauch, Phan, & Greenwald), and could increase the speed and effectiveness of PE therapy (Loflin, Babson, & Bonn-Miller, 2017). FAAH inhibitors, such as CBD, are also non-traditional anxiolytics, which may directly improve hyperarousal/insomnia symptoms, and improve engagement and retention in treatment (Roitman, Mechoulam, Cooper-Kazaz, & Shalev, 2014). Given these findings, adjunctive administration of CBD+PE could improve response rates to PE and reduce the number of sessions of PE needed to reach clinically meaningful change.

The proposed study is designed to test the efficacy of using CBD in conjunction with PE for the treatment of PTSD in US Military Veterans. A randomized, controlled, double-blind study will compare Veterans who receive PE+CBD to PE+placebo. Participants will include 136 male and female Veterans from all service eras with PTSD. The primary hypothesis is that PE+CBD will reduce PTSD symptoms to a greater degree than PE+placebo. There are three primary aims with four hypotheses:

Aim 1 (Primary Treatment Outcome): Examine the relative efficacy of PE+CBD compared to PE+placebo in reducing symptoms of PTSD at post-treatment and 1- and 3- month follow-up. Hypothesis 1: Participants receiving PE+CBD will show a greater reduction in number of PTSD symptoms at end of standard 12-session treatment and 1- and 3-month follow-up compared to participants receiving PE+placebo.

Aim 2 (Secondary Treatment Outcome): Examine whether CBD increases the rate of clinical response to PE therapy. Hypothesis 2: Participants receiving PE+CBD will show a faster clinically significant response to treatment compared to participants receiving PE+placebo.

Aim 3 (Mediation): Investigate whether extinction mediates the effect of treatment group on PTSD symptoms and rate of clinical response. Hypotheses 3 & 4: Patients receiving PE+CBD will show a greater reduction in exposure distress from the first to last exposure session compared to participants receiving PE+placebo, which will partially account for a greater reduction in PTSD symptoms at end of treatment (hypothesis 3), and a faster clinical response to treatment (hypothesis 4).

Exploratory Aims: Examine whether participants receiving PE+CBD will show: 1) lower drop-out rates, 2) greater improvements in sleep quality, 3) a greater reduction in trauma-related cognitions, 4) improved mood (anxiety, depression), and/or 5) greater improvements in

psychosocial functioning compared to those receiving PE+placebo.

The proposed study is well aligned with the goals of CSR&D and VA stakeholders. The trial will test a novel and innovative combination of medication and psychotherapy with the goal of improving the care of Veterans with PTSD. Evidence from multiple studies indicates that combining CBD with PE could increase the efficacy of PE in Veterans with PTSD, resulting in greater treatment gains in fewer sessions. The fundamental rationale for this study is to improve treatment for PTSD within VA.

Section 7 - Background and Significance

7) Provide a succinct discussion of relevant background information to justify performing the proposed study.

Post-traumatic stress disorder (PTSD) is a debilitating mental health condition that disproportionately affects US veterans (Atwoli, Stein, Koenen, & McLaughlin, 2015). One in ten VA healthcare patients and one in four treatment-seeking veterans from the most recent conflicts (OEF, OIF, OND) have been diagnosed with PTSD (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). When untreated, the condition carries enormous financial and social costs to veterans and their families, and increased health care costs to the public (Fang et al., 2015; Goldberg et al., 2013; Marmar et al., 2015; Nock et al., 2014; Schnurr, Lunney, Bovin, & Marx, 2009; Walker et al., 2003). For example, above and beyond the direct effects of the disorder, carrying a diagnosis of PTSD increases a veteran's risk for substance abuse, development of psychiatric comorbidities, hospitalizations, and suicide attempts(Schnurr & Spiro, 1999). PTSD also increases a veteran's risk for developing physical chronic health conditions, which further increases healthcare utilization and costs (Schnurr, & Jankowski, 1999; Schnurr, Friedman, Sengupta, Jankowski, & Holmes, 2000). Overall, veterans with PTSD report worse physical functioning compared to their veteran peers without PTSD, even when controlling for associated risk factors, such as alcohol and tobacco use (Walker et al., 2003). Given the severity of the condition and continued high rates of untreated PTSD in US Veterans, the DoD and VA have recently emphasized a need for development of novel psychopharmacological treatments for PTSD (Krystal et al., 2017)

The most well-validated treatment for PTSD is Prolonged Exposure (PE; Powers et al., 2010), which has been identified as a frontline treatment within the VA/DoD Clinical Practice Guidelines for the treatment of PTSD (Management of Post-Traumatic Stress Working Group, 2017). A significant number of patients who complete PE achieve full remission of the disorder, where they no longer meet criteria for PTSD at treatment completion and 12-month follow-up (Foa et al., 2005). Despite PE's strong empirical record, over 30% of military veterans who complete the therapy do not achieve clinically meaningful symptom reductions by the end of the standard 12 session protocol, and up to 60-70% retain their PTSD diagnosis (Steenkamp, Litz, Hoge, Marmar, et al., 2015). Moreover, dropout rates for all trauma-focused treatment, including PE, remain high (Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008). This low rate of response may be due to a mismatch between the pathology of PTSD and PE's theory and mechanisms.

The theory behind PE is consistent with the generally accepted model for PTSD etiology (VanElzakker et al., 2014). In this model, PTSD develops largely through a process of classical conditioning; where environmental cues present during trauma become associated with the traumatic event and when re-encountered provoke a conditioned fear response (VanElzakker et al., 2014). As the disorder develops, conditioned stimuli generalize (Kaczkurkin et al., 2017), producing strong fear reactions that trigger avoidance. Avoiding trauma reminders prevents the individual from encountering the conditioned fear cues in neutral and safe contexts that would normally facilitate safety learning and eventual extinction (Rothbaum & Davis, 2003). Exposure-based therapies, like Prolonged Exposure (PE), attempt to capitalize on this natural recovery process using similar behavioral principles (Foa & Kozak, 1986; Rothbaum & Davis, 2003). Within PE, patients are asked to repeatedly retell the traumatic memory within a safe environment and engage with, rather than avoid, objectively safe reminders of the trauma (Foa, Rothbaum, Riggs, & Murdock, 1991). Two primary mechanisms of action for PE's efficacy are habituation to the learned emotional response of remembering the event and extinction of over-generalized feared stimuli (Foa & Kozak, 1986; Hofmann, 2008).

Despite PE's theoretical consistency, a large number of patients do not fully extinguish fear cues or completely habituate to their trauma memory by the end of standard treatment (Bluett, Zoellner, & Feeny, 2014), which may account for poor response to treatment. This effect may be attributable to known neurological effects of the disorder that interfere in extinction learning (Lissek & van Meurs, 2015). Encoding and recall of extinction learning is dependent on activation of the hippocampus (HPC) and ventromedial prefrontal cortex (vmPFC; Quirk, Garcia, & González-Lima, 2006), regions that fMRI research suggest are less active in patients with PTSD (Acheson,

Gresack, & Risbrough, 2012; Dejean et al., 2015; Milad et al., 2009; C. Rabinak & Phan, 2014). Indeed, individuals with PTSD show severe deficits in extinction recall following classical Pavlovian fear conditioning (Blechert et al., 2007; Milad et al., 2008, 2009). Deficient activation of neural networks that facilitate extinction learning in individuals with PTSD may explain why many individuals with PTSD remain symptomatic following completion of PE. These findings also suggest a possible target for pharmacological augmentation.

A growing body of research suggests that adjunctive administration of Cannabidiol (CBD) could improve the effectiveness of PE in patients with PTSD by potentiating extinction learning and recall (Loflin, Babson, & Bonn-Miller, 2017; Rabinak & Phan, 2014; Steenkamp, Blessing, Galatzer-Levy, Hollahan, & Anderson, 2017). Neurobiological evidence highlights the critical role that the endocannabinoid system plays in learning and maintaining extinction to fear cues (Hill, Campolongo, Yehuda, & Patel, 2017; Lafenêtre, Chaouloff, & Marsicano, 2007). For example, antagonism of CB1 cannabinoid receptors within the vmPFC blocks consolidation of extinguished fear and profoundly impairs extinction memory recall (De Oliveira Alvares, Genro, Diehl, & Quillfeldt, 2008; Lin, Mao, Su, & Gean, 2009). Likewise, agonism of CB1 receptors, which increase anandamide signaling in the vmPFC, facilitates extinction learning and improves extinction recall (Chhatwal, Davis, Maguschak, & Ressler, 2008; De Oliveira Alvares et al., 2008; Lin et al., 2009). This work suggests that selective agonism of CB1 could be a target for pharmacological augmentation. CB1 agonists, however, carry extensive side effects (Pertwee, 2006). CBD, an exogenous cannabinoid found in the cannabis plant, is a selective allosteric modulator that indirectly acts on CB1 through possible inhibition of FAAH (an inhibitor of anandamide) (Laprairie, Bagher, Kelly, & Denovan-Wright, 2015; Stern et al., 2017; Vemuri & Makriyannis, 2015). CBD facilitates extinction learning through CB1 (Do Monte, Souza, Bitencourt, Kroon, & Takahashi, 2013), but carries a low side effect profile (Mateus Machado Bergamaschi, Queiroz, Crippa, & Zuardi, 2011).

Pre-clinical trials provide evidence that administering CBD before extinction learning reduces cue-elicited fear (Gomes et al., 2010; Lemos, Resstel, & Guimarães, 2010), blocks reconsolidation of fear memory (Stern et al., 2015; Stern, Gazarini, Takahashi, Guimarães, & Bertoglio, 2012), and facilitates faster extinction of fear memory in animal models of PTSD (Bitencourt, Pamplona, & Takahashi, 2008; Do Monte et al., 2013). Specifically, fear-conditioned rats administered CBD prior to extinction learning sessions showed less freezing (conditioned fear response) when re-exposed to the conditioned stimulus 24 hours after the extinction trials ended compared to rats administered placebo (Bitencourt et al., 2008). Notably, the effect of cannabinoid administration on reduced fear last well beyond any residual effects of the drug or its metabolites. For example, fear-conditioned rats that were administered CBD or Delta^{9}-Tetrahydrocannabidiol (THC; another prominent phytocannabinoid that acts on CB1) before re-exposure showed less freezing in response to conditioned fear cues than those receiving placebo even after the acute effects of both cannabinoids were no longer present (22 days post-administration) (Lemos et al., 2010; Stern et al., 2015).

CBD's ability to augment extinction learning has been replicated with human subjects, and specifically in participants with PTSD. Three human trials using previously fear-conditioned healthy controls found that administration of phytocannabinoinds (CBD and/or THC) before or during extinction learning decreased fear responding at later re-exposure at a greater rate than those administered placebo (Das et al., 2013; Rabinak et al., 2013, 2014). fMRI conducted during these trials found that administration of phytocannabinoids during re-exposure modulated the limbic-frontal brain networks (HPC and vmPFC), the underlying neural circuits involved in fear extinction in humans(Rabinak et al., 2014). These results indicate that administration of phytocannabinoids (CBD, THC) activate the same neural circuits that are under-active in patients with PTSD; regions that would normally inhibit those with PTSD from effectively learning extinction during exposure. Indeed, results from the first phase of an ongoing randomized, double-blind, between-subjects study of trauma-exposed patients (with and without PTSD) and healthy controls found that cannabinoid administration given prior to extinction trials in a Pavlovian fear conditioning paradigm facilitated significantly greater extinction learning and greater HPC activation compared to placebo among those with PTSD, and that cannabinoid augmentation was greater in participants with PTSD compared to those without PTSD and healthy controls (Rabinak, Peters, Elrahal, Milad, Rauch, Phan, & Greenwald, 2017). Taken together, the above work suggests that administering CBD during exposure may facilitate faster and greater extinction learning in patients with PTSD.

CBD could directly improve some clusters of PTSD symptoms through its role as a 5-HT$_{1A}$ modulator (Viveros, Marco, & File, 2005). Preclinical data suggest that CBD produces antidepressant-like effects on anhedonia (Linge et al., 2016; Sartim, Guimarães, & Joca, 2016; Zanelati, Biojone, Moreira, Guimarães, & Joca, 2009) (a clinical symptom of PTSD). In addition, phase I results suggest phytocannabinoinds, like CBD, could reduce hyperarousal and general anxiety symptoms (Bergamaschi et al., 2011; Fusar-Poli et al., 2009; Zuardi, Shirakawa, Finkelfarb, & Karniol, 1982). For example, a 2014 open-label study for patients with chronic,

unresponsive PTSD found that twice-daily administration of dronabinol (a synthetic analogue of THC) was associated with significant reductions in hyperarousal symptoms throughout the course of treatment and reduced nightmares (Roitman et al., 2014). A randomized control trial of CBD for Social Anxiety Disorder (SAD) also found that administration of 600mg of CBD significantly reduced social anxiety in patients diagnosed with SAD during stimulated public speaking compared to placebo, with large effects (d = 1.28; Bergamaschi et al., 2011). Perhaps the most interesting result of this study was the finding that patients with SAD who were administered CBD reported reductions in negative cognitive self-appraisals (a cognitive component of anxiety) to levels comparable to healthy controls. Taken together, this literature suggests that phytocannabinoids like CBD could improve hyperarousal, mood, and cognitive clusters of PTSD symptoms.

CBD's acute effects on anxiety and hyperarousal suggest that CBD could ultimately improve PE tolerability. Core PTSD symptoms of avoidance and hyperarousal can interfere with the ability to engage in or benefit from treatment. CBD could reduce these PTSD symptoms and may off-set PE-related PTSD symptom exacerbation that might otherwise lead to treatment dropout. Traditional anxiolytic medications (e.g., benzodiazepines) are not typically recommended for treatment of PTSD (Management of Post-Traumatic Stress Working Group, 2017) due to their potential to disrupt extinction learning(Rothbaum et al., 2014). Unlike traditional anxiolytics, however, CBD does not appear to blunt extinction learning (as discussed above), and instead may promote it (Bitencourt et al., 2008). Therefore, combining CBD with PE may facilitate faster and greater extinction effects in patients with PTSD, while reducing symptoms that may cause dropout or poor engagement early in treatment.

The proposed study will be the first phase II clinical trial to test a combined CBD+PE therapy. Phase II trials of CBD are already underway for several mental health conditions that rely on similar mechanisms reviewed above (facilitates extinction, anxiolytic), including Generalized Anxiety Disorder (NLM: NCT02548559), Substance Use Disorder (NLMs: NCT02559167; NCT02952196; NCT02083874; NCT01311778), Social Anxiety Disorder (Bergamaschi et al., 2011), and PTSD as a stand-alone treatment (NLMs: NCT02759185; NCT02517424). A recent phase II trial has also been approved testing administration of THC as an adjunctive to exposure therapy (NIH: 1R61MH111935-01). However, no trials have tested CBD (which does not carry the same risks of intoxication and abuse as THC (Babalonis et al., 2017) as an adjunctive treatment for PTSD.

There are several potential impacts of this line of research. First, despite being one of the most efficacious treatments for PTSD, PE does not always lead to clinically meaningful reductions in symptoms (Powers et al., 2010). By potentiating the effect of exposure with CBD, practitioners could increase the clinical response rate of patients receiving PE. Second, CBD augmentation could also increase how quickly patients respond to exposure while in therapy, thereby reducing the number of sessions needed to reach clinically meaningful change. Third, by reducing hyperarousal symptoms throughout treatment (without negatively impacting extinction), CBD could improve patient engagement and treatment completion rates.

Section 9 - Design and Methods

9) Describe the research design and the procedures to be used to accomplish the specific aims of the project. Provide a precise description of the planned data collection (include what systems or databases will be used/accessed to gather data), analysis and interpretation. For chart review studies, include the timeframe of collection. Address sample size, inclusion of women and minorities. Define in clear terms exactly what will be done to the human subjects.

Design. The study will involve a phase II double blind RCT to evaluate the efficacy of CBD compared to placebo as an adjunctive to PE for the treatment of Veterans with PTSD. Two hundred male and female Veterans will be consented through the PTSD and primary mental health treatment programs at the VASDHS. Based on investigors' experiences and estimates from the literature, approximately 300 Veterans will likely need to be screened to obtain 200 Veterans who meet criteria for inclusion. Approximately 200 patients will be consented and brought to baseline assessment in order to ensure that 136 patients are randomized, assuming an initial failure rate of ≤ 32%. Patients who prematurely discontinue after beginning treatment will not be replaced, consistent with an ITT approach. Women comprise up to 60% (PTSD clinics) of the Veterans seen in the clinics from which we will be recruiting. Approximately 24% of Veterans in the program are minorities.

All participants will receive 16 weeks of either CBD or placebo and 12 sessions of individual PE therapy. The adjunctive medication (CBD or placebo) will be administered sublingually starting one week before initiation of active PE therapy, which will allow for 3 weeks of drug

administration (to reach steady-state) before the first in-vivo exposure session of PE. Study drug will be administered for the entire duration of psychotherapy (12 weeks) plus four additional weeks to allow for flexibility in anticipated patient cancellations.

Prolonged Exposure (PE) is an evidence-based exposure therapy for the treatment of PTSD (Powers et al., 2010). PE therapy is delivered in 12 weekly, 90-minute sessions (Foa, Hembree, & Rothbaum, 2007). The therapy includes: breathing retraining, psychoeducation, prolonged and repeated exposure to trauma memories (imaginal exposure), repeated real life exposure to feared situations and objects (in-vivo exposure), and processing of trauma-related themes that emerge during in-vivo and imaginal exposures (Foa et al., 2007) . While in treatment, patients are asked to create recordings of their imaginal exposures and listen to those recordings at home. Patients are also asked to practice in-vivo exposures that were identified with the therapist between sessions. The safety and tolerability of PE is well documented for patients with PTSD (Cahill, Foa, Hembree, Marshall, & Nacash, 2006). The standard PE manual will be modified to include psychoeducation on cannabinoids and PTSD. Specifically, information will be added to clarify to the participant that CBD is not THC. Given that the participants are located in a state with access to medicinal and recreational cannabis, this psychoeducation will help to limit the likelihood that participants will initiate cannabis use upon termination from the study.

Treatment Setting
All assessment and intervention sessions will occur via telehealth and/or phone with providers from the the VASDHS.

Financial Incentives: Participants will be compensated up to $75 for their time and effort in completing assessments after treatment has concluded. Veterans will receive $25 for completion of the termination assessment, $25 for completion of the 1-month follow-up assessment, and $25 for completion of the 3- month follow-up assessment.

Data Collection. Assessments will occur by phone screening, during baseline telehealth sessions, weekly throughout active drug and psychotherapy sessions (telehealth), termination (telehealth), and during two follow-up assessments (telehealth). The research assessor will administer the baseline, termination, and two follow-up assessments. Baseline questionnaires will be exchanged between study staff and participant via VA-approved encrypted email (Azure RMS) following a successful virtual baseline assessment. The study nurse/physician will collect other health information during the baseline exam. The participant's therapist will collect all outcome measures during active psychotherapy and assess for changes in functioning, including suicidal ideation and clinically significant worsening of symptoms. A study nurse /physician will administer/collect assessments for changes in concomitant medication use and possible adverse events during the medication check-ins. Participants will be given the option of receiving their medication check-in through phone or VA Video Connect if preferred. Pre-visit questionnaires used to document medication adherence, non-study medication changes, and a standard battery of common side effects will be exchanged between study staff and participant via VA-approved encrypted email (Azure RMS). Any exacerbation of symptoms will be reported and discussed with the PI so that appropriate action can be taken if necessary. The research assessor will be trained prior to Veteran assessment through a minimum of two assessments for each measure and then be observed for a minimum of two assessments. Additionally, the research assessor will be tested for reliability (once every six months), and participate in weekly staff meeting to address questions or concerns. Training will also be provided on common issues associated with self-report measures.

Screening (30 minutes): Following oral consent, potential participants will undergo a telephone screening to determine possible qualification for inclusion. If the participant meets all basic eligibility criteria, the research coordinator will schedule a medical and psychological telehealth assessment visit. The screening is intended to detect clinically significant PTSD symptoms and determine whether participants likely meet inclusion/exclusion criteria.

Consenting Protocol: Post-screening, all eligible participants will be offered participation in an IRB approved research protocol for the treatment of PTSD. The voluntary nature of the study will be emphasized. If participants choose not to participate in the study, they will still receive treatment as usual from the referring clinic.

Baseline Assessment and Exam (2-3 hours): After consenting, participants will undergo telehealth-based screening to confirm eligibility and complete baseline measures. The condition-blinded research assessor will administer all quantitative assessments. Baseline assessment will include administration of screening items, including the clinician administered PTSD scale, and all self-report questionnaires selected to evaluate PTSD symptoms, mood, sleep, trauma-related cognitions, and psychosocial functioning. At this or a separate appointment, the participant will also meet via telehealth with a study physician to ensure they are healthy enough to participate. All concomitant medications (prescription and over-the-counter (OTC)) will be

recorded including dose and reason for use. If the participant has not completed recent labs, they will be asked to complete a blood draw at the San Diego VA, as part of routine care, to assess liver functioning. Patients' urine will also be collected for testing of illicit substance use (i.e., drug screening), and for urine pregnancy testing in female participants of childbearing potential.

Prior to randomization on the project, we will be adding a motivational interviewing session to the protocol. The assigned therapist will meet with the Veteran for one hour to review the Veteran's personal pros and cons of participation. During this meeting any barriers to participation will also be discussed. The Veteran will also be given the opportunity to discuss questions or concerns they may have about participating in the project.

Randomization and Dosing Session: Following baseline assessment, eligible participants will be randomized in a 1:1 ratio to PE + placebo or PE + CBD. Participants will be provided instructions on sublingual administration of the medication and the participant will be instructed to administer the first dose of study drug following the first medication phone/telehealth visit.

Weekly Assessments (approximate time = 10 minutes): The participant will complete brief self-report assessments prior to the start of each PE therapy session (12 weeks). These assessments will track PTSD symptoms, mood, sleep, psychosocial functioning, and any medication side effects. Therapists will also record subjective distress during exposures.

Termination Assessment (approximate time = 2 hours): One week after completion of the final treatment session of PE, the participant will complete via telehealth the same battery of clinical assessments given during the baseline evaluation.

1-Month Follow-up Assessment (approximate time = 2 hours): One month after completion of the final treatment session of PE, the participant will complete via telehealth the same battery of clinical assessments given during the baseline evaluation.

3-Month Follow-up Assessment (approximate time = 2 hours): Three months after completion of the final treatment session of PE, the participant will complete via telehealth the same battery of clinical assessments given during the baseline evaluation. After this assessment, the participant will have completed the study. Veterans who remain symptomatic and express interest will be given a referral for additional treatment.

Additional labs (5-30 mins each): Participants will only be asked to recomplete additional blood or urine labs if clinically indicated.

Analytic Plan.
Missing Data: All laboratory-based measures will be reviewed for completeness immediately following collection and while the participant is present. Even with the steps outlined in the protocol to increase participant completion, a conservative 25% attrition rate is anticipated based on a meta-analysis of PTSD treatment (Schottenbauer et al., 2008). Therefore, the primary outcome will be analyzed using an intent-to-treat (ITT) framework. Missing-at-random (MAR) analysis (Laird & Ware, 1982) will be computed to test whether missingness is dependent on observed covariates, outcome variables, or group assignment. Pattern-mixture modeling will be conducted as a check on the sensitivity of the assumption that the missing data are MAR. In these models, participants will be categorized into groups based on patterns of missing data over time. Missing data pattern groups will then be entered as covariates in the primary statistical models, so that the effect of missing data on outcomes can be determined.

Aim 1 Analysis (Treatment outcome). As stated in Aim 1, the primary outcome aim will be to evaluate the relative efficacy of PE+CBD compared to PE+placebo in reducing symptoms of PTSD at post-treatment and 1- and 3- month follow-up. This aim will be tested using generalized linear mixed-effects models for longitudinal data (GLMM) and weighted generalized estimating equations (WGEE). Unlike the parametric GLMM, the semi-parametric WGEE requires no distribution assumptions, yields valid inference for a broader class of data distribution, and allows for the inclusion of cases with missing data(Tu et al., 2007). If discrepancy arises between the two models, WGEE results will be reported. The models will include a factor for treatment condition (PE+CBD, PE+placebo), a set of indicators for time (baseline, termination, 1-month follow-up, 3-month follow-up), and treatment x time interaction terms. Dependent variables include: CAPS-5 total scores, CAPS-5 subscale scores, clinical response rate (defined as the proportion of patients with a ≥ 5-point reduction from baseline in total CAPS-5 scores) and the diagnosis rate (defined as the proportion of patients who no longer meet criteria for PTSD). Significance and effect size of the group x time interaction will be the primary test of treatment efficacy. If the preliminary analyses reveal group differences on any factors at baseline, the models will be expanded to include those factors as covariates (e.g., age, gender), so that an adjusted intervention effect can be computed.

Aim 2 Analysis (Treatment outcome). Survival analysis will be used to test whether participants who receive PE+CBD show a faster clinical response than participants who receive PE+placebo. Group differences (PE+CBD, PE+placebo) in median time-to-event end points will be analyzed using discrete proportional hazard regression (for estimation of hazard ratios). Time will be defined as the number of PE sessions since baseline (1-12). The primary time-to-event end points will include: 1) clinically significant response (defined as a ≥ 10-point reduction from baseline in total PCL-5 scores), and 2) diagnostic status change (defined as PCL-5 scores that no longer meet criteria for PTSD). As in Aim 1, if the preliminary analyses reveal group differences on any factors at baseline, the models will be expanded to include those factors as covariates.

Aim 3 Analysis (Mediation). Aim 3 will test whether extinction effects (reduction in average in-vivo and imaginal SUDs) mediate the main effect of treatment condition (PE+CBD, PE+placebo) on PTSD symptoms (CAPS-5) and diagnostic status change time-to-event. Structural equation models (SEM) will be used to test for mediation of PTSD symptoms. As with the longitudinal data analyses, both parametric and semi-parametric SEM-based models will be computed, and results from the semi-parametric approach will be reported if discrepancy emerges between the two. Likewise, an integrated SEM approach using discrete-time survival models(Hellevik et al., 2009) will be used to test for mediation of diagnostic status change time-to-event. In all models, if the null of full mediation is rejected, direct and indirect intervention effects and percent of mediation will be reported.

Exploratory Analyses: Exploratory aims will be tested using the same analytic plan as Aim 1 (GLMM, WGEE). The models will include a factor for treatment condition (PE+CBD, PE+placebo), indicators for time (baseline, weeks 1-12, termination, 1-month follow-up, 3-month follow-up), and condition x time interaction terms. Dependent variables will include: PSA total scores, IDAS subscale scores, PTCI subscale scores, and B-IPF total scores. Group differences in drop-out rates will be analyzed using the MAR pattern-mixture-modeling used to identify covariates of missingness.

Safety Analyses: Medication side effects reported on the UKU-SERS-Pat and/or any Adverse Events (AEs) will be tabulated by treatment group and classified by system organ class and preferred term using the Medical Dictionary for Regulatory Affairs (MedDRA). Side effects and AEs will be tabulated overall and by condition (CBD, Placebo). For each preferred term, the active group (PE+CBD) will be compared to the placebo group (PE+Placebo) with a Fisher Exact test.

Section 9.1 Clinical Procedures

9.1) Differentiate research procedures (or any procedures done for research purposes only) from clinical procedures (procedures that are done as part of standard care).

(Note: this differentiation should be clear in the consent form as well)

The experimental portion of this study is to test if the investigational new drug, cannabidiol (CBD), will be effective in improving the effectiveness of existing psychotherapy (PE). Clinical procedures employed in this study, which are standard of care, are: the use of Exposure therapy (PE) and medication management. Research procedures in this study include: randomization to receive either CBD or placebo (cellulose pills).

Section 9.2 IND Drugs

9.2) For each drug requiring an IND, provide the drug name, dose, and route of administration

Investigational New Drug (IND# 139668): The investigational drug is cannabidiol (CBD; C21H3002) oral (drug code: 7350). CBD is currently designated a schedule I controlled substance because in botanical form it is derived from the cannabis plant. However, CBD is devoid of intoxicating activity and does not carry a signal for reward or abuse. Moreover, we will be using pharmaceutical grade synthetic CBD (non-botanical). Phase I and II trials of oral CBD have demonstrated safety and tolerability in human subjects in doses ranging up to 1000mg/day for 6 weeks, chronically for up to 4.5 months (at 300mg/day), and within the proposed study's intended dose range (15-50mg/kg/day) for 12 weeks. CBD was chosen for the proposed trial for its high promise in delivering extinction promotion and non-traditional anxiolytic effects. The crystalline CBD will be sourced through AMRI and encapsulated for oral consumption by the on-site research pharmacist, Dr. Funk. Placebo control pills will contain only cellulose filler. The

investigational drug will be stored in the Research Pharmacy in accordance with 119-SOPP-10 /151-SOPP-38. The study physicians will be designated as authorized users for making prescription recommendations for participants to receive study drug under the PI's research schedule I registration. The first batch of the investigational drug will be sent back to AMRI for stability testing of the encapuslated produce at week 0, three months, and 6 months.

Dose considerations for study drug were informed by several prior studies that reported significant therapeutic effects with minimal side effects at daily doses of 600mg CBD. Active CBD dosing will consist of twice daily oral administration of one pill per day [Q12 H (± 2 hours)], which contains 300mg of active drug (total daily dose of 600mg CBD). Placebo dosing will consist of twice daily oral administration of one placebo cellulose pill per day [Q12 H (± 2 hours)]. Initial dosing will begin following randomization, where participants will return to the investigative clinic approximately one week after baseline testing to have their risk profile reviewed before dispensing of the investigative drug. Study drug will be dispensed weekly in 7-day supplies (14 pills). Medication (CBD, placebo) will be taken continuously throughout the trial for a total of 16 weeks of medication delivery.

Participants will have medication appointments weekly for the first six weeks and every other week until week 16. The first medication appointment will be conducted via telehealth and all remaining appointments will be conducted via phone or telehealth based on participant preference.
In order to maintain high compliance with the medication regimen, all participants will receive Medical Management Counseling (MMC) at their medication appointments. MMC is a manualized supportive counseling method designed by the National Institute of Alcohol Abuse and Alcoholism to promote adherence to the medication regimen and reduction in alcohol use. The 16-week double-blind treatment phase is designed to allow a 12-week period where active medication is at steady-state concentrations. Thus, both the medication period and the psychotherapy period will be 16 weeks, during which participants are anticipated to attend up to 12 medication and psychotherapy appointments. This schedule also makes it such that patients will reach their maximum therapeutic dose of CBD at the time that they begin imaginal exposure in PE.

Every attempt will be made to maintain participants at the target 300mg daily dose. However, participants who are unable to tolerate the specified dose will be allowed to continue in the study at a reduced dose (the maximum tolerated dose) as determined by the study physician and PI (under schedule I license). Such participants may continue to participate in all other aspects of the study. When CBD/placebo dose reductions are warranted due to adverse side effects, the medication dose will be reduced by 50mg at a time, titrating to the maximum amount clinically tolerated. Dose reductions are permissible for both conditions, so any necessary titration should not interfere with blinding. In the case of severe side effects, discontinuation of the study medication may be deemed clinically necessary.

9.2b) Enter the IND Number:

139668

9.2c) Identify who/what entity holds the IND and the status of the IND

Dr. Loflin will hold the IND until 10/23/20, at which point it will transfer to Co-I Dr. Brian Martis

9.2d) Identify the storage and security of the drug. For example, at the VASDHS, state "The investigational drug will be stored in the Research Pharmacy in accordance with 119-SOPP-10/151-SOPP-38." Also, identify whether the drug is a controlled substance.

The investigational drug is a controlled substance and stored in the Research Pharmacy in accordance with 119-SOPP-10/151-SOPP-38

Section 9.6 Specimens

9.6) Identify the biological materials, procedures for obtaining material, and the sources of the specimens. ***Effective 12/01/2019: Specify whether research or clinical staff (from which service) will be collecting the specimens and describe "hand-off" procedures to ensure that release of the specimens has been authorized by Pathology and Laboratory Medicine Service (PALMS).***

Participants will receive a laboratory diagnostic evaluation consisting of a chemistry panel,

complete blood count, liver function test, urine toxicology screen and pregnancy test during prior to their baseline assessment with the nurse/physician so that participants with any illnesses that might adversely be affected by their participation in the trial will be excluded. Participants will only recomplete laboratory tests if clinically indicated. Research staff will not conduct any of the laboratory tests or handle or come in contact with any blood/samples. Study clinicians will request the laboratory work and veterans will go to the VA clinical laboratory to have the above lab work done.

Section 9.8 Questionnaires & Surveys

9.8) Provide the name and a reference for questionnaires/surveys that are standard or identify them here and attach a copy of the questionnaire/survey. ***Questionnaires or surveys that are not clinical standard references must be uploaded. Reference the help link for additional information related to surveys administered to VA personnel and approved platforms for web-based surveys.***

PRIMARY OUTCOME MEASURES:
The Clinician-Administered PTSD Scale DSM 5 (CAPS-5)(Weathers et al., 2017) is the gold-standard, semi-structured interview that corresponds to DSM-5 criteria for PTSD. The CAPS-5 shows strong reliability and validity for diagnosis of PTSD.

The PTSD Checklist (PCL-5)(Bovin et al., 2016) is a 21-item self-report measure of PTSD symptoms with good psychometric properties. The PCL-5 maps directly onto DSM-V diagnostic criteria.

Subjective Units of Distress Scale (SUDs)(Kim, Bae, & Chon Park, 2008) is a one-item subjective anxiety scale that is administered at multiple time points to anchor patients' self-rated distress at baseline and monitor change over time. SUDs will be self-administered during in-vivo exposure and administered by the clinician during imaginal exposure. As a repeated-measure scale, it shows good reliability and predictive validity for anxiety and impact-of-events distress(Kim et al., 2008). SUDs ratings also correspond well to physiological indicators of fear expression(Foa, Riggs, Massie, & Yarczower, 1995).

EXPLORATORY OUTCOME MEASURES:
Posttraumatic Cognitions Inventory (PTCI)(Foa, Ehlers, Clark, Tolin, & Orsillo, 1999) is a 33-item self-report measure of trauma-related thoughts and beliefs. The measure demonstrates good internal consistency and test-retest reliability.

The Brief Inventory of Psychosocial Functioning (B-IPF)(Erb et al., n.d.) is a 7-item self-report measure of past month psychosocial functioning with good psychometric properties. The measure will be amended to assess past week functioning.

Inventory of Psychosocial Functioning (IPF) (Marx et al., 2009) is an 80-item self-report questionnaire, which assesses functional impairment across several domains, including relationships, work, parenting, education, and general daily functioning over the past 30 days.

Inventory of Depression and Anxiety Scale (IDAS)(Watson et al., 2007) is a self-report scale that measures 10 subscales of anxiety: suicidality, lassitude, insomnia, appetite loss, appetite gain, ill temper, well-being, panic, social anxiety, and traumatic intrusions. The subscales show good internal consistency reliability, and good convergent and discriminant validity with other symptom measures.

Pittsburgh Sleep Quality Index (PSQI)(Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) is a 19-item self-report assessment of past 30-day sleep quality and sleep difficulties. The measure will be amended to assess past week symptoms.

Insomnia Severity Index (ISI) (Bastien, Vallieres, & Morin, 2001) is a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia over the past month.

PROMIS Pain Intensity Instrument(PROMIS)(Revicki et al., 2010) is an 11-item self-report questionnaire, which assesses current and past week intensity of physical pain symptoms.

Fagerström test for nicotine dependence (FTND) (Heatherton et al., 1991) is a well-validated 6-item self-report questionnaire, which assesses tobacco use and symptoms of tobacco dependence.

Neurobehavioral Symptom Inventory (NSI) (Cicerone & Kalmar, 1995) is a 22-item self-report measure of postconcussive symptoms, and is the standard measure used to assess TBI

symptoms in VA.

Credibility/Expectancy Questionaire (CEQ) (Devilly & Borkovec, 2000) is a 6-item self-report measure used to assess participant perceptions of treatment credibility and expectations of treatment success.

SCREENING AND SAFETY MEASURES:
Demographics will obtain information related to sex, age, height and weight (BMI), ethnicity /race, education level, employment, and era of service.

Health History Checklist will be used during the baseline assessment to ensure that the participant meets all health-related inclusion/exclusion criteria. Information will be obtained related to individual and family history of physical and mental health conditions, psychiatric treatment history, and medication use.

Montreal Cognitive Assessment (MoCA) (Nasreddine, 1996) is a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains, including: attention and concentration, executive functions, memory, language, visoconstructional skills, conceptual thinking, calculations, and orientation.

STOP-BANG Questionnaire(Shahid, Wilkinson, Marcu, & Shapiro, 2011) is an 8-item self-report screening tool for sleep apnea with good validity and high sensitivity.

Columbia Suicide Severity Rating Scale (CSSRS)(Posner et al., 2008) is a clinician administered semi-structured instrument that assesses recent suicidal behavior, attempts, and ideation.

UKU Side Effects Rating Scale, Patient Version (UKU-SERS-Pat)(Lindström et al., 2001) is a patient-administered 48-item comprehensive side effect rating scale with well-defined and operationalized items to assess the side effects of psychopharmacological medications.

Medication Adherence form: A 2-item questionnaire regarding medication adherence.

The Mini International Neuropsychiatric Interview (MINI) is a short diagnostic structured interview (DSI) developed used to screen for 17 disorders according to ICD-10 and DSM diagnostic criteria.

Section 9.9 Data Safety Monitoring Board or Plan

9.9) Provide a Data Safety Monitoring Plan (DSMP) or the details of a Data Safety Monitoring Board; if a written plan is available, attach a copy of the plan to the submission form.

DATA SAFETY MONITORING PLAN (DSMP)
The DSMP will include periodic review and reporting of participant accrual, adverse event rates, treatment compliance, and drop-out rates. Study termination will be triggered by excessive drop-outs or adverse events. Adverse events includes 1) need to break confidentiality, 2) loss of data, 3) inadvertent harm caused by study participation, 4) patient suicidality. If treatment is needed during the follow-up phase due to serious psychiatric/medical symptoms, patients will be referred to appropriate treatment and followed by the PI and study therapist until treatment is initiated. Adverse events will be reported to the San Diego VA's IRB and the VA ORD (serious adverse events within 48 hours) and clinically managed as appropriate. A summary of all adverse events will be submitted to VA ORD and CSR&D annually. The PI will be available by phone 24-hours a day. The PI will be responsible for initial determination of serious adverse events from non-serious adverse events. This study will report to the VA DSMB and follow all criteria for reporting.

An Adverse Event (AE) is any unexpected medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. This includes any clinical or laboratory change that does not commonly occur in that participant and is considered clinically significant. All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study treatment will be recorded throughout the study. The study physician will also be responsible for determining causal relationship between the study treatment and all AEs. Withdrawal from the study as a result of an AE or of therapeutic measures taken to treat an AE shall be at the

discretion of the study clinicians. If a participant withdraws from the study for any reason, the study team will follow all participants with any ongoing AE until the AE is resolved or until it is deemed stable. FDA 21CFR312.32 defines a serious adverse drug experience (SAE) as any adverse drug experience occurring at any dose that results in any of the following outcomes: death; a life threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; or a congenital anomaly /birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse experiences when, based on appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes in this definition. The judgment of whether a particular AE meets the above criteria for an SAE shall be at the discretion of PI and the medical team.

It will also be the responsibility of the PI to document all SAEs and/or make referrals for appropriate care. All SAEs will be reported to the IRB, within 48 hours of their discovery. The blind can be broken at any point throughout the study as needed to protect participants' safety. The PI will meet with the research staff on a weekly basis to discuss study progress and potential problems, and will review collected data weekly, to ensure compliance with study protocols and data integrity. They will also have at least monthly meetings with all mentors and project staff to ensure high levels of communication within the study team.

Participants in need of additional services: A plan is in place for identifying and referring individuals who report suicidality, either through self-report on assessment measures (e.g., C-SSRS), or during a clinical contact. Participants identified as at imminent risk will be further evaluated by the site PI or, if needed, escorted to the emergency services at the VA. If indicated, referrals for treatment will be provided.

PROTECTION OF SENSITIVE DATA
Data will be obtained from VA patients in an outpatient setting using a clinical screening interview, medical record review, self-report questionnaires/surveys, urine drug and pregnancy screens, and psychological assessment batteries. Trained study personnel will conduct the clinical screening interview using a structured format in which the interviewer asks questions from a form document and also records answers on this document. The self-report questionnaires /surveys and psychological assessment battery consist of standardized protocols with specific /scripted questions and scoring systems that quantify answers. All study personnel who will be gathering data from these sources will be trained by the PI regarding the collection of data and will have professional education and training as required by these instruments.

Data will be de-identified and labeled with a code number that is unique to each patient in the study. All hard copy data will be stored in locked file cabinets in locked rooms in VASDHS Building 13, while all electronic data will be stored in password-protected files in a limited access folder on the secure VA network drive. The PI will maintain the key code that links participants with their coded identifier. This key code will be stored separately from all other study data and will be available only to the PI and research coordinator. Any materials with protected health information (e.g., informed consents) will be stored in separate locked file cabinets from de-identified, coded materials to ensure the security of patient privacy. All statistical transfer routines are inherently secure via their operating platform and they contain no patient names or personal data.

Participant confidentiality will be protected to the extent provided by law. Sensitive information that might be disclosed in this study and would be subject to mandatory reporting includes information regarding child or elder abuse. Evidence of suicidality or homicidality may also be disclosed to appropriate mental health personnel or others to ensure the safety of all parties. Raw and electronic data will be stored in the VASDHS in accordance with current VA research guidelines.

The PI and project coordinator will complete frequent quality control assessments, which will include regular data verification and protocol compliance checks. Regular monitoring will be conducted of the study protocol and collection of data to ensure participants confidentiality and safety are being maintained. The study coordinator will provide weekly reports detailing the study progress, accrual information, demographics, adherence to inclusion/exclusion criteria, and unexpected or adverse events.

Section 9.11 Pictures and Audio/Video Recordings of Patients

9.11) Describe the purpose of photographs (facial), or audio, or video recordings of patients. Describe

whether the recordings will contain, or potentially contain, identifiers. ***Note: use of photographs or recordings must be covered in the informed consent process and documented consent documents (e.g., consent form, information sheets, telephone screen scripts).***

Audio Recordings: All sessions will be audio-recorded, and study therapists will receive weekly feedback and supervision on their skillfulness and adherence to treatment guidelines using review standards developed by Carroll et al. and refined by mentor Dr. Norman. Audio recordings will only be reviewed for supervision, reliability, and treatment adherence purposes, and recordings will be erased as soon as data are analyzed. All treatment sessions and interviews will be recorded on digital audio recorders "Sony SOICDPC370", "Sony ICD-UX533""Sony ICDPX333", "Olympus VN-1800", "Olympus VN-6200PC", "Olympus Vn-7200", "Olympus DP-201", "Olympus VN-6300pc", "Olympus VN-541PC", or other VA-approved recording technology and will be placed on VA server for potential review by supervisors. Audio recordings will be reviewed by study investigators--a random sample for reliability and treatment adherence purposes. Each participant will receive a study audio recorder from the recorder list above to complete required PE therapy homework. Due to the potential for losses of recorders through patient drops/loss-of-contact and losses in mail, study staff will maintain a serialized log of each recorder distributed for tracking and purchasing audits.

Section 9.12 Off Station Activities

9.12) Describe each off-station activity including where it occurs, subject involvement, and any additional required protections. ***Note: if the off-station activity is being conducted under the approval authority of another institution, this is not VA offsite research and should be described as collaborative research effort. Please contact the HRPP office if you have any questions***

Off-station activity has been put into place to reduce the need for participants to travel to the San Diego VA hospital for study treatment delivery. This will involve video teleconference into a patient's home. Video teleconference will be delivered by the provider/assessor either from home when working remote or from the VA San Diego Hospital. No additional protections are needed. Assessors will use telemental health services, or telephone, to contact and coordinate patient care and participant interest.

Section 10 - Human Subjects

10) Describe the characteristics of the proposed subject population. Include age, gender, ethnicity, and health status as appropriate. ***Note: Data about people are still considered "human subjects" by the IRB, so even if you do not intend to contact the patients whose charts you will review, you still describe the characteristics related to the subjects whose charts you will review.***

- **Provide inclusion and exclusion criteria as appropriate. Provide a statement how non pregnancy is confirmed if pregnancy is an exclusion criteria.**
- **For multisite studies, provide the total number of subjects from all sites and include description of the local site's role as a coordinating center if applicable.**
- **Indicate the number of VA participants to be studied.**
- **Indicate the estimated number of consented subjects that will fail the screening process, if any.**

Up to three-hundred Veterans will be consented, so that 136 male and female Veterans with a diagnosis of PTSD will be randomized through the VASDHS.

Inclusion criteria:
(1) Over the age of 18 at the time of screening.
(2) Judged by the consulting physician to be in generally good health at the Screening Visit based upon the results of a medical history and/or screening exam.
(3) Meet clinical criteria for PTSD on the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5).
(4) History of previous treatment for PTSD is acceptable, so long as patient still meets current criteria for PTSD diagnosis.
(5) Females of childbearing potential must have a negative urine pregnancy test and and not currently be breast feeding. Females of childbearing potential and male patients with a partner of childbearing potential must use an acceptable method of contraception (as outlined below), from at least 21 days prior to the first dose of study drug and for 3 months after the last dose of study drug. Standard acceptable methods include use of a highly effective method of contraception,

including; hormonal contraception, diaphragm, cervical cap, vaginal sponge, condom, spermicide, vasectomy, intrauterine device.
(6) Patient agrees to abide by all study restrictions and comply with all study procedures.
(7) In the Investigator's opinion, the patient is reliable and is willing and able to comply with all protocol requirements and procedures.

Exclusion criteria:
(1) Patient has a history of significant allergic condition, significant drug-related hypersensitivity, or allergic reaction to cannabinoids.
(2) Patient has been exposed to any investigational drug or device < 30 days prior to screening, or plans to take another investigational drug at any time during the study.
(3) Patient has used cannabis, synthetic cannabinoid or cannabinoid analogue (e.g., dronabinol, nabilone), synthetic cannabinoid receptor agonist (e.g., spice, K2), or any CBD or THC-containing product within 30 days of the randomization or during the study.
(4) Patient has change in current tobacco product(s) use within 30 days of randomization or plans to change their use during the study.
(5) Patient has had a change in psychopharmacotherapy regimen in the last 4 weeks, or has any plans to change regimen over the following 4 months.
(6) Patient is engaged in psychotherapy for PTSD or any other DSM-5 diagnosis.
(7) Patient has a current or past primary DSM-5 diagnosis other than PTSD that the study investigator determines would interfere in treatment or interfere in evaluation of the study treatment.
(8) Patient has seizures secondary to illicit drug or alcohol use, infection, neoplasm, demyelinating disease, degenerative neurological disease or central nervous system (CNS) disease deemed progressive, metabolic illness, or progressive degenerative disease.
(9) Patient has acute or progressive neurological disease that is likely to require changes in drug therapy during the Maintenance Period of the study, or interfere with the objectives of the study, or the ability to adhere to protocol requirements.
(10) Patient is currently prescribed medications with known CBD-interactions (e.g., amiodarone, fluconazole, metronidazole, micronazole, sulfamethoxazole, clarithromycin, erythromycin, cyclosporine, verapamil, itraconazole, voriconazole, boceprevir, St. John's Wart, and carbamazepine).
(11) Patient has a history of serious suicide attempt resulting in hospitalization in the past year.
(12) Patient responded "yes" to Question 4 or 5 of C-SSRS during baseline assessment.
(13) Patient endorses current homicidal intent at baseline assessment or screening.
(14) Patient is at high risk for obstructive sleep apnea, which is untreated/unmanaged.
(15) Patient is involved in ongoing litigation related to a PTSD diagnosis.
(16) Patient has a positive drug screen for THC, barbiturates, benzodiazepines, or opiates. Patient will also be excluded if they have a positive drug screen for amphetamines when they are not currently prescribed amphetamine medications.
(17) Patient has any clinically significant condition or abnormal findings at baseline assessment that would, in the opinion of the Investigator, preclude study participation or interfere with the evaluation of the study treatment.
(18) Patient currently meets criteria for a moderate or severe SUD.
(19) Patient reports >4 heavy drinking days (defined by >=5 drinks/day for men, >=4 drinks /day for women) in the last 30 days prior to screening.
(20) Patient has a lifetime history of Cannabis Use Disorder.
(21) Patient is currently pregnant or breastfeeding.
(22) Patient demonstrates behavior indicating unreliability or inability to comply with the requirements of the protocol.

Section 11 - Recruitment

11) Describe, step-by-step, the plans for recruitment of subjects (or selection of subjects as in record review). This description must include how, when, and where potential subjects are approached as well as procedures for identifying potential participants (through medical records, physician referral, third-party sources, etc.). Include how selection is equitable. Indicate if vulnerability to coercion may be present and if so plans to ensure voluntary participation.

Potential participants will contact our study in response to 1) flyers posted in VA mental health, primary care, and PTSD specialty treatment programs; 2) advertisements in print and web-based media; 3) referrals from VA primary care, PTSD, and other psychiatry clinics, 4) from other research studies whose participants agreed to be re-contacted, 5) letters and follow-up calls to potential participants identified through the VA Data Access Request Tracker (DART), and 6) BuildClinical's targeted online recruitment services. Study details will also appear on a current research list posted to the VHASDC Clinical Research Teams channel. Providers from the Patient Assessment & Triage Hub (PATH) can access this spread sheet and refer veterans directly to

study during treatment planning. We plan to recruit 3-4 participants per month for this study. Potential participants will be contacted by phone, and following verbal consent, will undergo a phone-based screening that takes approximately 30 minutes to complete. The screening consists of screening items from the SCID and the PCL-5 for symptoms that are part of the inclusion and exclusion criteria. Study staff will review the potential participant's CPRS record to determine if there are any exclusion criteria that was not disclosed in the phone screening before eligibility is determined. Those who meet study criteria will attend an in-person interview where they will sign informed consent documents and take part in a baseline assessment. Following baseline assessment, participants will be randomized to the intervention or control condition.

Advertisements in print will be posted in designated research flyer areas on the 2nd floor of the main SDVAMC and in Building 13 (VMRF). Web-based flyers will be posted on the VASDHS website (http://www.sandiego.va.gov/studies.asp) and on the VMRF website (http://www.vmrf.org/studies.html)"

Regarding referrals from VA clinics, Veterans referred to the PTSD Clinical Team at the San Diego VA will have the study described to them during orientation group (which is part of normal clinical practice) by one of the group leaders and be provided a "Research Candidate Form" that gives research staff permission to contact the Veteran and describe the study and details of study participation. The orientation group leaders will be informed about the details of the study by the PI. Interested Veterans may have the opportunity to meet with the study coordinator to discuss participation. Veterans who sign the Research Candidate Form will have their CPRS record reviewed prior to determining eligibility to insure there is no exclusion criteria noted on their record. If appropriate, they will be scheduled for a phone-based screening to determined eligibility. Participants who are recruited through other VA clinics will be offered the option of study involvement via their clinicians at standard appointments (i.e., orientation session, intake appointment, regular psychotherapy/medication appointments). Interested participants will give their clinician either their verbal consent to be contacted regarding the study, and their information will be given to the study coordinator, via a CPRS note, or the Research Candidate Form to complete with their contact information which will be given to/collected by the study coordinator or a flyer about the study, with the study coordinator's information.

Regarding recruitment from other research studies, veterans who previously participated in a research study conducted by the Center of Excellence for Stress and Mental Health and who agreed to be re-contacted may be contacted to be screened for eligibility. For those potential participants, study staff will collect basic their last name and last four of their social security number so that they can first review their CPRS record to determine if there are any exclusion criteria prior to contacting the veteran to ensure there are no immediate exclusion criteria that would make the veteran ineligible. Contact information, such as phone number and mailing address will be collected from their record. Those veterans who might be eligible will be contacted by letter and/or phone after record screen if no immediate exclusion criteria are found. If the participant did not agree to initial contact by phone, a letter will be sent first. After a period of 2 weeks if a letter is sent, and if no contact is made by the veteran, study staff will follow up by phone to provide the veteran with more information about the study. If participants are interested, they will be contacted for a phone-screening to determine eligibility.

Regarding targeted mailings/calls, we will use VA Data Access Request Tracker (DART) requests to identify Veterans with PTSD to be mailed invitational letters informing them of this study. Any potential participant who is identified via a DART request will be sent a modified recruitment letter that provides basic information about the study. The letter will inform Veterans that they will be contacted by phone in the coming days regarding their interest in participating in the study. In the letter, potential participants will be given an "opt-out" number to call in order to decline participation and/or further contact regarding participation. Two weeks after the mailing, Veterans who have not called the tollfree number to decline participation will be called by the study coordinator to request their participation in the research study.

Regarding BuildClinical, this clinical recruitment service will advertise study specifics and provide a protocol-specific screening form for veterans to connect with study personnel for potential inclusion. Researchers will receive the names of potentially eligible participants to contact based on the company's electronic outreach services.

Section 11.1 Recruitment Materials

11.1) Identify all recruitment materials (flyers, advertisements, letters, etc.) that will be used; include the web address for any web-based advertisements. The text of all communications with prospective participants must be reviewed and approved by the IRB before it can be used. You will be reminded to attach copies of

recruitment materials to the initial submission packet. ***Note: Posting of flyers with pull tabs is not permitted within VASDHS (including the VMRF building). However, you may request to advertise on the e-boards (located at the elevators and throughout the facility) or on the VASDHS Research Opportunities web-page.***

Advertisements in both print and web-based media will be used for recruitment. Flyers and brochures will be available to interested participants and posted in various locations thought the VA. We will also provide flyers to interested therapists who work with Veterans with PTSD in the San Diego community, including therapists who work at San Diego Vet Centers. Targeted recruitment letters will be sent to potential participants identified by the VA Data Access Request Tracker (DART).

Advertisements for the study will also be virtually distributed through by BuildClinical. The company has aggregated comprehensive patient data sets from social media, online searches, health websites and online patient communities and has applied machine-learning and data mining to identify digital footprints of specific patient groups.

Section 12 - Informed Consent

12) Indicate whether or not each category of consent is involved in this study:

12a) Will the study team obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without (or prior to) obtaining informed consent of the prospective subject or the prospective subject's LAR?

○ Yes ◉ No

12b) **Signed** informed consent

◉ Yes ○ No

12c) Waiver of documented consent (e.g., **oral** consent) for all or part of the study.

○ Yes ◉ No

12d) Request for a **waiver** of consent for all or some study activities.

○ Yes ◉ No

12e) Alteration of **other required elements** of consent.

○ Yes ◉ No

12f) **Child** assent to participate (Director approval will be required)

○ Yes ◉ No

12g) Will any language **other than English** be used by those obtaining consent and understood by the prospective participant or the legally authorized representative?

○ Yes ◉ No

12h) **Decisional Capacity Assessment** to determine if participants have the capacity to consent for themselves.

○ Yes ◉ No

12i) **Surrogate** consent (legally authorized representative)

○ Yes ◉ No

Section 12.1 Informed Consent Process

12.1a) Will consent be obtained before any study procedures are performed (including screening procedures except screening procedures with Consent and/or HIPAA waiver when required)?

(•) Yes ( ) No

12.1b) Will the information being communicated to the participant or legally authorized representative during the consent process include exculpatory language through which the participant or legally authorized representative is made to waive or appear to waive any of the participant's legal rights or release or appear to release the Researcher, Sponsor, the VA or its agents from liability for negligence.

( ) Yes (•) No

12.1c) A master list of all VA subjects consented (written or not) under this protocol will be maintained.

(•) Agree ( ) Disagree

12.1d) Identify the circumstances under which consent will be obtained including where the process will take place; any waiting period between describing the research and obtaining consent including sufficient time for the prospective participant to consider participation, and any steps taken to minimize the possibility of coercion or undue influence.

After the veteran completes the phone screening, the project coordinator will discuss the results with the PI as soon as possible. This will also provide the veteran time to review the requirements of the study and their interest in participating. If it is determined that the veteran is eligible for the study, they will be scheduled for a consent and intake appointment to be conducted via telehealth. The consenting documents will be either mailed or emailed (using encryption) to the participant based on their stated preference. Consenting will take approximately 45 minutes – 1 hour. During the telehealth consent appointment, the member of the study staff performing the consent will witness the participant signing the document and then take screengrabs of each signature. The screenshot will be saved directly within CAG (if the consenter is working remotely). As an alternative to taking digital screenshots of real-time signed consents, participants may also sign and electronically return the consent documents via DocuSign during the informed consent session. The participant will be instructed to keep the signed copies of all forms for their records.

Immediately following consent, the veteran will complete their intake assessment. which can take around 3 hours. The veteran will be reminded that their consent must be given freely and that their VA benefits will not be affected should they choose not to participate or if they drop out of the study. The veteran is free to stop participation in the study at any time for any reason.

Section 12.9 HIPAA Authorization

For each category below, indicate whether or not this study involves the indicated process:

12.9a) **Signed** HIPAA Authorization. ***New Template is available in the ? Help section***

(•) Yes ( ) No

12.9b) HIPAA waiver to cover the entire study

( ) Yes (•) No

12.9c) HIPAA waiver for recruitment, screening, and/or for a portion of the study.

(•) Yes ( ) No

12.9d) HIPAA Authorization or waiver is **not required** for some or all of the study subjects (e.g. no health data).

( ) Yes (•) No

Section 12.10 HIPAA Waivers and Alterations

12.10a) Describe the purpose/nature of the HIPAA waiver or alteration and list specifically, what identifiers

and health information are being requested under the waiver/alteration and identify whether the waiver is for access, use, and/or collection of this information.

For potential participants that we contact through the target mailing identified through the DART system, BuildClinical, potential participants that call in from the flyers/brochures/websites, individuals that are referred from VA clinics, and potential participants who are recruited through re-contact list from other research studies, we will request a partial waiver of HIPAA Authorization for screening. Study staff will review their CPRS record to determine if there are any exclusion criteria prior to the phone screening to ensure there are no immediate exclusion criteria that would make the veteran ineligible (name and last 4 of SS# will be requested). Health information will be visually inspected; no health information will be recorded during CPRS record review. Patient's current medication and treatment history for PTSD and other co-occurring mental health conditions will be used to determine eligibility. If the participant is eligible based on their CPRS record findings and they are interested participating, the potential participant's phone and mailing address will be recorded. They will be contacted for a phone screening. If participants are eligible after the phone screening, they will be scheduled for a telehealth consent where Subject's Bill of Rights will be given, informed consent (VA form 10-1086) and HIPAA will be completed followed by baseline assessments. The nature of the study will be explained, portions repeated as necessary, and questions answered.

12.10b) The proposed access, use, and/or disclosure of PHI involves no more than a minimal risk to the privacy of individuals.

◉ Agree ○ Disagree

12.10c) The plan to protect the identifiers from improper use and disclosure is adequate.

◉ Agree ○ Disagree

Describe the plan

Hard copy data will be collected by approved research staff and stored with other sensitive information according to the data security plan. Full HIPAA forms will be signed along with the consenting process.

12.10d) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

◉ Agree ○ Disagree

12.10d2) Describe the plan:

The dataset will be de-identified after the study has closed.

12.10e) By signing this protocol for submission, the PI is providing written assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by the Privacy Rule. 38 U.S.C. 7332 Information: If the waiver of HIPAA authorization is for the use of 38 USC 7332 information (applicable to drug abuse, alcohol abuse, HIV infection, and sickle cell anemia records), by signing this protocol for submission the PI is providing written assurance that the purpose of the data is to conduct scientific research and that no personnel involved may identify, directly or indirectly, any individual patient or subject in any report of such research or otherwise disclose patient or subject identities in any manner. (Ref: 38 U.S.C. 7332(b)(2)(B))

◉ Agree ○ Disagree

12.10f) The research could not practicably be conducted without the waiver or alteration.

◉ Agree ○ Disagree

12.10f2) Describe how the waiver/alteration enables the research to be conducted

The HIPAA waiver enables the study to be conducted because it enables us to recruit participants and reduce our screening failure rate. By reviewing patients CPRS records we will be able to determine if there are any exclusion criteria prior to the phone screening to ensure there are no immediate exclusion criteria that would make the veteran ineligible (name and last 4 of SS# will be requested).

12.10g) The research could not practicably be conducted without access to and use of the PHI.

(•) Agree ( ) Disagree

12.10g2) Describe why it would be impracticable to conduct this research without the PHI described 12.10a. (v3 /8/18)

We request access to and use of PHI (name and last 4 of SS# will be requested) for screening purposes, appointment scheduling, and follow up (contact information), electronic payment as well as record review for inclusion exclusion criteria. The research could not be practicably be conducted without the waiver; and the research could not be practicably be conducted with without access to and use of the requested information.

Section 13 - Alternatives to Participation

13) Describe the alternatives to participation in this research study (see ? for guidance)

Alternatives are to not participate in the study. All participants who do not wish to participate in the study or who are not eligible will complete the regular outpatient program at the VASDHS. Referrals to appropriate mental health services within VASDHS will be given if needed and/or requested.

Section 14 - Potential Risks

14) Describe any potential or known risks or discomforts and assess their likelihood and seriousness (see ? for guidance)

Risks to participants in the current study are minimal and outweighed by potential benefits. Potential risks associated with participation in the study include: 1) loss of confidentiality, 2) possible side effects from study drug or placebo, 3) feeling uncomfortable during the assessment or therapy process either due to exposure or due to talking about emotional topics or symptoms, 4) becoming more anxious, depressed, or developing suicidality, and/or risks associated with completing a blood draw for screening, such as bruising, pain,
infection, etc.

Confidentiality. As with all research, there exists the small chance that a breach of confidentiality may occur. Breach of confidentiality could lead to negative economic and legal consequences, such as loss of a job or imprisonment as well as negative social consequences, such as disapproval or social stigma. Related to loss of confidentiality regarding psychiatric status is the low probability of social stigmatization if other patients and staff learn that some participants in the proposed study have a particular diagnosis (e.g., PTSD). Substantial procedures have been put in place to further limit the possibility of a breach in confidentiality or privacy.

Treatment. Although it is not expected that any adverse health problems will occur due to either the experimental drug or psychotherapy, it is possible that subjects may experience a temporary increase in physiological arousal from PE and/or side effects from the study drug or placebo. Side effects for CBD are rare, but may include: dry mouth, somnolence, psychomotor slowing, light headedness, weight loss, and/or insomnia. To minimize these risks, symptom checklists will be administered weekly throughout psychotherapy (including assessment of suicidality), and side effects will be monitored qualitatively and quantitatively using the UKU-SERS-Pat.

CBD carries a 50% H361 Category 2 GHS Hazard [Warning Reproductive toxicity (suspected of damaging fertility or the unborn child]. To reduce risk, female participants of childbearing potential must have a negative urine pregnancy test to be eligible to participate. Female participants of childbearing potential and male participants with a partner of childbearing potential will also be required to use an acceptable method of contraception, starting at least 21

days prior to the first dose of study drug and for 3 months after the last dose of study drug. Standard acceptable methods include use of a highly effective method of contraception, including; hormonal contraception, diaphragm, cervical cap, vaginal sponge, condom, spermicide, vasectomy, intrauterine device.

Self-report questionnaires, clinical interview, assessments. There are minimal risks associated with self-report measures and clinical interviews. However, it is possible that some participants may be hesitant to record their symptoms on assessment forms and/or may be uncomfortable describing their symptoms and history of exposure to traumatic events to a mental health professional. Some participants may also experience fatigue, stress and frustration from completing assessment batteries. However, participants may also derive benefit from assessment, as it increases awareness of functioning and may increase their awareness of the connection between environmental, cognitive, and interpersonal factors that affect their symptoms. Moreover, appropriately spaced breaks and supportive test administration techniques will be used to reduce possible patient discomfort.

Section 15 - Risk Management

15) Describe the procedures for protecting against or minimizing any potential risks/discomforts, and the adequacy of resources for conducting the study and resources participants may need as a consequence of the research. When applicable, include detail of the following safety measures: (a) The type of safety information to be collected, including AEs; (b) Frequency of safety data collection; (c) Frequency or periodicity of review of cumulative safety data; (d) Statistical tests for analyzing the safety data to determine if harm is occurring; and (e) Conditions that trigger an immediate suspension of the research. See ? for further requirements.

Protection from Risk Associated with Treatment (Drug). To minimize the risk associated with the study drug/placebo all patients will be given a 24-hour contact phone number to call and report side effects and Adverse Events (AEs). When CBD/placebo dose reductions are warranted due to adverse side effects, the medication dose will be reduced by .10mL at a time, titrating to the maximum amount clinically tolerated. In the case of severe side effects, discontinuation of the study medication may be deemed clinically necessary. AEs, including those unlikely to be the result of participation in the research (e.g., hospitalization due to an automobile accident), will be monitored at every study contact, including therapy and assessment sessions. AEs will be reported to the appropriate human subjects committees as per policy, and the study investigators will evaluate whether best clinical care indicates a need for continuation in the study or more intensive treatment. If more intensive treatment is appropriate, study staff will assist the participant in getting into the appropriate treatment, then discontinue the participants from the study following a final evaluation. In addition, the study will be overseen by the CSR&D safety monitoring board (SMB), which meets regularly to review side effects and AEs of overseen studies.

Protection from Risk Associated with Treatment (Psychotherapy). To minimize the risk of patients becoming more anxious or depressed, every patient will be given a 24-hour contact phone number to call in the event of increased symptoms. If either the study coordinator or the person conducting the intervention detects these symptoms, a study clinician will be available to evaluate the patient and refer to appropriate treatment. When in doubt, the decision whether continued participation in the study is safe and clinically warranted will always err on the side of patient safety. While PE typically reduces suicidality in PTSD populations, there is still risk associated with the management of patients with PTSD that they will develop suicidality. This risk will be carefully mitigated by the systematic and careful assessment of suicidality throughout the protocol. This will be carefully done via in-session assessments made by the therapists, through comprehensive suicide risk assessments that are part of standard VA care, and weekly check-ins assessing for any changes to the patient's suicide risk assessment. The therapist will evaluate subjects who develop suicidality to determine whether continued participation in the study is safe and clinically warranted. If the study personnel and participant feel that a different form of psychotherapy, medication, or hospitalization is indicated, an endpoint evaluation will be done, the participant will be discontinued from the study, and the participant will be immediately referred for appropriate treatment.

Protection from Risk Associated with harm to self or others. Active suicidal or homicidal intent are exclusionary criteria for the current study. Based on this and prior experience, it is expected that incidence of such events will be low. In addition, the safety profile of this study is greatly enhanced by its execution within the context of an outpatient PTSD clinic. Specifically, upon admission to the treatment program, all Veterans will complete a screening to assess for active intent of harm to self or others. Individuals with active intent for harm to self or others are not considered appropriate for this treatment facility and are referred to a higher level of care within

VASDHS (in the case of harm to self), or the VA police will be contacted (in the case of active intent to harm others). In the event that an individual reports active suicidal intent to research staff, the mentoring team and staff from the outpatient PTSD treatment program will be notified. The local suicide prevention coordinator will also be notified and participants will be escorted to the VASDHS emergency room for immediate care. The outpatient PTSD treatment program will provide crisis intervention and transfer/admission to a higher level of care, if needed, and monitor risk on an ongoing basis with the goal of preventing harm to self and others. Should an individual endorse intent to harm self or other during initial phone calls, staff will respond to callers by following the VASDHS system-wide Suicide/Crisis Flow chart.

Protection against risk associated with self-report questionnaires, clinical interview, and assessment. As discussed above, completion of clinical interviews and self-report questionnaires typically carry a very minimal risk to participants. The information that is being collected is information that they likely will have discussed with members of the treatment intake team in preparation for beginning PTSD treatment before their referral to the study. Participants will be informed that they may cease participation in the study at any time without impacting their previous compensation or participation in treatment. Additionally, the study environment will be made as comfortable as possible and participants will be given frequent breaks throughout the course of the procedures at each time point.

Additional safety measures. To ensure safety, the following additional steps will be taken: 1) Only patients with PTSD who are willing to receive treatment for their symptoms will be recruited. 2) A careful intake assessment will be conducted and patients in need of immediate psychiatric treatment for severe depression or other conditions will not be enrolled and provided referrals. 3) The study therapists will review all active cases weekly with Dr. Loflin, who will have access to lateral supervision from the mentorship team. 4) All members of the study team will immediately communicate any health or psychiatric-related problems to the PI who will ensure that necessary safety steps are implemented. 5) Participants who are discontinued from the study will be scheduled for a final evaluation within one week and given appropriate treatment referrals. 6) Medical staff will clinically follow participants who are discontinued due to a serious adverse event until the adverse event is resolved or becomes stable. Reasons for discontinuation and referrals made will be documented in the participants' casebooks. 7) Participants will be told they will be contacted for follow-up whether or not they complete the trial. 8) Participants will be provided psychoeducation on cannabinoids and PTSD to reduce the likelihood that they will initiate cannabis use following termination from the study. 8) To ensure safety with service delivery via teleconference, study staff utilizing telehealth will follow the Standard Operating Procedures Manual developed by Peter Shore for Home-Bases Telemental Health in VISN 20. For all practical purposes, the provision of mental health services by telemedicine is considered routine clinical care within the VHA.

Section 17 - Potential Benefits

17) Discuss benefits that may be gained by the subject as well as potential benefits to society in general (see ? for guidance)

The potential benefits for participants include decreased distress related to PTSD and improved quality of life. Study of the effectiveness of Cannabidiol and PE will also benefit individuals who have PTSD and society more generally by providing information about how to improve PE therapy and identification of new targets for development of novel psychopharmacology.

Section 18 - Risk/Benefit Analysis

18) Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

The potential benefits of improving treatment of PTSD outweighs the potential risks of this study.

Section 20 - Compensation for Participation

20) Provide all details and justifications of the compensation plan. See ? for detailed requirements.

Participants will be compensated $25 for the 1st post-treatment assessment (at the end of

treatment), $25 for your 2nd post-treatment assessment (1 month after completing treatment), and $25 for your 3rd post-treatment assessment (3 months after completing treatment). Therefore, Veterans will be compensated up to $75 for your time and effort in completing the follow-up assessments after treatment has concluded. Compensation is needed to provide incentive for participants to complete follow-up measures after treatment has concluded.

Section 21 - Responsibilities and Qualifications

Here are the identified study staff members

Catherine R. Ayers, PhD

Abigail Candare Angkaw, PhD, Brian Martis, MD, Brittany C Davis, Murray B. Stein, MD, Scott Christian Matthews, MD, Sonya B. Norman, PhD, Tina Louise Mayes, PhD, Alan R Gonzalez, Brian H. Blanco, MSW, Chad Vacco, Jae Eun Park, James O. E. Pittman, PhD, Julie M. Holcomb, Arthur L. Brody, MD, Emily R. Wilhite, PhD, Steven F. Huege, MD, Alexis Carty-Campbell, Kira Renee Abirgas

21) For each staff member listed above, describe their role and qualifications. Also indicate which of the study staff are authorized to obtain consent, when applicable to the study.

Catherine Ayers, PhD (Principal Investigator) - Dr. Ayers will be responsible for oversight of all study-related activities.

Brian Martis, MD (Co-I) - Dr. Martis will take on responsibility for study-drug related activities in the trial. Dr. Martis will be the DEA schedule 1 registration holder.

Sonya Norman, PhD (Co-I) - Dr. Norman is a VA Merit-funded Investigator at VASDHS and will be providing expertise on PE delivery within in psychotherapy trials.

Abigail Angkaw, PhD (Co-I) - Dr. Angkaw will provide supervision for all assessment within the trial.

Emily Wilhite, PhD (research psychologist) - Dr. Wilhite will provide supervision of PE and supervise all trainee therapists on the trial.

Scott Matthews, MD (study physician) - Dr. Matthews will be responsible for training the study NP and will also act as a a physician on the study. He will provide prescription recommendations for participants to receive study drug under the PI's research schedule I registration (as an authorized user).

Steven Huege, MD (study physician) - Dr. Huege will be a physician on the study and provide prescription recommendations for participants to receive study drug under the PI's research schedule I registration (as an authorized user).

Arthur Brody, MD (study physician) - Dr. Brody will be a physician on the study, and provide prescription recommendations for participants to receive study drug under the PI's research schedule I registration (as an authorized user).

Brittany Davis, PhD (research psychologist) - Dr. Davis will be responsible for Prolonged Exposure fidelity efforts and clinical supervision for therapist trainees.

Tina Mayes, PhD (research psychologist) - Dr. Mayes will deliver psychotherapy to randomized participants on the trial and/or provide clinical supervision for therapist trainees, as well as provide assistance with study regulatory processes.

James Pittman, PhD (research psychologist) - Dr. Pittman will provide clinical supervision for therapist trainees.

Julie Holcomb, MS - Ms. Holcomb will be responsible for administrative and research support for the study, including obtaining informed consent from participants, as well as deliver structured outcome assessments with blinded study participants.

Jae E. Park - Ms. Park will act as an assessor for the study. She will conduct outcome assessments with study participants.

Kira Abirgas - Ms. Abirgas will act as an assessor for the study. She will conduct outcome assessments with study participants.

Alexis Carty-Campbell, MSW - Ms. Carty-Campbell will be responsible for psychotherapy under supervision and administrative and research support for the study, including obtaining informed consent from participants, as well as deliver structured outcome assessments with blinded study participants.

Brian Blanco, LCSW - Mr. Blanco will deliver psychotherapy to randomized participants on the trial.

Chad Vacco, CMHC - Mr. Chad Vacco will be responsible for psychotherapy under supervision and administrative and research support for the study, including obtaining informed consent from participants, as well as deliver structured outcome assessments with blinded study participants.

Alan Gonzalez, PhD - Mr. Gonzalez will deliver psychotherapy to randomized participants on the trial.

Section 22 - Bibliography

22) List relevant articles that the IRB can use to provide necessary background for the protocol. Do not include an extensive NIH-grant-style bibliography. (Up to 5 recommended, but use more if needed to support the protocol or citations above.)

1. Loflin, M. J., Babson, K. A., & Bonn-Miller, M. O. (2017). Cannabinoids as therapeutic for PTSD. Current opinion in psychology, 14, 78-83.

2. Krystal, J. H., Davis, L. L., Neylan, T. C., Raskind, M. A., Schnurr, P. P., Stein, M. B., ... & Huang, G. D. (2017). It is time to address the crisis in the pharmacotherapy of posttraumatic stress disorder: A consensus statement of the PTSD Psychopharmacology Working Group. Biological psychiatry, 82(7), e51-e59.

3. Blechert, J., Michael, T., Vriends, N., Margraf, J., & Wilhelm, F. H. (2007). Fear conditioning in posttraumatic stress disorder: evidence for delayed extinction of autonomic, experiential, and behavioural responses. Behaviour research and therapy, 45(9), 2019-2033.

4. A Rabinak, C., & Phan, K. L. (2014). Cannabinoid modulation of fear extinction brain circuits: a novel target to advance anxiety treatment. Current pharmaceutical design, 20(13), 2212-2217.

5. Machado Bergamaschi, M., Helena Costa Queiroz, R., Waldo Zuardi, A., & Crippa, A. S. (2011). Safety and side effects of cannabidiol, a Cannabis sativa constituent. Current drug safety, 6(4), 237-249.

Section 23 - Sponsors and Collaborators

23) Clarify any industry financial or other support (e.g., NIH funds the study or Company X provides the assay kits). Identify non-VA Research collaborators and their role in this protocol, including whether or not they have access to subjects or identified data.

We have no additional financial support to disclose.

Igor Grant, MD, University of California San Diego - Dr. Grant is a non-VASDHS collaborator on the study and will provide consultation on conducting cannabinoid clinical trials as needed. Dr. Grant will not have access to identifiable data.

Mohini Ranganathan, MD, VA Connecticut Healthcare System & Yale University School of Medicine - Dr. Ranganathan is a non-VASDHS collaborator on the study and will provide consultation on the study drug, CBD, as needed. Dr. Ranganathan will not have access to identifiable data.

Mallory Loflin, PhD, University of California San Diego - Dr. Loflin is a non-VASDHS collaborator on the study and will provide consultation on the study design as needed. Dr. Loflin will not have access to identifiable data.

In the submission form, upload a copy of the grant, subaward, CRADA, etc. as appliable to the study.

Section 25 - Impact on Clinical Services

25a) Which VA Clinical Services participate in the performance of the project? (NOTE: All clinical trials and any use of clinical services will require project review and approval by the Office of Research Agreements Management (ORAM) to assure availability of those clinical resources. Prior discussion with the appropriate clinical service chief is strongly encouraged)

Check all that apply

- [ ] Pharmacy
- [x] Laboratory
- [ ] Cardiology
- [ ] Radiology
- [ ] Nursing
- [ ] Pathology
- [ ] Nuclear Medicine
- [ ] MAS (Charts)
- [ ] Other (list below)

25b) Describe the specific impact or service that will be provided for this protocol.

The VA Lab will process all safety-related laboratory blood and urine samples.

Section 27 - Privacy, Confidentiality, and Information Security

27a) Provide a brief description of how participant privacy and confidentiality will be protected in this study. Describe the circumstance under which it may be possible for a research team member to identify subjects and any related protections or assurances to prohibit or avoid identification. Describe how the number of people with access to identifiers for research purposes is limited in order to protect a participant's privacy.

All participant forms, tracking sheets, etc. are de-identified. Only the identification key can connect participant identifying information with their participant ID number. Only the study PI and coordinator have access to this key.

27.b) Entry of a CPRS Research Informed Consent Note is required when subjects will be admitted as inpatients or treated as an outpatients for research *and* the study involves research medical care or may affect medical care.

- ***If a Research consent Note is required, then a Research Progress Note should also be entered for each procedure or intervention.***
- ***Scanning the Consent and HIPAA Authorization into CPRS is not required. Linking the Consent to the Research Informed Consent Note may be permitted and can be useful for trials involving the Research Pharmacy or when research will be performed in conjunction with clinical procedures.***
- ***For Non-Veterans, if Research Informed Consent Notes are entered, then the NOPP Acknowledgment must be scanned into the record. Otherwise a copy of the signed NOPP must be retained with the Investigator's research records and a copy sent to the Privacy Officer; see the ? Help for more information.***

27.b1) Is entry of CPRS notes required based on the above criteria?

- (•) CPRS notes are needed for ALL subjects
- ( ) CPRS notes are needed for SOME subjects

○ CPRS notes are NOT needed for any subjects

27c) Select the VA Sensitive Information (VASI) use category

○ This study does not collect or use any VASI
○ This study uses but does not save, collect, copy, or record VASI
◉ This study does collect or record VASI

Section 27.1 VA Sensitive Information (VASI)

27.1a) For each type of VASI, indicate all that apply:

Indicate which of the following will be collected/recorded:

☑ Protected Health Information (PHI)
☑ Names
☐ Device identifiers and serial numbers
☐ E-mail addresses
☐ Medical record numbers
☐ URLs (Universal Resource Locator)
☐ All elements of dates (except year) or any age over 89
☐ Health plan beneficiary numbers
☐ IP Addresses (Internet Protocol)
☑ Telephone numbers
☑ Account numbers
☐ Biometric Identifiers including finger and voice print
☐ Fax numbers
☐ Certificate or license numbers
☐ Full face photographic images and comparable images
☐ All geographic subdivisions smaller than a state
☐ Vehicle ID and serial numbers including license plate numbers
☑ Social security numbers or scrambled SSNs (describe below)
☐ Other unique identifying number, characteristic, or code (describe below)

27.1a1) Describe why SSN are needed for this study

Participants' last four of their SSNs are needed to be able to access their CPRS medical chart.

27.1b) Consent Forms and/or HIPAA Authorization

◉ Yes ○ No

27.1c) Images with personal identifiers are used for this study (x-rays, MRI images with patient names, record numbers, dates, etc.)?

○ Yes ◉ No

27.1d) Photos with faces or audio video recordings are used for this study.

○ Yes ◉ No

27.1e) Biological specimens with identifiers are used for this study.

◉ Yes ○ No

Section 27.2 Data Collection, Tools, and Resources

27.2a) Will any specially obtained software be used?

○ Yes ◉ No

27.2b) Will any mobile devices (laptop, tablet, portable hard-drive, etc.) be used in support of this study?

◉ Yes ○ No

27.2b1) Provide details of the device/s. Indicate whether the device is FIPS 140-2 encryption validated and confirm that the device is listed in the VA EIL. Provide details regarding the nature of the data that will be stored or transmitted on the device and confirm whether a copy of all data will be stored on the VA network.

Study staff will deliver psychotherapy using secure video conferencing on their personal laptops. No data from the secure video conference will be stored on the device.

27.2c) Does the study require use of an electronic data capture system?

○ Yes ◉ No

27.2d) Will any other web-based applications be used (e.g., for recruitment, completing online questionnaires, or processing data)?

◉ Yes ○ No

27.2d1) Provide the web address, details regarding their security features, the nature of the data involved, and the research purpose. Also include a description of how VA retains a copy of the data generated using these tools.

Due to recruitment challenges and competition with other PTSD-related studies, the lab will recruit Veterans through the community directly using Build Clinical. VASDHS staff will collect all study data directly from participants. Therefore, due to COVID-19, in addition to items specified above, VASDHS staff will also be responsible for the below:

1. Recruitment of Veterans through various online community platforms

2. Determining preliminary eligibility for the study.

BuildClinical (https://www.buildclinical.com/) will collect name, phone number and email and share that with the investigator. The information is transferred through a website where the data

is encrypted at rest and in-transit. BuildClinical will destroy the data after the work has concluded with the investigator.

BuildClinical's Secure Socket Layer (SSL) software, which encrypts all inputted information, keeps information private and HIPAA compliant. Their backend servers are stored in the USA at some of the most secure data centers in the world through Amazon Web Services.

Data elements collected by BuildClinical will consist solely of name, phone number and email. This data is not retained for any other purposes.

The data is provided directly by prospective participants and is passed to the VA for engagement after. No VA data will be transferred to BuildClinical.

Data is transferred through the website in encrypted form. The website is hosted by BuildClinical. No VA data/information will be sent to BuildClinical. This is a recruiting platform only.

27.2e) Will coded data that excludes personal identifiers be used? Coded data excludes *all* HIPAA identifiers (per VHA Handbook 1605.1 Appendix B), including dates

(•) Yes ( ) No

27.2e1) Identify where the code key is stored and in what format (electronic, paper).

The code key is electronic and stored in the PI's R drive, and is password protected.

Section 27.3 Data Sharing and Transportation

27.3a) Does this study involve collecting, sharing or transporting any type of data outside of the local VA?

( ) Yes (•) No

Section 27.4 Research Record Storage and Retention

For each type of record, indicate whether it is collected for this study

27.4a) Hardcopy records/data (includes paper, pictures, film, etc.)

(•) Yes ( ) No

27.4a1) Identify precisely where hardcopy data will be stored to include physical site, building, and room number, etc. For each location identify whether VASI or non-sensitive information is stored at that location. For VASI, identify how the data is secured.

Participant questionnaires and therapist/physician weekly checklists will be stored in PI, Dr. Ayers', locked office in locked filing cabinets (VMRF, Building 13)

27.4a2) Are all of the above locations at VA?

(•) Yes ( ) No

27.4b) Electronic study records (includes computer files, removable disk files, digital files, etc.).

(•) Yes ( ) No

27.4b1) Identify precisely where ***non-sensitive*** electronic records/data will be stored to include the full map drive, network location/server name, etc., and a brief description of what data/information is stored at each location.

Non-sensitive electronic data is stored in the PI's R drive:
\\R01SDCHSM02.R01.MED.VA.GOV\Research\Ayers

27.4b2) Identify precisely where ***VASI*** electronic records/data will be stored to include the full map drive, network location/server name, etc., and a brief description of what data/information is stored at each location.

If no VASI is collected or recorded for this study, simply indicate that the "Study does not collect or record VASI".

Sensitive electronic data is also stored in the PI's R drive, but within password protected files:
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27.4b3) Are any of the locations described in 27.4b outside of the VA Secure Network? *Note: this includes storage on a computer local hard drive.*

( ) Yes (•) No

27.4c) Record Retention - VHA requires compliance with Records Control Schedule (RCS-10) for retention of electronic and hard copy records. Following study closure, these temporary records must be retained for six years and then destroyed. Longer retention may be permitted if required by other Federal regulations or requirements. Will RCS-10 requirements be followed (i.e., 6-year retention)?

(•) I will adhere to VHA Records Control Schedule-10 requirements
( ) I request an exception to RCS-10 requirements

Section 27.5 Additional Privacy or Information Security Details

Provide any other privacy or information security details here.

Modification to telehealth delivery was initiated due on 3/17/2020 to the COVID health emergency to limit in-person contact. No safety-related or security issues have arisen due to this change in procedures.

Section 27.6 Attestations

In the event of real or suspected breach of security, the Information Security Officer, Privacy Officer, VA Police (if appropriate), and the individual's supervisor will be notified within one hour of learning of the event.

(•) Agree ( ) Disagree

Study staff will be up to date on any required VHA Privacy Policy and Information Security training or they will not be allowed access to VA Sensitive Information.

◉ Agree ○ Disagree

Access to research sensitive information, if any, will be removed when study personnel are no longer part of the research team.

◉ Agree ○ Disagree

At least one copy of all study records (whether sensitive or non-sensitive) will be retained under VA control and only destroyed in compliance with the approved Records Control Schedule

◉ Agree ○ Disagree

The VA retains ownership of the research data. Should the investigator leave the VA, custody of the research records will be assigned to another investigator and the Research Service notified in writing, or custody of the research records will be transferred to the Research Service.

◉ Agree ○ Disagree

Section 28 - Protocol Association to New or Existing Project

28) Is this a new R&D Project? Before you go on to complete the *Initial Review Submission Form* (which is used for attachments), please address the association of this Protocol to an R&D Committee Project. This Protocol may represent a new R&D Project, or it may be an additional Protocol under an existing R&D Project (such as when a single grant supports multiple Protocols). Will this Protocol be submitted to the R&D Committee as a new Project?

○ Yes ◉ No

Section 29 - Existing Project Association

29) The associated R&D Project should already exist in the database. Identify the R&D Project(s) that correspond to this protocol.

Project Status	Proposal Number	Project Title	Principal Investigator
No Projects are Linked to this Study			

The Protocol Application is now complete for a Protocol attached to an existing Project.

Next you will go on to the Initial Review Submission Form. This form is used to collect the Application and any other needed attachments for submission to the IRB for review.

Press *Save and Continue*