PROTOCOL

Neurosteroids as Novel Therapeutic Agents for PTSD in OEF/OIF/OND Veterans

PI: Steven T. Szabo, MD, PhD

NCT03491007

Purpose

This is a parallel-group, double-blind, placebo (PBO)-controlled, randomized Phase 2 pilot study using adjunctive dehydroxyepiandrosterone [DHEA (400 mg)] will be evaluated to establish Proof of Concept (POC) for this agent in Veterans with PTSD.

Our first objective is POC target engagement to evaluate a one-time adjunctive oral dose of DHEA (400 mg) relative to PBO on the neuronal circuity of fear-anxiety-emotion connectivity. This will be achieved by comparing pre- to post-treatment changes in amygdala-hippocampal functional connectivity to DHEA and PBO during fMRI activation. We hypothesize that compared with PBO, DHEA will increase task-associated fMRI functional connectivity between the amygdala and hippocampus (primary outcome).

Our second objective is to determine if an 8-week treatment with adjunctive DHEA is superior to PBO in reducing symptoms of PTSD (CAPS-5) and depression (BDI) in OEF/OIF/OND Veterans, and enhancing resilience (CD-RISC). We hypothesize that 400mg DHEA will result in reduced PTSD and depression symptom severity relative to PBO, as determined by a pre- to post-treatment decrease in CAPS-5 and BDI scores, respectively, with enhancement in resilience scores using the CD-RISC at 6-weeks.

Our third objective is to evaluate the impact of DHEA relative to PBO on serum neurosteroid levels in OEF/OIF/OND Veterans with PTSD. We hypothesize that DHEA will result in a statistically-significant increase in serum neurosteroid levels (DHEA, DHEAS, androsterone) relative to PBO, as determined by pre- to post-treatment reductions in PTSD symptoms severity. This association will be evaluated by correlating neurosteroid levels with PTSD, depression, and resilience scores over 6 weeks of treatment.

Our exploratory objective is to determine preliminary evidence for an association of fMRI and myelin integrity measures of fear-anxiety-emotion circuits with serum neurosteroid levels and treatment response to DHEA. Changes in myelin integrity following DHEA treatment will be evaluated using novel susceptibility diffusion imaging [STI]), as DHEA impacts myelination in preclinical rodent models. We will also determine if serum neurosteroid levels are correlated with myelin integrity on STI. We hypothesize that fMRI and myelin integrity of fear-anxiety circuits will correlate with serum neurosteroids and treatment response.

Background and Significance

Background: Posttraumatic stress disorder (PTSD) is extremely common among Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) Veterans, impacting approximately 20% of OEF/OIF/OND Veterans enrolled in VA healthcare. Pharmacological management of PTSD is unfortunately frequently suboptimal, and many OEF/OIF/OND Veterans experience persistent and

unalleviated symptoms. Currently there are *only two* FDA-approved pharmacological treatments for PTSD (sertraline and paroxetine, each approved ~15 years ago). **There is thus an acute and urgent need for the development of new pharmacological treatments for PTSD that are effective and well-tolerated.** Neurosteroids are endogenous molecules that are enriched in human brain, and many neurosteroids exhibit anxiolytic-like actions and modulate the HPA axis. In addition, neurosteroids such as dehydroepiandrosterone (DHEA) are immediately accessible for translation to clinical trials, as DHEA is available over-the-counter as a dietary supplements in the U.S. Neurosteroid interventions may represent an important new lead for the management of PTSD symptoms in OEF/OIF/OND Veterans. Based on our preliminary data in 660 OEF/OIF/OND male Veterans (indicating DHEAS levels as significantly reduced in PTSD) and rodent data from multiple research groups demonstrating anxiolytic actions of neurosteroids.

Several groups of investigators have reported that serum DHEA and/or DHEAS levels are altered in PTSD (Kanter 2000; Spivak et al., 2000; Sondergaard et al., 2002, and Rasmusson et al., 2004; Yehuda et al., 2006). Possibly contributing to somewhat mixed findings, prior studies contained relatively small numbers of participants with PTSD (the largest study reports findings for 52 participants with PTSD), and few studies controlled for age and smoking in their analysis plans (two critical co-variates). In contrast, our DHEAS findings support the current project include 213 OEF/OIF/OND Veterans with PTSD, controlling for age and smoking (we report DHEAS levels in a total over 660 OEF/OIF/OND Veterans). It has been hypothesized that greater DHEA release following ACTH administration may represent a compensatory response to severe stress (Rasmusson et al 2004). In a small sample of untreated Israeli male combat Veterans with chronic PTSD, higher plasma DHEA and DHEAS levels were observed in comparison to healthy male control subjects without PTSD (Spivak et al., 2000); however, it is unknown if DHEA and/or DHEAS levels were correlated with PTSD symptoms specifically in that investigation. Perhaps even more importantly, serum DHEAS levels are positively associated with resilience in several recent studies (Petros et al., 2013; Radant et al., 2001, Taylor 2013), and a series of innovative investigations in Special Forces also support the concept that DHEAS is associated with enhanced resilience (Morgan et al 2009, 2004). It is thus possible that treatment with DHEA has the potential to increase resilience among OEF/OIF/OND Veterans with PTSD. Although difficult to quantify as a variable that is sensitive to change, initial studies suggest that the Connor-Davidson Resilience Scale (CD-RISC) may be a useful tool to begin to understand the construct of resilience (Davidson et al 2008), as the neurobiological underpinnings of resilience continue to be elucidated (McEwen et al 2015, Russo et al 2012). Recent neuroimaging evidence also supports a possible role for DHEA in the treatment of PTSD. Specifically, efforts in collaboration with investigators at the University of Michigan (Dr. Rebecca Sripada and Dr. Israel Liberzon) demonstrate that *one-time DHEA administration (400 mg orally) appears to alter functional connectivity between the amygdala and the hippocampus (Sripada et al 2013, 2014),* brain regions that are implicated in the pathophysiology of PTSD. *In*

addition, peripheral DHEA levels were associated with neuroimaging parameters on fMRI (Sripada et al 2013, 2014). It is thus possible that characterization of serum neurosteroids during fMRI tasks implicating anxiety behaviors may help clarify the neurobiological mechanisms of the anxiolytic actions of these molecules. DHEA administration in humans (healthy controls) was also associated with greater activity in anxiety regulatory processes and with reductions in negative emotion circuits (Sripada et al., 2013). These fMRI findings following DHEA administration support the possibility that Veterans with PTSD and co-occurring symptoms may benefit from the enhancement of levels of this neurosteroid (Sripada et al., 2014). Resting state brain activity in response to DHEA administration both reduces amygdala and dorsolateral prefrontal cortex connectivity, and shifts the balance between salience and default networks for anxiety reduction (Sripada et al., 2014b). Recently, a fear generalization paradigm in Veterans with PTSD using fMRI indicated that amygdala-thalamus and amygdala-calcarine sulcus connectivity are increased, which may represent neurobiological correlates of triggering PTSD symptoms by threat cues resembling index trauma (Morey et al., 2015). Serum levels of DHEAS in healthy subjects also negatively correlate with fear-potentiated startle (Grillon et al, 2006), an experimental paradigm viewed largely as one with possible relevance to PTSD (Norrholm et al., 2011).

The majority of research in Veterans with PTSD that has focused on white matter assessment has utilized diffusion tensor imaging (DTI). Reductions in fractional anisotropy in cingulum (white matter fibers that project from the amygdala to prefrontal cortex; involved in emotion processing) and other areas near the prefrontal cortex (Kim et al., 2005; 2006; Schuff et al., 2011; Zhang et al., 2011) have been reported in patients with PTSD. Overall, however, DTI studies in PTSD have been somewhat mixed (Daniels et al., 2013 review). Technological limitations of DTI may be contributing to these disparate results among PTSD investigations, as DTI lacks the resolution and sensitivity required for the optimal assessment of white matter microstructure (Cao et al., 2014). As an exploratory aim, we are thus proposing to use a new neuroimaging technology - quantitative susceptibility mapping and susceptibility tensor MRI (QSM/STI), which provides superior resolution and sensitivity to non-invasively assess *in vivo* fiber tract alterations in Veterans with PTSD. This is a promising new technology created by our collaborator at Duke, Dr. Chunlei Liu.

Significance: This project may lead to a novel new therapeutic for OEF/OIF/OND Veterans with PTSD that is safe, efficacious, inexpensive, and well-tolerated. It could also identify serological and/or neuroimaging biomarkers for therapeutic response, potentially leading to personalized treatments for Veterans with PTSD. There is currently a paucity of safe and effective pharmacological agents for the treatment of PTSD, a disorder that impacts large numbers of OEF/OIF/OND Veterans and is frequently accompanied by co-occurring conditions that include depression and TBI. DHEA may be a promising new therapeutic in PTSD, as it demonstrates anti-anxiety effects in rodent models and fear-anxiety circuit regulation in humans. Based on our

preliminary data in OEF/OIF/OND Veterans, treatment with DHEA has potential as a safe, effective, well tolerated, immediately accessible, and inexpensive treatment for PTSD and multiple associated symptom domains.

Design
This is a parallel-group, double-blind, placebo (PBO)-controlled, randomized Phase 2 pilot study using adjunctive dehydroxyepiandrosterone [DHEA (400 mg)] will be evaluated to establish Proof of Concept (POC) for this agent in OEF/OIF/OND Veterans with PTSD.

Aim 1. To determine the effects of an acute oral administration of adjunctive DHEA (400 mg) on neuroimaging measures of functional connectivity. We will conduct a parallel-group, double-blind, placebo (PBO)-controlled, randomized Phase 2 pilot study with one-time oral DHEA 400 mg in target engagement. To establish POC, we seek to determine if DHEA is superior to PBO in target engagement of neural circuits related to fear-anxiety-emotion regulation using the shifted-attention emotion appraisal (SEAT) paradigm (see below). Following a two-week placebo lead-in period (all participants), subjects will be randomized to receive a one-time oral dose of adjunctive DHEA (400mg) or PBO. Neuroimaging will occur 2 hours following drug administration for peak level effects on target engagement of fear-anxiety emotion circuit connectivity, as previously conducted by Sripada, Marx, Liberzon et al).

Primary Outcome Measure The primary outcome measure will be functional connectivity between amygdala-hippocampus assessed using fMRI based SEAT Paradigm as a target engagement endpoint. The fMRI based SEAT Paradigm has been previously validated to an acute administration of DHEA (400 mg) in healthy volunteers by members of my career development team, Drs. Liberzon and Marx (Sripada et al., 2013).

Aim 2. To evaluate a sustained 6-week adjunctive DHEA treatment compared to PBO on PTSD symptoms severity (CAPS-5), co-occurring depression (BDI), and other secondary outcome measures such as resilience (CD-RISC). Following randomization to acute DHEA administration or PBO the subject will continue to receive study drug for 6 weeks (for DHEA, fixed escalating doses: 100 mg per day in divided doses x 1 week, followed by 200 mg per day in divided doses x 1 week, followed by 400 mg per day in divided doses x 4 weeks).

Secondary Outcome Measures
Secondary outcome measures will include: Change in the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). The CAPS-5 is a structured interview for assessing PTSD diagnostic status and symptom severity. The clinical coordinators in our research group have been trained in the administration of the CAPS by Frank Weathers, PhD. We will use a threshold of ≥ 33 on the CAPS-5, consistent with recently reported pharmacological intervention studies in Veterans with combat PTSD (Sullivan et al

2016; ACNP annual meeting). Depression symptoms (as assessed with the Beck-Depression Inventory (II), HAM-D, and NIH derived PROMIS scales for depression; anxiety symptoms, as assessed by the HAM-A and PROMIS-Anxiety scale; overall assessment of psychological functioning, as assessed by the SCL-90R CGI component; pain symptoms, as assessed by the PROMIS-Pain Intensity scale and Brief Pain Inventory (BPI); sleep disturbance, as assessed by the PROMIS-Sleep Disturbance scale; anger, as assessed by the PROMIS-Anger scale; impulsivity as assessed by the Barrat Impulsivity Scale (BIS-11) and resilience, as assessed by the Connor-Davidson Resilience Scale (CD-RISC).

Aim 3. To determine the metabolic profile of DHEA in order to identify specific downstream neurosteroid alterations that may contribute to its clinical effects using mass spectrometry based techniques. We will use highly sensitive and specific mass spectrometry-based technology for neurosteroid quantifications, as previously described and as outlined below. While neurosteroids such as DHEA and DHEAS have been measured in serum by immunoassay for many years, some high-impact journals are now requiring mass spectrometry approaches - and will no longer publish papers that utilize other methods such as immunoassay (as of January 1, 2015 for the *Journal of Clinical Endocrinology and Metabolism*). Thus, the reliable quantification of the neurosteroids proposed in this study requires mass spectrometry-based techniques. The PI's primary mentor, Dr. Chris Marx, has optimized and validated a highly sensitive and specific GC/MS method for quantifying neurosteroids (preceded by HPLC purification), and her laboratory will donate these mass spectrometry analyses for this CDA-II application. This equipment is located in her Durham VA laboratory and dedicated solely to neurosteroid analyses. Dr. Marx has conducted numerous clinical studies in which she has quantified neurosteroid profiles following pregnenolone administration, and determined that increases in neurosteroids post-treatment appear to be predictive of treatment response (Marx et al, 2016 – pregnenolone in mild TBI; Marx et al 2014 – neurosteroid intervention in schizophrenia; Brown et al 2014 –bipolar depression and pregnenolone; Marx et al 2009 – neurosteroid intervention in schizophrenia). We will conduct neurosteroid analyses in approximately 40 participants across 5 visits (approximately 400 neurosteroid assessments, although it is anticipated that there will be a 20% drop-out rate among the total of 40 participants who are randomized).

Tertiary Outcome Measures
Tertiary outcome measures will include: Radioimmunoassay for Neurosteroid quantifications of serum levels of DHEA, DHEAS, and androsterone. These neurosteroids will be correlated with symptomatic rating scales.

Exploratory Aim: To investigate if treatment with DHEA impacts myelin integrity (as assessed by susceptibility tensor imaging/STI), and to examine myelin integrity as a possible biomarker for PTSD treatment response. We will also determine if serum neurosteroid levels are correlated with neuroimaging parameters utilizing STI (QSM)

and fMRI. We estimate that approximately 80% of all participants enrolling in the proposed randomized controlled trial will also receive neuroimaging to an acute administration of DHEA or PBO placebo and post-treatment with DHEA or PBO. We thus anticipate that approximately 32 or more participants will undergo neuroimaging to an acute treatment with DHEA or PBO and at study completion (a minimum of approximately 16 participants per group in this pilot POC study). Susceptibility tensor imaging is a new methodology created by our collaborator at Duke, Dr. Chunlei Liu.

Exploratory Outcome Measures

The exploratory outcome measures will include: STI (myelin integrity); fMRI measures (amygdala and hippocampal connectivity); serum neurosteroid levels (DHEA; DHEAS; androsterone); PTSD symptom severity (CAPS-5); and other rating scale measures of co-occurring symptoms.

Experimental Design: The proposed design is a parallel-group, double-blind, PBO-controlled, randomized Phase 2 pilot study of adjunctive DHEA vs. PBO to determine target engagement of fear-anxiety-emotional circuit regulation and potential efficacy of DHEA in 40 OEF/OIF/OND Veterans with PTSD. Subjects will be randomized to receive a one-time oral dose of DHEA (400mg) or PBO and sustained administration of the study drug for 6 weeks. There will be a 2 week placebo lead-in period [all participants], followed by subjects continuing in the randomization block of DHEA or placebo for 6 weeks following acute administration). 40 subjects will be randomly assigned to one of two groups; assuming approximately a 20% drop-out rate, we anticipate that 32 participants will have at least one visit post-randomization and will be included in the statistical analysis plan (approximately 16 participants per group); a modified intent-to-treat approach will be utilized. The research pharmacist at the Durham VA will be responsible for randomization of participants in this study; a randomized block design will be utilized (4 participants).

Shifted-Attention Emotion Appraisal (SEAT) Paradigm: In order to investigate the brain basis of fear-anxiety emotional response and regulation, Dr. Liberzon's laboratory has developed an emotion appraisal task (Klumpp et al, 2011; Sripada et al., 2013), modifying the task of Anderson et al (2003), and collaborating with Dr. Chris Marx to evaluate the impact DHEA in healthy volunteers. My mentoring and collaborative team has thus demonstrated that the SEAT paradigm is an effective probe of neurosteroid regulatory effects (Sripada et al, 2013). The SEAT task uses compound stimuli that include emotional faces and neutral scenes. Stimuli include pictures of faces in front of buildings, as well as 20 pictures of faces or buildings alone. The face pictures represent neutral, angry, or fearful expressions, and the buildings are of indoor or outdoor portraits.

Participants are asked to respond to three different questions, in three different conditions: (1) 'Gender': whether the face is male or female; (2) 'Inside/Outside':

whether buildings are indoors or outdoors; or (3) ‘Like/Dislike': whether the face is liked or disliked. This task probes emotion regulation: (1) implicit emotional processing, (2) attentional modulation of emotion, and (3) modulation of emotion by appraisal. The ‘Gender' condition probes implicit emotional processing, as attention is focused on an emotional face while identifying its gender, and it is established that negative emotional faces induce negative emotions. The ‘Inside/Outside' condition engages attentional modulation of emotion as in focusing attention on the building components superimposed on the emotional face. Attention modulation is recognized as a core component of emotion regulation. The ‘Like/Dislike' condition engages cognitive appraisal of one's emotional/evaluative state and engaging appraisal increases activation of dorsal medial prefrontal cortex (Liberzon et al, 2000; Phan et al, 2004). Behavioral studies of emotional appraisal find that this strategy lowers distress (Lieberman et al, 2011). The ability of DHEA to impact functional connectivity between the amygdala and hippocampus in healthy volunteers undergoing the SEAT paradigm will be evaluated in Veterans with PTSD to an acute target engagement dose of DHEA (400 mg) and following a sustained 6-week treatment.

Risk/Benefit Assessment

1. Human Participants Involvement and Characteristics Research participants will be recruited from Durham VA IRB-approved local advertising (flyers), Durham VA IRB-approved letters (and follow-up phone calls utilizing a Durham VA IRB-approved phone script), the VA Mid-Atlantic MIRECC Repository and Post-Deployment Mental Health Study (which currently contains 3,200 OEF/OIF/OND Veterans; over 94% of these Registry participants have already provided permission to be re-contacted for future research studies), and by referral from their Durham VA medical and behavioral health providers, for a target number of 40 randomized participants; of these 40 randomized participants, it is estimated that at least 32 participants will receive at least one study visit following randomization (20% drop-out assumed). We thus estimate that approximately 16 participants per group will be randomized to either adjunctive DHEA or placebo and will complete at least one study visit post-randomization; these 32 participants will thus be included in the modified intent-to-treat analyses.

Enrolled participants will 1) Be OEF/OIF/OND Veterans; 2) 18 – 65 years of age; 3) Have a diagnosis of PTSD as assessed using the CAPS-5 (minimum CAP-5 score ≥ 33); 4) Be on a stable medication regimen (no change in past 4 weeks); 5) Have no anticipated change in medications during study; 6) Only OEF/OIF/OND Veterans will be enrolled into this study; 7) No non-Veteran participants will be included; and 8) fully participate in the informed consent process.

2. Sources of Materials. All of the data for this study will be collected specifically for research purposes. All study data will be kept in a secured file to which only study investigators and study personnel will have access. Each participant will be assigned a

study number and all data and specimens will be identified by that study number. The list linking this number to participant identity will be kept in a file on a secure, password-protected computer to which only the Principal Investigator and study staff have access. Five sources of data will be maintained for this study and all collected information will be de-identified: a) the initial telephone screening, b) diagnostic interviews, c) physical examinations, d) psychiatric rating scales (both self-report and clinician administered, e) neurosteroid profiles and other laboratory measurements.

3. Potential Risks
a) *Physical Risk:* Physical risks associated with participation in this study include the risks of drawing blood and adverse effects from the study medication. Possible side effects from drawing blood include bruising, bleeding, or pain at the injection site, and (rarely) fainting and infection. Blood draws at each visit are minimal risk. In terms of the study medication, DHEA has been well-tolerated at doses up to 1,600mg per day over several weeks of administration. Side effects exceeding placebo that have occurred in previous clinical trials with DHEA have included mild acne, hirsutism, and decreased HDL levels. If a participant develops side effects at any dose, they may be brought down to the previously tolerated dose or they may be withdrawn from the study and, as by the PI or MD members of the research team (Drs. Szabo, Marx, and Hertzberg), referred for evaluation and treatment. We will perform laboratories at each study visit (Chem 7, CBC, GI Panel) and an ECG at study entry and completion. No serious adverse events have been reported to date utilizing DHEA (sold as a dietary supplement over the-counter in the U.S.). Of note, participants will NOT be tapered from their current stable medication regimen; DHEA will only be “added on” to treatment-as-usual.

Similar to multiple prior investigations that have utilized at least the proposed dose and duration of DHEA administration in patients with psychiatric illness, it is important to obtain a personal and family history of breast, uterine, and prostate cancer in these individuals. For example, in the report by Bloch et al., 1999 published in *Biological Psychiatry* entitled "Dehydroepiandrosterone Treatment of Mid-Life Dysthimia" and Schmidt et al., 2005 published in *The American Journal of Psychiatry* entitled "Dehydroepiandrosterone Monotherapy in the Treatment of Midlife onset Major and Minor Depression" (conducted at the NIMH), men and women up to the age of 65 needed to be physically healthy and exclusion criteria included symptoms of prostatism, family history of breast cancer, and abnormal laboratory mammograms or gynecological examination findings. For our study, we thus plan to follow these same exclusionary criteria, specifically: 1.) Abnormally elevated PSA at screening will be exclusionary in males. In men below 50 years of age a serum value of PSA < 2.5 ng/ml is considered normal and will be exclusionary if greater than this value. Men 50 years and older having a serum PSA of greater than 4.0 ng/ml will be exclusionary. These are generally considered to be conservative values as PSA cut-off scores and will be used to guard against enrolling an individual than may have an undiagnosed prostate cancer. 2.) Female participants must have had a normal mammogram within the last year (if older

than 40), and 3.) Female participants must have had a normal pelvic exam in within the last year. The National Cancer Institute does not recommend screening for uterine cancers and the American Cancer Society advocates that at the time of menopause women should report any unexpected bleeding or spotting to their physician. Given that endometrial biopsy and transvaginal ultrasound are not appropriate screening methods according to the National Cancer Institute, during the screening interview for this study we will obtain a detailed history related to onset of menopause (if appropriate), and whether bleeding or spotting has occurred since then; unexpected bleeding or spotting will be exclusionary. This will help guard against placing a subject in the study that may have an undiagnosed uterine cancer.

b) *Emotional Distress:* Participants may potentially experience emotional distress as a result of participating in this study. The study procedures could potentially lead to emotional distress from discussing trauma histories during PTSD assessments. Being placed in an MRI machine can at times induce feeling associated with claustrophobia. Each participant will be closely monitored for emotional distress, suicidal ideation and homicidal ideation at screening and each study visit (the Columbia Suicide Severity Rating Scale) will be administered at each study visit). If a participant becomes significantly distressed or their psychiatric symptoms worsen and intervention is deemed appropriate, they will be walked to the emergency psychiatry clinic (on site) for evaluation and treatment (including potential hospitalization). The study medication will be discontinued and they will be withdrawn from the study if the patient is hospitalized, or if medical and/or psychiatric issues take precedence over study participation.

c) Safety Plan: We will implement a rigorous safety plan that encompasses close monitoring and care of medical issues in this study. The conduction of safety monitoring includes the following procedures outlined in the Physician On-Call Cascade. The FDA has issued an IND number #129,623 for the conduction of this study; once the study has been approved by the Durham VA IRB, we will enroll the first participant; we will follow all FDA guidelines for annual progress, adverse event, and other reporting procedures for this outpatient randomized control trial.

Overview of Facilities: The Durham VA Medical Center has acute psychiatric care available onsite 24 hours per day/7days per week provided by the Psychiatric Emergency Care (PEC) team, which is staffed by a Duke psychiatry resident, psychiatric social worker, and VA psychiatry attending. Should participants require immediate psychiatric care, they will be escorted to the PEC for further assessment and care. Dr. Szabo is the PEC attending once a week.

Vital Sign and Side Effect Monitoring: Vital signs will be assessed at each study visit. Blood pressure greater than 160/95 will addressed by a study physician. If vital sign abnormalities require same-day medical follow-up, the patient will be assessed in the Durham VAMC Acute Care Clinic/Emergency Department. Patients will receive an extensive side effect scale at each study visit and will be queried regarding potential

side effects during follow-up telephone phone calls (after study medication has been discontinued). Potential side effects will be monitored closely by the PI and MD members of the research team (Drs. Szabo, Marx, and Hertzberg). A participant may be asked to return for an unscheduled appointment to assess a potential side effect if clinically indicated.

Laboratory Results: Patients will receive a CBC, clinical chemistry panel, and GI panel at each study visit. Laboratory results that are outside of the normal range will be addressed by a member of the physician team. All labs will be reviewed by the study physician within 24 hours, and clinically relevant laboratory abnormalities will receive prompt follow-up attention. The Durham VA's Clinical Chemistry Laboratory will page the PI with any "alert" laboratory values that require immediate attention. Female patients will receive a serum pregnancy test. Male participants will receive a prostate specific antigen test (PSA).

ECG Monitoring: Final ECG readings issued by a cardiologist are available from the Durham VAMC Heart Station within 48 hours. Each patient will have an ECG at baseline and completion of the study. If the patient does not complete the study and withdraws prior to the final study visit, every effort will be made to obtain an ECG at the patient's last study visit. Any abnormal ECG findings will be discussed with a VA cardiologist by study physician (Dr. Szabo, Marx, or Hertzberg). If additional medical follow-up is suggested, we will proceed according to their recommendation. Additional potential follow-up actions may include, but are not limited to: Primary care provider notification by pager or email, the placement of a cardiology consult, a repeat ECG (if lead placement is suspected to have been suboptimal, for example), or referral to an onsite Acute Care Clinic/Emergency Department for assessment.

B. Adequacy of Protection from Risks

1. Recruitment and Informed Consent. Study participants who are receiving outpatient care will be recruited from the Durham VA Medical Center by local advertising (flyers placed in VA-approved areas), via the VA Mid-Atlantic MIRECC Repository and Post-Deployment Mental Health Study, and by referral from Durham VA psychiatrists, PCPs and other providers. Potential participants who are not self-referred will be sent a recruitment letter followed by a phone call from a study member. A participant who is judged likely to meet all of the inclusion criteria and none of the exclusion criteria will meet with a member of the research team to discuss the research protocol, and to determine if the patient is capable of providing informed consent. The participant will be provided with a description (verbal and written) of the informed consent form, which includes the risks along with procedures to minimize these risks, and the participants' rights and responsibilities.

Participants will be given the opportunity to read the consent form and ask questions. Participants will be assured that participation in this research study is voluntary and that they may withdraw from the study at any time without adversely affecting their medical

care or any benefits they might be receiving. They may also refuse to answer any research questions during interviews. Participants who are eligible for the study and choose to participate will sign the consent form in the presence of a member of the research team and a witness.

2. Protection Against Risk.
a) *Physical Risk and Participant Safety*: Possible side effects from drawing blood (as mentioned above) will be attended to as usual in the phlebotomy laboratory. If a participant experiences serious adverse effects from the study medication, it will be discontinued and s/he will be withdrawn from the study. The participant will immediately be referred for appropriate evaluation and treatment. All serious adverse effects will be documented and reported as required by the FDA and local IRB committee.

b) *Emotional Distress and Participant Safety*: All participants will be carefully assessed before the study and will be made aware of emergency services. In addition, they will be closely monitored at screening and each study visit. During the informed consent process, they will be advised that the study procedures could potentially lead to distress and that they may withdraw from the study at any time without adversely affecting their medical care or any benefits they may be receiving. If a participant withdraws from the study and they are not currently in psychiatric or medical treatment, they will be referred to the appropriate mental health clinic (MHC, PTSD clinic, etc.) and/or primary care provider. If a participant is significantly distressed during a study visit and intervention is deemed appropriate, they will be walked to the emergency psychiatry clinic onsite for evaluation and treatment (including potential hospitalization if clinically indicated). Dr. Szabo and the physician study team will be available by cell phone (per the schedule outlined below) at all times for any concerns regarding potential worsening psychiatric symptoms, including suicidal and homicidal ideation. In terms of risks to confidentiality, pertinent information regarding potential harm, including suicidal and homicidal intent will be shared as necessary and required by law with clinicians and/or the appropriate authorities. In such circumstances, records may be made available to authorities, even without the participant's consent. Upon completion of the study any participants not currently in psychiatric treatment will be referred for treatment as deemed appropriate.

Medical Monitoring and Physician On-Call Schedule / Cascade:
Physician Cell Phone / Pager
1. Steven Szabo, MD PhD - 919-970-2769
2. Chris Marx, MD MA - 919-323-6205
3. Michael Hertzberg - 919-614-7484

Dr. Steven T. Szabo will be the 1st-call physician for any medical issues involving the proposed randomized controlled trial with an adjunctive neurosteroid intervention. If Dr. Szabo is not immediately accessible within 5 minutes on his cell phone, then Dr. Chris Marx will be called on her cell phone - who will function as the 2nd-line physician if Dr. Szabo is unavailable. Dr. Marx has extensive experience in the conduction of

randomized controlled trials. Should Dr. Marx not be available, the cell phone cascade would then move to the 3rd-line physician, Dr. Michael Hertzberg There will be a master schedule available that adapts the above call-schedule to the annual leave and travel schedules of the individual MDs listed in this cascade. This on-call schedule will be circulated weekly, so that the order of the call cascade is always up-to-date for any particular week (and incorporates any changes that may be necessary secondary to individual MD schedules).

The designated physician on-call will have the following responsibilities: The designated study team MD will conduct physical exams at baseline and study completion, medical chart review, determination of patient eligibility for study entry, review of all clinical laboratory results and ECG tracings within 24 hours (with ECG confirmation by a Durham VA cardiologist), assessments of potential to study medication by reviewing a structured rating assessment administered to each research participant at each study visit and by interviewing and examining the participant as clinically indicated, and will attend to any other medical issues that arise during the course of this study.

Should any emergent issues arise that require immediate medical and/or psychiatric attention, the Durham VA has fully staffed Emergency Department and Psychiatric Emergency Care (PEC) services – which provide acute medical and psychiatric care 24 hours per day/7 days per week. The PEC is staffed by a psychiatry resident, psychiatric social worker, and a VA psychiatry attending, of which Dr. Szabo is available there one day a week. In addition, the Durham VA has a 28 bed, onsite inpatient psychiatric unit, staffed by three VA Mental Health Service Line psychiatry attendings, three Duke Medical Center psychiatry residents, and other mental health care professionals.]

c) *Potential Difficulties and Limitations*: One potential limitation of any pharmacological clinical trial is medication compliance. In order to increase the likelihood of patients taking study medication as prescribed, we will conduct “pill counts” of returned/unused study medication. Patients who miss more than 6 consecutive doses of medication or are less than 80% compliant will be withdrawn from the study. [In addition, serum levels of DHEA and DHEAS will be determined using GC/MS post-treatment, which will provide us with additional compliance information for individuals randomized to the DHEA treatment arm.

Blood samples for serum analysis will be collected in three red-top vacutainers at each study visit. All blood and serum samples will be de-identified. Blood will be centrifuged, and serum will be aliquoted into 1.5 ml cryovials and stored in a -80 degree freezer at the Durham VAMC. GC/MS analyses will be conducted when all participants have completed the study.] Another potential challenge with any clinical trial is patient recruitment.

d) *Data Monitoring and Confidentiality*: Reports from participants’ clinical records concerning research observations will not be made available to outside medical facilities

without the written consent of the patient. All clinical and biological data obtained from research interviews and the laboratory will be deidentified. The data will be kept in locked file cabinets and accessible only to qualified research personnel. Only coded study numbers will appear on data and documents used for evaluation or statistical analysis. In addition, any publications resulting from this research will not identify individual participants.

3. Risks for Study Personnel.
There is minimal risk involved to study personnel. A trained laboratory phlebotomist will draw patient blood for laboratory analysis and serum/blood storage. There is a slight risk of potential needle stick, however the Durham VA Chemical Laboratory provides extensive risk prevention training for all phlebotomists, thus the likelihood of an accidental needle stick is low. The blood samples will be transported to -80º freezer for storage by study personnel. In order to reduce the risk of direct exposure, personnel will wear personal protective equipment while transporting patient serum/blood

C. Potential Benefit of the Proposed Research to the Participant and Others.
While study participants may not receive benefits from the proposed research other than monetary compensation ($75 per visit), their participation may lead to a better understanding of their symptomatology. A travel stipend will also be provided (averaging $15, depending upon distance traveled).

For those not currently treated, study participation may lead to referral for treatment upon completion (or withdrawal) of the study. In terms of benefit to others, knowledge gained from the study may help the evaluation and treatment of patients with PTSD and co-occurring symptoms in the future. No serious adverse events have been attributed to DHEA to date.

Selection of Subjects
Forty OEF/OIF/OND Veterans with PTSD between the ages of 18-65 will be randomized. Both male and female subjects and all ethnic groups will be eligible to participate in this study. All subjects will be currently experiencing PTSD, as evidenced by a CAPS-5 score that is ≥ 33 at baseline. We chose a CAPS-5 score of ≥ 33 after review of the available limited literature on this area. For example, a recent poster presented at the American College of Neuropsychopharmacology (ACNP) provided for rationale on use of CAPS-5 score of ≥ 29 for non-combat PTSD vs ≥ 33 for combat PTSD (Sullivan, G et al., 55th Annual Meeting; ACNP, December 7, 2016). We anticipate that a number of participants will have co-occurring depression symptoms and a history of mild TBI (mild TBI and major depression are not exclusionary); we will thus control for the presence of major depression and a history of mild TBI in the statistical analysis. Patients who have a history of moderate or severe TBI will be excluded. Veterans will be recruited from the Durham VA Medical Center and VA Mid-Atlantic MIRECC Repository and Post-deployment Health Study in OEF/OIF/OND Veterans. This Repository has enrolled over 3,200 OEF/OIF/OND Veterans to date, and

over 94% of these participants have provided permission to be re-contacted for future research studies such as the one proposed.

Inclusion of Women and minorities: Women comprise a significant proportion of the Veteran population and will be recruited into the proposed study at a rate expected to match the standard female percentage in the Veteran population. In addition, minorities will also be included similarly. We estimate that our study population will be approximately 20% female and approximately 40% African American (based upon demographics of the VA Mid-Atlantic MIRECC Repository and Post-Deployment Mental Health Study).

Inclusion Criteria:

1. OEF/OIF/OND era Veterans, 18-65 years of age,
2. PTSD diagnosis (CAPS-5 score ≥ 33).
3. Negative pregnancy test if female. Sexually active subjects are required to use a medically acceptable form of birth control if they are of childbearing potential and could become pregnant during the study. A medically acceptable form of birth control includes non-hormonal intrauterine devices, surgical sterilization, or double barrier methods (e.g., diaphragm with contraceptive jelly, condom with contraceptive foam, cervical caps with contraceptive jelly). Sexual abstinence with agreement to continue abstinence or to use a medically acceptable method of contraception should sexual activity occur is permissible.
4. Female participants must have had a normal mammogram within the last year (if older than 40)
5. Female participants must have had a normal pelvic exam within the last year
6. No change in medications less than 4 weeks before baseline assessment.
7. No anticipated need to alter medications for PTSD for the 6-week study duration (as determined by study physician's review of records and/or discussion with prescribing physician).
8. Ability to fully participate in the informed consent process.

Exclusion Criteria:

1. Unstable medical or neurological illness, including seizures, renal impairment or CVA and inability to participate in neuroimaging (fMRI).
2. Use of oral contraceptives or other hormonal supplements, as it is unclear if DHEA metabolism to other neurosteroids such as estradiol may potentially impact contraceptive efficacy.
3. Significant suicidal or homicidal ideation.
4. Current DSM-5 diagnosis of bipolar disorder, schizophrenia, or other psychotic disorder (including major depression with psychotic features), or cognitive disorder due to a general medical condition.
5. Female patients who are pregnant or breast-feeding. 6. Known allergy to study medication.
6. History of moderate or severe TBI.

7. Substance dependence within past three months, per DSM-5 criteria (excluding caffeine and nicotine).
8. Abnormal prostate specific antigen (PSA; >2.5ng/ml in males age 49 or less; >4ng/ml in males age 50 or greater) or history of prostate cancer, breast cancer, or uterine cancer.
9. A family history of prostate, breast or endometrial cancer in a first-degree relative
10. Presence of any factors/conditions, medical or non-medical, that may interfere with conduction of study assessments in the judgment of the study team,
11. Serious or unstable cardiovascular, hepatic, renal, metabolic, respiratory, or hematologic illness, symptomatic peripheral vascular disease, or other medical condition or psychiatric conditions or behaviors that would compromise participation and/or likely to lead to worsening of symptoms during the course of the study in the opinion of study physician and research team.
12. Are non-ambulatory or require the use of crutches or a walker.
13. Taking Narcotic medications or benzodiazepines for any reason.

Subject Recruitment
Participants will be recruited from Durham VA IRB-approved local advertising (flyers), by referral from their Durham VA medical and behavioral health providers and from the OEF/OIF/OND cohort who previously participated in the PDMH study. We will obtain contact information from the VISN 6 MIRECC Data Repository (Repository) (which currently contains 3,200 OEF/OIF/OND Veterans; over 94% of these Registry participants have already provided permission to be re-contacted for future research studies) that contains contact information provided by participants at the time of their PDMH Study participation. Prospective participants will be sent Durham VA IRB-approved letters and follow-up phone calls utilizing a Durham VA IRB-approved phone script.

Once an individual has been successfully contacted, research staff will read a brief script introducing the study and providing context related to the participant's previous enrollment in the PDMH Study. Early in this script, the individual will be asked if they are interested in hearing about the current study. If the individual is not interested, they will be thanked for their time and the call will end. If the individual is interested, the remainder of the script will be read providing information about what activities will occur should the individual choose to participate. Any questions regarding participation will be answered. If the participant wishes to participate, they will then be rescheduled to report in-person to complete the study. Additionally, decision-making capacity will be evaluated by consulting clinical records (if available) and by asking the patient if they have a legal guardian. Individuals without decision-making capacity and/or with a legal guardian will not be contacted.
, for a target number of 40 randomized participants; of these 40 randomized participants, it is estimated that at least 32 participants will receive at least one study visit following randomization (20% drop-out assumed).

Consent Process
The informed consent process, including completion of the Informed Consent and HIPAA forms will occur in a private room at the Durham VA Health Care System and will be completed prior to the initiation of any study activities. The informed consent process will be conducted by a member of the research team who has been trained in the proper procedures and language to be used so as to minimize the possibility of coercion or undue influence and to ensure that the individual understands the information being provided

A participant who is judged likely to meet all of the inclusion criteria and none of the exclusion criteria will meet with a member of the research team to discuss the research protocol, and to determine if the patient is capable of providing informed consent. Individuals without decision-making capacity will not be enrolled. Eligible participants will be provided with a description (verbal and written) of the informed consent form, which includes the risks along with procedures to minimize these risks, and the participants' rights and responsibilities. Participants will be given the opportunity to read the consent form and ask questions. Participants will be assured that participation in this research study is voluntary and that they may withdraw from the study at any time without adversely affecting their medical care or any benefits they might be receiving. They may also refuse to answer any research questions during the interview. Participants who are eligible for the study and choose to participate will sign the consent form in the presence of a member of the research team.

Digital Audio-recording:
Participants will be explicitly asked for permission to digitally audio-tape CAPS-5 interviews in the IRB-approved written Informed Consent Form. Participants will be informed that audiotaped sessions may be reviewed by an expert (Dr. Sara Kleiman) for the purposes of interviewer fidelity. We anticipate that the expert will review CAPS-5 interviews of the first 2 participants seen by each assessor, and 1-2 randomly selected interviews every 3-6 months. Digital audio recordings and corresponding CAPS-5 assessments will be identified only by subject ID and stored on the S-drive, behind the VA firewall at S:\MIRECC\Collaborators. Audio recordings will be captured using a Philips Pocket Memo Voice Recorder DPM8000 or other approved audio recorder. Only approved study staff and the expert reviewer will have access to this file path/folder. No other portion of study visits will be recorded.

Study Interventions
We will conduct a parallel-group, double-blind, placebo (PBO)-controlled, randomized Phase 2 pilot study with 400mg DHEA to test whether we can establish proof of concept (POC) for this agent. 40 OEF/OIF/OND Veterans with PTSD will be randomized to receive a one-time oral adjunctive treatment with DHEA or PBO in the fMRI paradigm (same day). Participants will then continue to receive a 6-week sustained treatment of DHEA or PBO. To establish POC, we seek to determine whether DHEA is superior to

PBO on neural circuits related to fear-anxiety-emotional regulation. We will determine potential fear-anxiety circuit target engagement following one-time oral adjunctive dose of DHEA (400 mg) using a same-day fMRI paradigm (the SEAT procedure, see below) to assess derived functional connectivity measures between the amygdala and the hippocampus as compared to PBO (primary outcome). Further, we will also determine if fMRI and serum neurosteroids (DHEA, DHEAS, androsterone, and/or other neurosteroids) may be candidate biomarkers of PTSD symptoms (CAPS-5) that predict therapeutic response to a DHEA intervention (secondary outcomes). The proposed set of studies will enable us to investigate these neurosteroids as novel pharmacological interventions for PTSD, and to identify biomarkers of therapeutic response in PTSD. Finally, as an exploratory goal, the current study will determine if treatment with DHEA impacts myelin integrity (as assessed by STI), and if peripheral neurosteroid levels are potentially associated with myelin content, other neuroimaging parameters, or therapeutic response.

Schedule of Events:

Week	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Follow up**
Study Visit	**1**	**Phone Call**	**2**	**Phone Call**	**3**	**Phone Call**	**4**	**Phone Call**	**5**	**Phone Call**
Informed Consent	X									
Demographics, Medical History	X									
Mental Health Diagnosis	X									
Physical Exam and ECG	X								X	
Clinician Adminstered PTSD Scale	X		X		X		X		X	
Adverse Events		X	X	X	X	X	X	X	X	X
Mental/Physical Health Assessments	X		X		X		X		X	
Suicide Assessment	X	X	X	X	X	X	X	X	X	X
Blood draw and Vital Signs	X		X		X		X		X	
Urine Drug Test	X		X		X		X		X	
Urinalysis	X		X		X		X		X	
Urine Pregnancy Test	X		X		X		X		X	
Dispense Drug or Placebo	X		X		X		X		X	
MRI			X						X	

Treatment Compliance

Compliance for each visit interval is defined as taking between 80% and 100% of the study drug prescribed for that interval. For subjects who demonstrate noncompliance, the PI and/or study coordinator will counsel patients on the importance of study drug compliance and drug accountability.

The following procedures will be employed to assure appropriate drug accountability:
-Drug accountability will be emphasized at the screening visit and throughout the clinical trial.
-Drug accountability forms will be provided in the clinical trial records binder or similar file.

-Drug accountability will be monitored throughout the study.
-Each patient will be instructed to return all study drug packaging and unused study drug at each visit.
-Records will be kept of all drug dispensed to and returned by participants throughout the study.

Adverse Events
This protocol presents minimal risks to participants. In the unlikely event than an adverse event occurs, serious and unanticipated and related adverse events or unanticipated problems involving risks to participants or others will be reported in writing within 48 hours to the IRB at the Durham VA Health Center and any appropriate funding and regulatory agencies. Adverse events will be recorded by administration of a side effect rating scale (Hillside Adverse Events Form) and reviewed by a study physician. Adverse events will be assessed at all study visits after the screening visit (i.e. Visits 2-5). In addition to receiving these regular adverse effect assessments, patients will be given a toll-free study number that they can call if they have questions regarding the dose escalation schedule or medication side effects. Participants will also be provided with the cell phone numbers of Dr. Szabo and Dr. Marx.

We will also summarize all adverse events (cumulative to date) in our reports to the FDA, Clinical Science Research & Development Central Data Monitoring Committee at Hines (CSR&D DMC), and annual request for continuing approval to the IRB. The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at intervals appropriate to the study. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Specifically, the principal investigator will assess whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (at Risks to Subjects) or consent form (at Risk and Inconveniences) are required. The investigator will apprise fellow investigation and study personnel of all adverse events will be reported to the appropriate regulatory and oversight agencies in accordance with their reporting requirements and regulations.

a) Physical Risk: Physical risk associated with participation in this study include the risks of drain blood (for serum and clinical lab tests). Possible side effects from drawing blood include bruising, bleeding, or pain at the injection site, and (rarely) fainting, infection and peripheral nerve damage. Blood draws are minimal risks. Pregnant women tend to be more anemic than non-pregnant women. Therefore, the risk of blood draw (90 mL) in a pregnant woman could represent negligibly greater risk by increasing the magnitude of anemia. There are no known long-term health risks to use of magnetic resonance imaging per se when operated under FDA guidelines. However, there are safety concerns posed by strong magnetic fields used to produce images. All sequences conducted under this protocol are clinically approved by the FDA. Our scanner meets the FDA's guidelines for non-significant risk for static field strength,

specific absorption ate (SAR), time varying magnetic fields (dB/dt), and acoustic noise. If a subject has previously worked with metal, they will need a skull x-ray prior to the MRI scan. The skull x-ray involves a small amount of radiation. The radiation received in this x-ray is the same as from living in a high-altitude city such as Denver for 4 weeks, or taking 8 airplanes flights from New York to Los Angeles.

b) Emotional Distress: Participants may experience emotional distress because of participating in this study. The study procedures could potentially lead to emotional distress from discussing medical histories or deployment experiences. Being placed in an MRI machines can at times induce feeling associated with claustrophobia. Each participant will be closely monitored for emotional distress and emergent suicidal ideation and homicidal ideation at screening and each study visit (it is anticipated that this will be rare). If a participant becomes significantly distressed or if intervention is deemed appropriate, they will be escorted to the Durham VA Emergency Room for additional assessment.

c) Unauthorized Access to Data: There is a possibility of an unauthorized party gaining access to secure PHI contained in the database. This is also a low risk, and several precautions have been implemented to minimize unauthorized access. First, reports from participants' clinical records concerning research observations will not be made available to outside medical facilities without the written consent of the patients. All clinical biological data obtained from research interviews and the laboratory will be coded. The data will be kept in a locked file cabinets and accessible only to authorized research personnel. Only study numbers will appear on specimens, data and documents used for evaluation or statistical analysis. In addition, any publication resulting from this research will not identify individual participants.

Costs and/or Payments to Subjects
Participants will be reimbursed $75 for each study visit plus an additional $100 for each MRI. Therefore, if they participate in all 5 study visits and 2 MRIs, they will receive $575. There will be an additional allowanced based on distance traveled by the participant. For ease of calculation, concentric zones will be used as summarized in the table below.

Distance (miles)	Allowance	Typical towns and cities
0-25	$10	Raleigh, Durham, Cary, Chapel Hill
25-50	$20	Henderson, Wake Forest, Burlington
50-100	$30	Greensboro, Fayetteville, Goldsboro
100-150	$35	Salisbury, Greenville, Rocky Mount

150-200	$40	Wilmington, Charlotte, Hickory
> 200	$50	

Data and Safety Monitoring
We will follow all IRB, Clinical Science Research & Development Central Data Monitoring Committee at Hines (CSR&D DMC), and FDA guidelines for annual progress, adverse event, and other reporting procedures for this outpatient randomized control trial. We will collect only the minimum amount of information required to report SAE's to reporting agencies; SAE date, date of study visit, and medical information related to the SAE. The SAE information will be collected during the study visit, by telephone calls with study participants, and by data collection from study files and Electronic Medical Records. Safety data collection will begin upon study enrollment. The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting and submitting the safety reviews to the IRB, CSR&D DMC, and FDA at intervals appropriate to the study. During the review process the principal investigator, along with monitoring committees will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Specifically, the principal investigator will assess whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (at Risks to Subjects) or consent form (at Risks and Inconveniences) are required.

Privacy, Confidentiality, and Information Security

1. **Lists of Data Reviewed and/or Collected for Screening/Recruitment and Conduction of Study:**

The Personal Health Information that will be obtained, used, and/or shared for this study includes:

2. **Data and/or Specimen Acquisition:**

Data for this study will be collected through:

Identifier(s)	Source(s) of Health Information
☒ Names	☒ Medical history & physical exam information
☒ All geographic subdivisions smaller than a State, including street address, city, county, precinct, and zip code. Describe: street address, city, county, and zip code	☒ Photographs, videotapes, audiotapes, or digital or other images CAPS-5 interviews will be audio-recorded
☒ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date,	☒ Biologic specimens (e.g., blood, tissue, urine, saliva). Describe: Blood, urine

Identifier(s)	Source(s) of Health Information
discharge date, visit or treatment dates, etc.; and all ages over 89, Describe: Date of birth, date of death, visit dates, treatment dates, admission and/or discharge dates.	
☒ Telephone numbers	☒ Progress notes
☐ Fax numbers	☒ Diagnostic / Laboratory test results
☐ Electronic mail addresses	☐ Operative reports
☒ Social Security Numbers	☒ Imaging (x-ray, CT, MRI, etc.)
☒ Medical record numbers	☒ Discharge summaries
☐ Health plan beneficiary numbers	☒ Survey / Questionnaire responses
☒ Account numbers: Bank routing numbers for EFT payment for participant payment	☐ Billing records
☐ Certificate and/or license numbers	☐ HIV testing or infection records
☐ Vehicle identifiers and serial numbers, including license plate numbers	☐ Sickle cell anemia information
☐ Device identifiers and serial numbers	☒ Alcoholism or alcohol use information
☐ Web Universal Resource Locators (URLs)	☒ Drug abuse information
☐ Internet Protocol (IP) address numbers	☒ Mental health (not psychotherapy) notes
☐ Biometric identifiers, including finger & voice prints	☒ Psychological test results
☐ Full-face photographic images and any comparable images	☐ Genetic testing
☒ Any other unique identifying number, linked study ID, characteristic, or code, describe: Unique study ID and unique study blood sample barcode	☒ Other, describe: Emergency contact's name, address, and phone number

☒ Prospective data and/or specimen collection obtained from participants. Provide description of processes: This is a prospective study administering study drug (DHEA) or placebo for 8 weeks with 5 in-person visits. Prospective data will be collected via self-report, questionnaires, brain images (collected by MRI), and blood specimen (collected via venipuncture).

☒ Retrospective data collection and/or specimens obtained from medical chart review/data access. Describe how data will be obtained (e.g., fileman, CDW, etc.): Electronic Medical Chart review by study staff.

☒ Retrospective data collection and/or specimens obtained from an IRB-approved data and/or specimen repository. Indicate the repository source including name, VA location, and IRB number: VISN 6 MIRECC Post-Deployment Mental Health Data Repository, Durham VAHCS, VISN 6 MIRECC, 3022 Croasdaile Dr., Durham, NC 27705 – IRB #1706.

3. Level of Data:

The following level(s) of data will be acquired/maintained for this study:

☒ Identified (e.g., names, addresses or other identifiers included)
☒ Coded (direct and/or all identifiers removed, but study code/ID included)
☐ De-Identified (all HIPAA 18 and study ID/code removed):
- ☐ Verified Statistically

OR

- ☐ Verified by Absence or Removal of HIPAA 18 and study ID

☐ Limited Data Set
☐ Other: Describe:

4. Location of Data and/or Specimens, and Data Retention Plan:

A. Data and/or Specimen Location:

Data will be stored electronically behind the VA firewall in S:\MIRECC\PI Folders\Szabo\Szabo Study Files. Data stored electronically will include PHI and Study Assessment responses. PHI will be stored in the database separate from any Study Assessment responses.

Paper records of data include Study Assessments, Informed Consent Form, HIPAA Authorization, Subject Payment Forms, and will be stored at the DVAHS in Building 15, 4th floor; building 1, room D3009; and/or the MIRECC Croasdaile Building, 3rd floor. PHI in paper form will be stored in file cabinets separate from the coded data.

Specimens include coded subject blood and serum samples, and will be frozen at -80° Celsius and stored in the freezer rooms in MIRECC Croasdaile Building, 3rd floor; Building 6 and/or Building 15 at the DVAHS.

Audio recordings and CAPS-5 assessments will be coded with a subject ID and stored on the VA S-drive at: S:\MIRECC\Collaborators. This folder will be accessible to approved study staff and to the expert PTSD assessor, Dr. Kleiman. Dr. Kleiman will not have access to the key code and will not be able to identify participants from the audio tape or written CAPS-5 assessment.

☒ Data will be also be placed at the VA Informatics and Computing Interface (VINCI; http://vaww.vinci.med.va.gov/vincicentral/VINCIWorkspace.aspx). The VA Informatics and Computing Infrastructure is a partnership between the VA Office of Information Technology and the Veterans' Health Administration Office of Research and Development. Researchers and operations staff can use VINCI to access data and statistical analysis tools in a virtual working environment through a certified VHA network computer using the VA Intranet or Virtual Private Network (VPN).

B. Data Retention Plan

☒ Research records will be maintained and destroyed according to the National Archives and Records Administration, Records Schedule Number: DAA-0015-2015-0004. Records destruction, when authorized, will be accomplished using the then current requirements for the secure disposal of paper and electronic records. Currently, destruction of research records (see DAA-0015-2015-0004, section 7.6 "Research Investigator Files" for materials included in research records) is scheduled for 6 years after the cut-off (the cut-off is the completion of the research project) and may be retained longer if required by other federal agencies. Records will not be destroyed without pre-notification to the facility records manager.

☐ Other data retention plan, describe:

5. Data Access and Data Recipients:

Only members of our DVAMC research team will have access to identifiers and coded data, whether it resides behind the VA firewall or in paper form. All VA research personnel who have access to VHA records are instructed, in accordance with VA policy, on the requirements of Federal privacy and information laws and regulations, VA regulations and policies, and VHA policy. All study personnel who are VA employees working within the VA system have fulfilled all required HIPAA and other VA security and privacy policy training requirements and have agreed to follow guidelines pertaining to the protection of patient data. All research staff sign VA Rules of Behavior, and all study staff are up-to-date with VHA Privacy Policy Training and the VA Office of Cyber and Information Security Awareness Training Course. The data security and privacy procedures summarized in that course include logging off or locking the computer when walking away from it; no sharing of access codes, verify codes or passwords; not allowing anyone else to use the computer under one's password; and disposing of sensitive information using VA-approved methods (e.g., shredder bins).

Access to study data will be removed for all study personnel when they are no longer part of the research team.

6. Data and/or Specimen Transportation and/or Transmission for all data and/or specimens involved in the study:

I. ☐ Data and/or specimens will not be transported or transmitted outside of Durham VAMC environment.

II. ☒ Data and/or specimens will be transported BETWEEN sites that are under the auspices of the Durham VA Medical Center. Blood samples will be transported for lab testing or storage in -80 freezers by trained study staff between the main study site at 3022 Croasdaile Drive and the DVAHS building 1, 6, or 15. Specimens will be contained in a biohazard zip-lock bag within a marked biohazard cooler. Data files will be securely boxed and labeled. Trained study staff will use the VA shuttle van or personal automobile. No additional stops will be made during transportation.

III. ☐ Data and/or specimens will be transmitted to other VA sites using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted disk (encryption is optional).

☐ Data are coded or contain identifiers and thus will be sent

☐ Other, describe:

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional).

☐ Specimens are coded or contain identifiers and thus will be sent via VA-authorized carrier with tracking.

☐ Other, describe:

IV. ☒ Data and/or specimens will be transported to non-VA/VHA sites (e.g., academic affiliates, laboratories, etc.) using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted CD.

☐ Data are coded or contain identifiers and thus will be sent via using VA—approved carrier with tracking.

☒ Data are coded or identified and will be sent via the Safe Access File Exchange (SAFE) at https://safe.amrdec.army.mil/safe/. SAFE is a secure method of exchanging files <2GB to and from individuals with a valid .gov, .mil, .com, or .edu email address. Data will be sent via SAFE to Duke University for statistical computing purposes (including Ryan Wagner, PhD).

☐ Data are coded or identified and will be uploaded to sponsor website using electronic case report form (eCRF)

☐ Other, describe:

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional) or will be hand-delivered by research study personnel. Specify method of delivery:

☐ Specimens are coded and thus will be sent via VA-approved carrier with tracking or will be hand-delivered by research study personnel. Specify method of delivery:

In accordance with the HIPAA and the Privacy Act, for any coded or identifiable data or specimens released from the Durham VAMC (with the exception of Limited Data Sets), an Accounting of Disclosure (AOD) will be maintained (e.g., in a database or spreadsheet) that includes the participant's name, date of the disclosure, description of the nature of the Individually Identifiable Information (III) disclosed, purpose of each disclosure, and the name and address of the person/agency to whom the disclosure was made.

C. ☒ Local DVAMC memorandum "Authorization to Use, Process, Store, or Transmit VA Sensitive Information Outside VA Owned or Managed Facilities" has been pre-filled out for each study team member who may transport the data and/or specimens off-site. This (these) forms are included with the IRB materials.

D. ☒ Containers (e.g., briefcase, bin) are labeled with the following notice (label placed on the outside of container):

NOTICE!!!

Access to these records is limited to: AUTHORIZED PERSONS ONLY. Information may not be disclosed from this file unless permitted by all applicable legal authorities, which may include the Privacy Act; 38 U.S.C. §§ 5701, 5705, 7332; the Health Insurance Portability and Accountability Act; and regulations implementing those provisions, at 38 C.F.R. §§ 1.460 – 1.599 and 45 C.F.R. Parts 160 and 164. Anyone who discloses information in violation of the above provisions may subject to civil and criminal penalties.

V. ☒ We will communicate with veterans enrolled as participants in this research study through MyHealtheVet.

7. Risk Mitigation Strategies:

☐ Data are fully de-identified (stripped of HIPAA 18 and study ID/code) before being shared outside of Durham VAMC.

☐ Specimens are fully de-identified (stripped of HIPAA 18 and study ID/code before being shared outside of Durham VAMC.

☒ Direct identifiers will be maintained separately from data and or specimens by using a code to “identify” subjects. In a separate database (i.e., a “linking” or “cross-walk” database) this code will be linked to identifying subject information. All study staff have been trained on the requirements of Federal privacy and information laws and regulations as described in section #5 above. The PI bears the responsibility for overseeing the privacy and security of the data.

☐ Other, specify:

8. Suspected Loss of VA Information:
Should any incident such as theft or loss of data, unauthorized access of sensitive data or non-compliance with security controls occur it will be immediately reported according to VA policy. All incidents regarding information security/privacy incidents will be reported to the ISO and PO within 1 hour of acknowledgement of issue and done so using the VHADUR Research Events Report e-mail group (VHADURResearchEventReport@va.gov).

9. Reporting of Results:

☒ Reporting of results, such as in scientific papers and presentations, will never identify individual subjects. Data will be presented in aggregate and individual-level data will not be published.

☐ Other results reporting plan, describe:

10. Future Use of Data:

☐ Data will be retained for future use. This is described elsewhere in the protocol and is noted in the HIPAA authorization.

☐ Future Use of data is optional (i.e., not required by the research subject).

☐ Future Use of data is required for participation in the study.

☒ No future use of data is currently planned.

11. Use of Mail Merge Technology
☒ Mail merge programs will be used to generate letters and/or address labels for mailings to potential or already enrolled research subjects. The study team is aware that to reduce risk of mail merge related privacy incidents, use of mail merge programs requires a 25% accuracy check to verify that (potential) research subject name and mailing address are properly "matched". If discrepancies are found, a 100% accuracy check is required before letters may be mailed.

12. Use of Non-Standard Software
☒ I do NOT intend to use any new specialized software (i.e. Software that's not already approved OR installed) in this study.

☐ I intend to use specialized software that has not already been installed and it has been approved for use by the VA Technical Reference Model (TRM) Group.
(Note: All new software must be approved by TRM before it can be installed on VA systems.)

☐ I intend to use previously installed software on my VA computer.

13. Use of Cloud Computing Services
☒ Cloud computing services will NOT be used in this study.

☐ Cloud computing services WILL be used in this study as described below and have been approved nationally by the VA Chief Information Officer (CIO). (Note: ONLY cloud computing services that have been approved nationally may be used.)

Data Analysis and Statistical Considerations

The analysis plan is organized around the study's hypotheses using a variety of statistical techniques. Univariate summary statistics, including means, medians, rates, proportions, and variances, will be calculated as appropriate for all variables. In addition to statistics, outcome measures will be examined graphically to assist in determining distributional form as a precursor to model selection. Preliminary bivariate analyses by treatment condition will use standard Chi-square procedures for categorical outcomes; continuous outcomes meeting distribution requirements will be tested using Student's t-test, whereas data not meeting distributional requirements will be analyzed by nonparametric (e.g., Kruskal-Wallis) procedures. Differences between covariates will be tested at baseline to assess randomization. Putative covariates with significant asymmetry between groups will be considered for inclusion in subsequent modeling and testing (However, see Miller & Chapman, 2001). Inference for all analyses will be evaluated relative to p=0.05 within a given hypothesis.

Analysis of primary outcomes in the Shifted-Attention Emotion Appraisal (SEAT) Paradigm will present compound stimuli that include both emotional faces (e.g. sad, happy, angry) and neutral scenes (Sripada et al 2014). In three different conditions, participants will be asked to respond to three different questions: (1) 'Gender': Whether the face in the foreground is male or female; (2) 'Inside/Outside': Whether the scene in the background is indoors or outdoors; or (3) 'Like/Dislike': Whether the face in the foreground is liked or disliked. This allows multiple components of cognition to be probed including (1) implicit emotional processing, (2) attentional modulation, and (3) cognitive modulation of emotion. Item-specific memory will be tested first using yes/no recognition judgments. The conjunctive memory test will require participants to make "match" (previously viewed faces and buildings presented in a combinations seen during encoding) or "mismatch" (items in combinations not previously seen together) judgments.

For fMRI analysis we will use FSL supplemented by BIRN tools for signal averaging, ROI analysis, and visualization of time series waveforms (Smith SM 2004). We use FreeSurfer for surface reconstruction and automatic segmentation. FMRIB Software Library (FSL) preprocessing will be used for motion correction, slice time correction, temporal and spatial filtering, and co-registration with the individual subject's high resolution anatomical image. A first level analysis will be performed on each run separately using a standard GLM approach with regressors determined by the task timing convolved with a delayed canonical hemodynamic response. The first level analyses from a subject will then combined in a fixed effects second level analysis. These second level analyses are then combined into between group third level analyses using a mixed effects model. The functional MRI data will be analyzed by comparing whole brain voxelwise neural activity (BOLD) associated with cognitive processing between pre- and post-treatment, between active and placebo arms, between-face types (e.g. angry, fearful, neutral), and between-task conditions (e.g. gender, indoor/outdoor, like/dislike), which is neurosteroid relevant (Sripada et al 2013a, Sripada et al 2013b). Dr. Isreal Liberzon was the

senior author on these pivotal trials and is a collaborator (please see accompanying letter) along with Dr. Marx who was a co-investigator and is the primary mentor for the CDA. Subsequent testing with functionally defined ROIs will be used to make statistical inferences about treatment response and to identify correlations with cognitive changes, CAPS-5 scores, and neurosteroid levels. In addition, we propose to study the correlation between PTSD symptom severity and disruption in fear systems interrogated by the task paradigms. This will be probed further by examining correlation between the hypothesized clinical behaviors and fear system activation during the associated task (e.g., severity of hypervigilance symptoms and activation. Correction for the family-wise error rate will be based upon the Gaussian random field (GRF) theory that is implemented in FSL (Worsley et al., 1996).

Primary outcome analyses will be based on maps of activation, reaction time, and on-line accuracy judgments via a 2 (drug type: DHEA or Placebo) × 3 (face type: angry, fearful, neutral) × 3 (condition: male/female, inside/outside, like/dislike) repeated-measures ANOVA for main effects and interactions. Follow-up effect analyses will be performed with two-tailed *t*-tests and significance threshold at 0.05 with correction for multiple comparisons. *Z*-score images from the individual activation maps will be entered in second-level random-effects analyses using SPM8 and corrected for multiple comparisons, $p<0.05$. Activation threshold and cluster size will be determined using AlphaSim (Ward, 2000) to correspond to a false-positive rate of $p<0.05$, corrected for multiple comparisons within ROIs. Voxel coordinates that will be reported will correspond to standardized MNI space. The time series from significant clusters within regions of group difference will be used in a psychophysiological interaction (PPI) analysis. Deconvolved time series in the anatomical right amygdala will be extracted for each subject and represent the first regressor in the PPI analysis (physiological variable). The experimental condition is the second regressor (emotion processing; psychological variable). The regressor of interest will be the interaction between the time series of the seed region and the experimental condition.

Secondary outcome analyses will be based on a repeated measures ANOVA approach modeling difference-from-baseline scores at Weeks 2, 4, 6, and 8. These time-dependent outcomes will be estimated using a class of statistical models variously referred to as hierarchical linear models (HLM), linear mixed-models, (LMM) or multilevel models. Within this approach, each individual's measurements over time are initially modeled as an individual growth trajectory plus an error term. The individual trajectories are subsequently modeled as a function of differences between individuals on covariates of interest (e.g., treatment proxies, etc.). These models extend traditional approaches for modeling longitudinal data (e.g., time-series analyses or repeated measures ANOVAs) by allowing for missing values, covariance structures other than compound symmetry (e.g. unstructured typically is a first option), varied measurement intervals, and likelihood estimates based on all available (outcome) data. These procedures are be implemented in SAS v9.4 using PROC MIXED for normally distributed data and GLIMMIX for non-normally distributed data. The latter can estimate a variety of categorical outcomes including Poisson and binomial distributions.

Analyses will be based on a modified intent-to-treat methodology; all participants who reached one or more study visits post-randomization will be included in the statistical analysis plan. We will randomize a total of 40 participants; it is estimated that at least 32 participants will receive at least one study visit post-randomization and will be included in the statistical analyses (10% drop out rate assumed). Analyses thus utilize an n=32 for power calculations in the proposed modified intent-to-treat analysis. We will make significant efforts to obtain final interviews with drop-out subjects to determine if drop-out is in fact treatment-related as opposed to MAR. In instances where contact is not possible or assumptions of MAR are confirmed by interview, missing data will be augmented where assumptions that the pattern of 'missingness' are ignorable (e.g., MAR - Schafer, 1997) hold using multiple imputation procedures including maximum likelihood (e.g., PROC MIXED: see above) or, in instances where missing data include independent measures, multiple imputation (e.g., SAS: PROC MI; R: MICE). Subsequent sensitivity analyses comparing results based on various methodologies are of course essential in determining how robust results are to missing data.

Change in total DSM5-defined PTSD symptoms from pre- to post- treatment, as assessed by the CAPS-5, the gold standard method for assessing PTSD symptoms in pharmacological treatment trials; measurements will be gathered at two-week intervals beginning at baseline and continuing through Week 8. Measures of pre-post treatment differences at the four study intervals will be regressed on a dichotomous proxy measure denoting treatment status coded positive for subjects randomized to the DHEA condition. In addition to the treatment proxy, all models will include covariates for measurement interval (time), and an interaction term crossing the treatment proxy with time. Test of the secondary hypothesis will be based on a 1 df test of the contrast of difference between drug and placebo at the final time point (SAS: LSMESTIMATE statement). Specifically at Week 8, H0: LSMEdhea >= LSMEplacebo versus Ha: LSMEdhea < LSMEplacebo. We hypothesize rejection of a null hypothesis positing that difference in PTSD symptoms from baseline will be equivalent or greater among subjects randomized to DHEA at the final time point in lieu of an alternative hypothesis positing a reduction in PTSD symptoms in the DHEA cohort relative to placebo.

Measures of serum levels of three neurosteroids: DHEA, DHEAS, and androsterone will also be analyzed. As above, the outcome measure will be the change in steroid level from baseline (i.e, following 2 week placebo lead in) to Week 8 with measurements at two-week intervals. Models will be estimated as described above with tests of the primary hypothesis based on a 1 df test of the estimated contrast of the difference between drug and placebo at the final time point. In all cases, the following hypothesis will be tested: H0: LSMEdhea <= LSMEplacebo versus Ha: LSMEdhea > LSMEplacebo. Results for tests of Aim 2 will be adjusted for multiple comparisons using the method of Hochberg (1998).

As secondary test of the hypothesized association between change in PTSD status and change in neurosteroid levels, Week 8 changes CAPS-5 scores will be regressed on Week 8 change in neurosteroid levels. Models will include, as above, covariates for age, gender, smoking status, depression, TBI status, and a measure of the baseline level of the tested neurosteroid. Based

on anticipated collinearities between the dichotomous randomization proxy and change, models will initially be estimated without the former. A significant inverse association between change in steroid levels and change in CAPS-5 scores would support the hypothesized efficacy of DHEA as an adjunctive therapy in treating PTSD. As above, results would be corrected for multiple comparisons.

Tests of secondary measures will be conducted as described above. Thus, proposed measures will be regressed as change from baseline scores on a model controlling for the baseline level of the tested outcome measure, the dichotomous randomization proxy, and an interaction term crossing the latter with time. Tests will again be based on a 1 df test of the estimated contrast (LSME: see above) of the difference between drug and placebo at the final time point. Expectations are that change in adverse outcome measures will be significantly mitigated in the DHEA intervention arm; measures associated with salubrious outcomes will be, conversely, improved. All results will be adjusted for multiple comparisons.

Appendix A: Expedited Review of Research

The categories of research that may be reviewed by the IRB through the expedited review procedure include research activities that present no more than minimal risk to human subjects **AND** involve procedures listed in one or more of the specific categories listed below.

The expedited review procedure is not to be used when identification of the subjects or their responses would reasonably place them at risk of criminal or civil liability; be damaging to the subjects' financial standing, employability, insurability, or reputation; or be stigmatizing, unless reasonable and appropriate protections are implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal. The IRB must apply the standard requirements for informed consent (or its waiver, alteration, or exception) to all studies that undergo expedited review.

EXPEDITE CATEGORIES
1-Drugs and Devices: One of the following must be met: (1) The research is on drugs for which an IND application is not required. (2) The research is on medical devices for which an investigational device exemption (IDE) application is not required; or the medical device is cleared or approved for marketing, and the medical device is being used in accordance with its cleared or approved labeling.
2-Blood Samples: Collected by finger / heel / ear stick or venipuncture: (1) From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 milliliters (ml) in an 8-week period, and collection may not occur more frequently than two times per week; or (2) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kilogram (kg) in an 8-week period, and collection may not occur more frequently than two times per week.
3-Noninvasive Collection of Biological Specimens: Collected prospectively for research purposes by noninvasive means: (1) Hair and nail clippings in a non-disfiguring manner. (2) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction. (3) Permanent teeth if routine patient care indicates a need for extraction. (4) Excreta and external secretions (including sweat). (5) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue. (6) Placenta removed at delivery. (7) Amniotic fluid obtained at the time of rupture of the membrane prior to, or during, labor. (8) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques. (9) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings. (10) Sputum collected after saline mist nebulization.

EXPEDITE CATEGORIES
4-Noninvasive Collection of Data: Data must be collected through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. (1) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy. (2) Weighing the subject. (3) Testing sensory acuity. (4) Magnetic resonance imaging (MRI). (5) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography. (6) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing, where appropriate, given the age, weight, and health of the individual.
5-Collected Material: Research involves: (1) Materials (data, documents, records, or specimens) that have been collected for any purpose, including previous research; or (2) Materials (data, documents, records, or specimens) that will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
6-Collection of Data From Voice, Video, or Photographs: Research involves collection of data from voice, video, or photographs.
7-Group Characteristics, Surveys, Interviews, and Quality Assurance: Research must be on individual or group characteristics or behavior (including, but not limited to: research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior), or will employ survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. ***NOTE****: Some research in this category may be exempt from the VA regulations for the protection of human subjects (38 CFR 16.101(b)(2) and (b)(3)). This listing refers only to research that is not exempt.*