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Title: A pilot study of the effects of dexamethasone administration on virtual reality exposure therapy for PTSD

Principal Investigator: Barbara Rothbaum, PhD

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Principal Investigator*:* Barbara Rothbaum, PhD

Co-Principal Investigator: Tanja Jovanovic, PhD

Co-Investigators: Kerry Ressler, MD, PhD
Sheila Rauch, PhD
Boadie Dunlop, MD

Corresponding: Department of Psychiatry and Behavioral Sciences
Emory University School of Medicine
12 Executive Park Drive, NE
3rd Floor, Suite 300
Atlanta, GA 30329
404-712-8866
brothba@emory.edu

Summary: Evidence from preliminary studies suggests that subjects with PTSD have exaggerated expression of fear responses to danger and safety cues after fear acquisition, and that cortisol suppression reduces this pathological fear. Further pilot research has shown the drug dexamethasone (DEX), a cortisol suppressor, to reduce startle response in civilians with PTSD. This current research proposal represents a blinded, randomized, placebo-controlled efficacy study with the goal of determining whether a drug that suppresses the stress-hormone cortisol and an exaggerate startle response will increase the efficacy of exposure therapy. Specifically, it is proposed that a single dose of DEX, given the night before (approximately 10 hours before) each of 5 to 10 individual virtual reality exposure (VRE) therapy sessions, will significantly enhance the rate of response and possibly the efficacy of treatment. Comprehensive multi-modal outcomes will be assessed by independent assessors blind to subject condition on interviews, self-report measures, psychophysiological measures, and a behavioral avoidance test. Participants will be assessed pre- and post-treatment and at a follow-up of 3, 6 and 12 months to assess long term effects.

This type of combined treatment -- specific pharmacotherapeutic augmentation of psychotherapy -- would be novel and would potentially be generalizable to many different forms of psychotherapy for a wide range of disorders. If this translational research is successful, the ability of a relatively benign agent administered acutely before a psychotherapy session to facilitate the psychotherapeutic process could have important clinical, humanitarian, and economic advantages.

1. Preliminary Studies

Exaggerated Fear Responses in PTSD

Overgeneralization of trauma-related stimuli or situations can lead to hyper-vigilance and exaggerated physiological responses that are part of the PTSD clinical presentation. Neuroimaging studies have shown that the brain structures that are activated in response to

fearful stimuli, such as the amygdala, show hyperactivation in PTSD subjects compared to controls (Liberzon & Martis, 2006; Shin, Rauch, & Pitman, 2006). These patients show overgeneralization of fear and in tandem an inability to inhibit fear responses in the presence of safety; impaired fear inhibition may be a specific biomarker of PTSD (Jovanovic, Norrholm, Blanding, Davis, et al., 2010). Early studies with Vietnam and Gulf War veterans found enhanced fear conditioning in PTSD (Grillon & Morgan, 1999; Grillon, Morgan, Davis, & Southwick, 1998; Orr et al., 2000). A recent meta-analysis of 15 studies using fear conditioning found that patients with anxiety disorders showed greater levels of fear responses compared to healthy controls (Lissek et al., 2005). Fear conditioning is based on a simple Pavlovian conditioning model in which a neutral conditioned stimulus (CS, for example, a light) is paired with an aversive unconditioned stimulus (US, for example, electric shock). After a number of pairings, the association is formed so that the CS alone elicits the conditioned response (CR, for example, a fear response). This basic model is used in animal as well as human research to investigate mechanisms of fear acquisition. The amygdala, part of the limbic system located in the temporal lobe of the brain, is an integral part of the fear circuitry (Davis, Falls, Campeau, & Kim, 1993; LeDoux, 2000). Since the amygdala is one of the neural structures that has been found to be hyperactive in PTSD (Shin, et al., 2006), fear conditioning methods provide good laboratory tools for testing exaggerated fear symptoms of PTSD. In humans, the acoustic startle response provides an ideal translational tool to investigate fear conditioning, since the amygdala is directly connected with the startle circuit (Davis, 1992; Grillon & Morgan, 1999). Fear-potentiated startle (FPS) is the relative increase in the startle magnitude elicited in the presence of a conditioned stimulus (CS+) that was previously paired with a US; this psychophysiological measure can be used to index both the increase in fear during conditioning, as well as the reduction of fear during extinction, which is the repeated presentation of the CS without the US. Extinction provides a laboratory analog of exposure therapy; thus developing methods that enhance extinction may also facilitate exposure-based therapies for PTSD.

In addition to FPS, the skin conductance response (SCR), an index of sympathetic nervous system activity, is frequently used in measuring fear acquisition and extinction in tandem with brain imaging studies (Bremner et al., 2005; Knight, 2005; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Milad et al., 2007; Phelps, Delgado, Nearing, & LeDoux, 2004). Studies using both FPS and SCR have found fear extinction deficits in subjects with PTSD (Guthrie & Bryant, 2006; Milad et al., 2008). We have recently developed a startle paradigm that measures fear potentiation and inhibition of fear. Using this paradigm, we found that PTSD subjects with higher current symptoms showed impaired inhibition of fear in the presence of safety cues (Jovanovic et al., 2009). We have also found that traumatized individuals with PTSD show exaggerated FPS compared to trauma controls (Jovanovic, Norrholm, Blanding, Phifer, et al., 2010) during fear conditioning as well as during fear extinction (Norrholm et al., 2011). Finally, we found that individual variability in hyper-arousal symptoms of PTSD were associated with impaired fear inhibition (Jovanovic, Norrholm, Blanding, Davis, et al., 2010), while individuals with the highest re-experiencing symptoms showed the most exaggerated fear during conditioning and extinction (Norrholm, et al., 2011). Heightened “fear load” can hinder effective therapy; thus developing strategies for reducing fear expression may significantly increase treatment efficacy. A potential pharmacological target for reducing fear is the glucocorticoid system, given that elevated cortisol releasing hormone (CRH) levels are associated with increased fear responses (Kalin & Takahashi, 1990) and anxiety (Sutton, Koob, Le Moal, Rivier, & Vale, 1982), including the startle response (Keen-Rhinehart et al., 2008; Lee & Davis, 1997; Liang et al., 1992) and enhanced fear conditioning (Roozendaal, Brunson, Holloway, McGaugh, & Baram, 2002; Swerdlow, Britton, & Koob, 1989).

Glucocorticoid Receptor Sensitivity in PTSD

Recently, genetic markers have been discovered that interact with early childhood abuse to increase risk for PTSD; specifically, polymorphisms of the *FKBP5* gene have been associated with PTSD symptoms (Binder et al., 2008; Xie et al., 2010). This gene is involved in regulating cortisol feedback function (Binder, 2009; Binder, et al., 2008), the stress hormone mechanism that is one of the most frequently reported neurobiological alterations in PTSD (Baker et al., 1999; de Kloet et al., 2007; Yehuda, 2009; Yehuda, Giller, Southwick, Lowy, & et al., 1991). Heightened cortisol reactivity in response to psychosocial stress has been observed in victims of physical and sexual childhood abuse (Heim et al., 2000). On the other hand, exaggerated suppression of hypothalamic-pituitary-adrenal (HPA) axis activity following administration of dexamethasone, a cortisol analogue, has been a consistent finding in PTSD (Yehuda, Golier, Halligan, Meaney, & Bierer, 2004; Yehuda, Halligan, Golier, Grossman, & Bierer, 2004; Yehuda, Halligan, Grossman, Golier, & Wong, 2002), although recent studies indicate that this effect is strongest in individuals with higher genetic risk, i.e., carriers of the *FKBP5* risk allele (Binder, et al., 2008). Taken together, these studies suggest that HPA dysregulations are long-term sequelae of trauma (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Yehuda, et al., 2002) that are associated with genetic risk for PTSD. Another component of the HPA axis is glucocorticoid receptor (GR) hypersensitivity (Yehuda, 2009), which is evident from exaggerated negative feedback (Yehuda, et al., 2002), and may be due to increased numbers of GR receptors in PTSD (Yehuda, Lowry, Southwick, Mason, & Giller, 1991) or altered receptor binding properties. GR alterations may be related to early environment, epigenetic effects (McGowan et al., 2009), or genetic risk factors (Binder, et al., 2008). While peripheral levels of cortisol, which is the end product of the HPA axis, have not been consistently associated with PTSD, the current status of the literature has been to focus on glucocorticoid receptor sensitivity, rather than hormone levels (Yehuda, 2009). The proposed study will use dexamethasone suppression of cortisol, which specifically targets GR hypersensitivity as a mechanism, rather than absolute values of baseline or suppressed cortisol levels.

Cortisol Suppression and Fear Expression in PTSD

As described above, the amygdala is part of the fear neurocircuitry that is dysregulated in PTSD. In addition, the amygdala has outputs to hypothalamus (Figure 1), which is the target of negative feedback by cortisol via GR. A study using fear-potentiated startle in healthy subjects found that high cortisol to dehydroepiandrosterone-sulfate (DHEA-S) ratios after fear conditioning were associated with increased startle potentiation (Grillon et al., 2006). Our data using dexamethasone suppression of cortisol with fear-potentiated startle in PTSD patients suggest that GR sensitivity to cortisol may interact with amygdala activation to enhance fear responses in PTSD (Jovanovic et al., 2011). Given the neuroimaging findings of amygdala hyperactivity in PTSD (Shin, et al., 2006), and the well-known association between glucocorticoids and the amygdala in nonhuman studies (Roozendaal, Barsegyan, Lee, E. Ronald De Kloet, & Eric, 2007), this understudied area of research is of paramount importance to progress in the field of PTSD neurobiology.

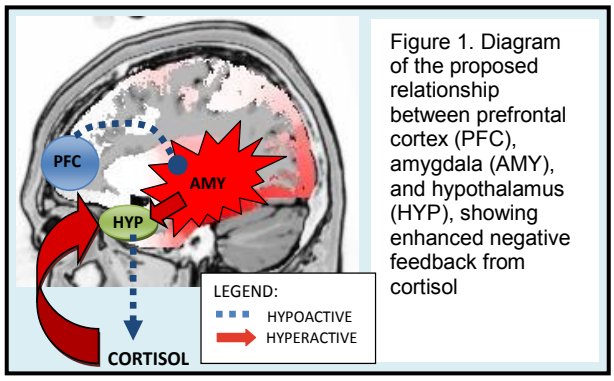

Figure 1. Diagram of the proposed relationship between prefrontal cortex (PFC), amygdala (AMY), and hypothalamus (HYP), showing enhanced negative feedback from cortisol

Virtual Reality Exposure Therapy:

Exposure therapy was chosen for its direct translation from extinction paradigms in animals and the efficacy of exposure therapy in the treatment of chronic PTSD. Virtual reality was chosen as the medium for exposure therapy based on its efficacy to date and primarily for the experimental control it affords. An obvious anxiety disorder to target is posttraumatic stress

disorder (PTSD), as it has been conceptualized as resulting from a failure of extinction (Rothbaum & Davis, 2003). Results from our current trial of VRE with the virtual Iraq and virtual Afghanistan augmented with various medications, ongoing but closed to enrollment, has shown VRE to be safe, acceptable, and effective across augmentation groups with statistically significant improvement in PTSD symptoms from baseline assessment to post-treatment assessment as well as 3, 6, and 12 month follow-ups. These veterans are younger and "cleaner" with fewer concomitant medications and comorbid disorders than the Vietnam veterans.

Virtual reality offers a human-computer interaction paradigm in which users are no longer simply external observers of images on a computer screen but are active participants within a computer-generated three-dimensional virtual world. Virtual environments differ from traditional displays in that computer graphics and various display and input technologies are integrated to give the user a sense of presence or immersion in the virtual environment. The most common approach to the creation of a virtual environment is to outfit the user in a head-mounted display. Head-mounted displays consist of separate display screens for each eye, along with some type of display optics, stereo earphones, and a head-tracking device. The user is presented with a computer-generated view of a virtual world that changes in a natural way with head and body motion. For some environments, users may also hold a second position sensor in their hand that allows them to manipulate their environment.

The Virtual Environments (VE) to be used in the proposed study were developed with input from veterans returning from Iraq and Afghanistan The VE includes not only a series of diverse *scenario settings* (i.e. city) but also the creation of options for providing the user with different first person *user perspective options*. These options, when combined with real time clinician input via the clinical *interface,* are envisioned to allow for the creation of a user experience that is specifically customized to the varied needs of patients who participate in treatment. This is an essential component for giving the therapist the capacity to modulate client anxiety as is required for an exposure therapy approach. Such customization and real time stimulus delivery flexibility are key elements for these types of VR exposure applications. The software has been designed such that clients can be exposed to specific scenario settings based on a determination as to which environments most closely match the client's needs, relevant to their individual combat related experiences. All scenario settings are adjustable for time of day or night, weather conditions and lighting illumination.

1. **City Scenario** –This setting has the appearance of a typical urban environment including various desolate, low populated streets as well as old buildings, apartments, and mosques. The city scenario also includes more highly populated areas with more traffic activity, marketplace scenes, and monuments. Some of the City Scenario buildings (i.e. the mosque) have interiors modeled that will allow the participant to navigate through them. 2. **Desert Road Humvee** – This scenario consists of a single Humvee travelling on a paved desert highway; views from the vehicle include desert scenery and the occasional highway overpass. Stimuli within this environment include battle wreckage, debris, human figures by the side of the road, insurgents, explosions, and IED blasts. Subjects may be seated in the driver position, passenger position or the gunner position of the vehicle. 3. **Desert Road Humvee Convoy** - This scenario is the same as described above (single Humvee). However, added stimuli include a convoy of vehicles.

The VR system is designed such that once the scenario setting is selected, it is possible to select from a variety of user perspective and navigation options in order to provide flexibility in how the interaction in the scenario settings can be customized to suit the client's needs. The current VE also includes trigger stimuli based on reports on relevancy by returning soldiers and military subject matter experts. These include: 1. Auditory (i.e., weapon fire, explosions, vehicle noise, wind, human voices), 2. Static Visual (i.e. wounded civilians and combatants, wrecked vehicles), 3. Dynamic Visual (i.e., distant views of human and vehicle movement), 4. Dynamic

Audiovisual (i.e., nearby human and vehicle movement). A variety of auditory trigger stimuli (i.e., incoming mortars, weapon fire, voices, wind, helicopter flyovers above the user's position etc.) that can be actuated by the clinician via mouse clicks on a clinical interface.

The VE allows for the addition of two additional types of stimuli, olfactory and tactile. Scents may be employed as direct stimuli (e.g., scent of burning rubber) or as cues to help immerse persons in the world (e.g., ethnic food cooking). This allows for the simultaneous delivery of these stimuli with visual and audio events to create a multi-modal experience. The amount of scent to be released is specified in seconds. The scents are concentrated and gelled much like an air freshener cartridge and enclosed within the Scent Palette in an airtight chamber that fills with compressed air. When activated, the scent is released into an air stream provided by 4 electric fans so that it moves past the user and then dissipates into the volume of the room. The scents that have been selected for this application thus far include burning rubber, cordite, garbage, body odor, smoke, diesel fuel, Iraqi spices and gunpowder. Scent has been shown to be related to emotional responding and will allow clinicians greater range of options when applying VR in clinical settings. Similarly, tactile input in the form of vibration adds another sensory modality to the virtual environment, again to enhance presence. Vibration is obtained through sound transducers located beneath the client's floor platform driven by an audio amplifier. The sound files embedded in the software are customized to provide vibration consistent with relevant visual and audio stimuli in the scenario. For example, explosions and gunfire can be accompanied by this additive sensation and the vibration can also be varied as when a virtual vehicle moves across seemingly uneven ground.

Clinical Interface. The clinical interface allows the clinician to customize the therapy experience to the client's individual needs via the systematic real-time delivery and control of "trigger" stimuli in the environment. The clinician uses a separate computer monitor/mouse or tablet laptop to display and control the clinical interface. The clinician can adjust the time of day, weather options, ambient sounds, scent and vibration configurations and user perspective. Once these options are selected, the client can experience this customized environment setting while the clinician then may focus on the judicious delivery of trigger stimuli. These interface options have been designed, with the aid of feedback from clinicians, with the goal to provide a usable and flexible control system for conducting thoughtfully administered exposure therapy that can be readily customized to suit the needs of the client.

1. Significance of the Proposed Research

This type of combined treatment -- specific pharmacotherapeutic augmentation of psychotherapy -- would be novel and would potentially be generalizable to many different forms of psychotherapy for a wide range of disorders. If this translational research is successful, the ability of a relatively benign agent administered before a psychotherapy session to facilitate the psychotherapeutic process could have important clinical, humanitarian, and economic advantages. Although exposure therapy is highly effective in treating PTSD in those patients who complete the full regiment, it is sometimes difficult for patients to overcome the initially aversive component of imaginal or virtual exposure. In addition to enhancing the therapeutic effect of exposure therapy, we expect that reducing fear prior to the onset of the therapy session will make recalling traumatic memories more tolerable for the patients, resulting in fewer drop-outs and better compliance with therapy. This could have profound effects on improving patients' long-term outcomes.

Understanding the neurobiological underpinnings of PTSD is crucial to improving both psychotherapy and pharmacotherapy for these patients. Discovering brain-based phenotypic biomarkers of the disorder will optimize diagnosis and treatment strategy resulting in better and faster treatment response. These new strategies will be invaluable as the number of patients increases. There is no question that PTSD is a serious and urgent public health problem and that the biological mechanisms of vulnerability to developing psychopathology after trauma must

be investigated very closely. A promising candidate neurobiological mechanism involves the neurocircuitry of fear, which, according to several lines of evidence, appears to be dysregulated in PTSD (Jovanovic, et al., 2009; Liberzon & Martis, 2006; Milad et al., 2009; Norrholm, et al., 2011; Shin, et al., 2006).

2. Objectives

Specific Aims and Research Hypotheses

The proposed study is designed to achieve the following specific aims:

Aim 1. To explore whether dexamethasone (DEX), a cortisol analogue, administered 10+ hours prior to the virtual reality exposure (VRE) therapy session, enhances exposure therapy in humans with PTSD as compared to pill placebo;
Aim 2. To explore whether any enhancement in exposure therapy produced by DEX in VRE evidenced within session and immediately post-treatment results in long-term gains in treatment response as compared to pill placebo.

The following hypotheses will be tested:

1) DEX will facilitate fear extinction in humans. It is predicted that the patients who receive VRE combined with 0.5 mg DEX + 10hr will evidence more improvement on symptom measures, and on reduced psychophysiological arousal measured via startle, skin conductance, and heart-rate responses during exposure to Iraq or Afghanistan military scenes, than the placebo group. Furthermore, DEX + VRE will result in faster improvement in symptoms (fewer sessions to reach 70% reduction in symptoms), and fewer drop-outs (i.e., better tolerance of exposure therapy).
2) Facilitation of therapeutic response aided by DEX will result in long-term gains. It is predicted that the group of patients who receive VRE combined with 0.5 mg of DEX will evidence more improvement on a follow-up assessment gathered 3, 6, and 12 months post-treatment as compared to baseline on symptom measures and reduced startle, skin conductance, and heart-rate responses during exposure to Iraq or Afghanistan military scenes than the group who receives placebo.

Exploratory analyses of genetic markers will examine predictors of treatment response. The long-term goals include furthering translational research and directly applying paradigms shown successful in animals to humans. For this specific paradigm, we plan to establish whether DEX can facilitate exposure therapy and apply this knowledge to other disorders. Random assignment of participants to placebo or active conditions, standardized treatment delivery, homogeneous DSM inclusion criteria, and blind independent assessment will assure a methodologically rigorous study.

3.0 Participant Selection

3.1 Eligibility Criteria

Participant Inclusion Criteria:

(a) Participants will be 100 males and females between ages of 21 and 65.

(b) Participants must meet DSM-V criteria for PTSD due to exposure to a trauma while serving in Operation Iraqi Freedom and/or Operation Enduring Freedom-Afghanistan and Operation New Dawn.

(c) Patients must be literate in English.

(d) Patients must be medically healthy or medically stable such that the stress of VR and DEX are not contraindicated. (e) Participants must comprehend his or her role in the study and the risks involved in order to be entered.

Gender and Minority Participants' Inclusion Plan. Males and females of all races and ethnic groups will be entered. The racial composition of Atlanta is 71% white, 26% black, and 3% other (based on the 1990 US Census). Approximately 1% of these persons are of Hispanic origins. The gender composition of Atlanta is 51% female. This study will provide free treatment and will be advertised in the popular press, thus ensuring equal opportunities for all to learn about and participate in this study. The treatment setting is located in a racially diverse county (DeKalb County), is easily accessible by public transportation and is wheelchair accessible. It is therefore expected that the study sample will closely approximate the demographic composition of Atlanta, except that only 15% of the military is currently female. Based on our current study of VRE, we expect that the current sample will be approximately 40% Caucasian, 60% non-caucasian, and 5% female. Persons between18-21 will not be included, as there are specific treatments for children and younger people with PTSD and the effects of dexamethasone are unknown in children.

3.2 Ineligibility Criteria

Participant Exclusion Criteria:

(a) Patients with a history of mania, schizophrenia, or other psychoses;
(b) Patients with prominent suicidal ideation;
(c) Patients with current alcohol or drug dependence;
(d) Patients unable to tolerate wearing the VR helmet;
(e) Patients unwilling to take study medication;
(f) Patients on psychotropic medication(s) must have been on a stable dose for at least 2 weeks prior to beginning the study and must agree not to change their current medication regimen throughout the course of the study. The concomitant use of psychotropic medications will be recorded and examined in data analyses.
(g) Patients with special medical conditions such as pregnancy, renal insufficiency, or a history of significant head injury
(h) Active medical disorders contributing to psychiatric sx e.g. hypo or hyperthyroidism, SLE, advanced cirrhosis, etc. (per clinical judgment of study physician)
(i) Patients stabilized on potentially data-obscuring medications (glucocorticoids).

3.3 Any current unstable medical illness or medical illness that represents a contraindication to taking low-dose dexamethasone, such as osteoporosis, diabetes, narrow-angle glaucoma, immunosuppressed state (e.g. HIV infection), current infection, as assessed by one of the study physicians, Dr. Boadie Dunlop or Dr. Jeffrey Rakofsky.

3.4 Issues related to medication stabilization

(a) we currently request no less than a two week period of time between the last change in a daily chronic psychotropic medication (such as SSRI or mood stabilizer) before the initiation of the first study drug administration
(b) for long-acting benzodiazepines, such as clonazepam and valium, this stabilization period off of benzodiazepines should be 1 month.
(c) For short-acting, and PRN benzodiazepines (e.g. ambien or xanax) 2 weeks stabilization should be sufficient.

(d) For other non-benzo PRN medications with short half-life (trazadone for sleep, pain medication, etc.) we request that these are not used for 24 hours prior to the medication – therapy combination.

4.0 Pretreatment Evaluation

See Data Collection below.

5.0 Registration/Randomization

Participants will be self-referred or referred by professionals; phone screening will be conducted by a member of the study team to determine appropriateness of this study for each participant and to inform the participant of study procedures. Patients may be referred from both VA personnel and non-VA sources. At this time, basic inclusion and exclusion criteria, including medical history, chronic medical issues, suicidality, and alcohol/substance abuse/dependence will be briefly reviewed according to a structured telephone screening interview. The investigators are requesting an IRB waiver of consent for the various pre-randomization screening activities, including any review of relevant records and the telephone screening process. If an individual is potentially eligible and interested in participating, an initial evaluation will be scheduled. All assessments will be conducted by independent assessors who will be blinded to treatment condition once randomization occurs, individually and in person. All assessment interviews will be videotaped for use in assessing inter-rater reliability.

Study staff will not recommend that a potential participant discontinue current medications, nor assess response to those current medications. If a potential participant indicates interest in being evaluated for participation in the study but is currently on exclusionary medications, they will be told that study staff will not render an opinion on whether someone should discontinue current medications and that this decision should be made between the individual and their treating physician. Study staff will note that there are risks associated with discontinuing medications, and that there is no guarantee that they would be eligible for entry into the study even if they do discontinue their current medications.

6.0 Therapy

Treatment will commence following the pre-treatment assessment and all participants will be then randomized and seen for an introductory session and then treated once or twice per week for 6-11 therapy sessions, including one information gathering and preparation for VRE sessions. Patients will be randomized to receive dexamethasone or pill placebo before the VRE sessions. VRE will be limited to a minimum of 6 sessions and a maximum of 11 sessions, based upon reaching criterion of 70 % symptom improvement as indicated on the PTSD Symptom Scale or an agreement between clinician and participant that maximum treatment response has been achieved. All sessions will be individual and weekly or twice weekly. The first session will last approximately 90 minutes and will be spent in information gathering, treatment planning, and explaining the treatment rationale to the patient. Information gathering will review the history of PTSD and their military service and will include a brief psychosocial history, including review of prior treatment. The VRE sessions will last 90-minutes each. During VRE sessions patients will wear a head-mounted display with stereo earphones that will provide visual and audio cues consistent with Iraqi or Afghan military scenarios. The therapist will make appropriate comments and encourage continued exposure until anxiety has habituated. During exposure, information will be gathered on the participant's anxiety level through the use of a 0-100 SUDs scale. All therapists will have been trained in Prolonged Imaginal Exposure therapy (PE) followed by training in VRE by Drs. Rothbaum and Rauch. Drs. Rothbaum and Rauch will supervise all therapy.

Medication

As described above, we will compare pill placebo to dexamethasone in a double-blind manner. Patients will be instructed to take the single pill the night before each VRE session and will be given a reminder call the night before the VRE session to reinforce medication compliance.

Patient Compliance

Individual patient compliance with treatment will be evaluated based on attendance at therapy sessions, pill count, completion of assessments and cortisol levels present at onset of each therapy session.

7.0 Pathology

Participants must meet DSM--V criteria for Posttraumatic Stress Disorder due to military service in Iraq or Afghanistan.

8.0 Patient Assessment

Pre-Treatment Assessment

Potential subjects will be asked to provide a copy of their DD214 to verify combat exposure. Once a potential participant has met all screening inclusion and exclusion criteria and consented to participate, the CAPS will be administered to determine current PTSD status.

The Clinician Administered PTSD Scale (CAPS-5; Blake et al., 1995; updated for DSM V) is an interviewer-administered diagnostic instrument that measures PTSD. The CAPS provides a diagnostic measure of PTSD and a continuous measure of the severity, frequency, and intensity of the three symptom clusters (intrusion, avoidance, and arousal) and overall PTSD. If positive for current PTSD on the CAPS, and all other eligibility criteria are fulfilled, the rest of the pre-treatment measures will be administered.

The Columbia–Suicide Severity Rating Scale. (Columbia; Posner et al., 2011). The Columbia–Suicide Severity Rating Scale was initially designed to assess suicidal ideation and behavior in clinical trials. It assesses occurrences, types, and severity of suicidal ideation and all types of behavior.

Neurobehavioral Symptom Inventory (NBI; Mererko et al., 2012). This is a 22 item measure designed to assess postconcussive symptoms following deployment-related mild traumatic brain injury among veterans.

Patient-Reported Outcomes Measurement Information System 8a and 4a -Satisfaction with Social Roles and Activities (PROMIS 4a, PROMIS8a, (Cella et al., 2010). The PROMIS item bank assesses satisfaction with performing one's usual social roles and activities.

The Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams 2001). The PHQ-9 is assesses each of the 9 DSM-IV criteria for depression as "0" (not at all) to "3" (nearly every day).

The Alcohol Use Disorders Identification Test—Consumption (AUDIT-C; Frank, Danielle et al. 2008). The AUDIT-C is a brief validated self-report screen for risky drinking and alcohol abuse and dependence (alcohol misuse). It has three questions that ask the frequency and amount of alcohol consumed.

Life Events Checklist for DSM-V (LEC-5; Weathers, et al., 2013). This is a self-report measure designed to screen for potentially traumatic events in a respondent's lifetime. It is useful in more specifically identifying the Criterion A stressor queried during the CAPS interview.

The Demographics Questionnaire covers demographics; family composition; personal psychiatric history; and income and education to obtain a *Hollingshead Four Factor Scale of Socioeconomic* Status.

The Childhood Trauma Questionnaire (CTQ; Bernstein, 1995) is a self-report measure which assesses history of childhood trauma employing a Likert-scale format with 5 responses per item.

PTSD Symptom Scale-Interview for DSM-5 (PSS-I-5; Foa & Capaldi, 2013) assesses current symptom frequency and intensity for the past month.

The MINI International Neuropsychiatric Interview (M.I.N.I. .; Sheehan, D. V. et al., 1998) will be administered to screen axis 1 disorders and to establish co-morbid diagnosis.

The Beck Depression Inventory-II (BDI; Beck, Steer, & Brown, 1996) is a 21-item measure of cognitive and vegetative symptoms of depression is widely used in a variety of populations, including trauma victims and is sensitive to treatment effects on depression.

State Trait Inventory (STAI; Spielberger et al., 1983). The STAI-State is a 20-item self-report scale employing a Likert scale format with 4 responses per item (1-4). Ten of the STAI items measure feelings of stress and anxiety, while the remaining ten items measure feelings of relaxation.

Deployment Risk and Resiliency Inventory (DRRI; King et al., National Center for PTSD, 2003) is a self-report measure of pre-deployment, deployment and post-deployment experiences and trauma specific to the veteran population. The scale employs yes-no and Likert scale format responses ranging from 1-5.

The Quality of Life Inventory (QOLI; Frisch et al., 1992) The QOLI consists of 16 items selected to include all areas of life that have been empirically associated with life satisfaction. Respondents rate how important each of the 16 domains is to their overall satisfaction and happiness; they then rate how satisfied they are in the area. The total score reflects one's satisfaction in areas that one considers important to them. The QOLI's sensitivity to treatment-related change has been demonstrated with clinical samples of depressed, socially anxious/phobic, and chemically-dependent patients.

Clinical Global Impressions Scale, Severity of Illness (CGI-Severity; Guy & Bonato, 1970). This is a study personnel rated measure of severity of illness ranging from 0 (not assessed) to 7 (among the most extremely ill patients).

Mini-Mental State Examination (MMSE; Folstein et al., 1975). The MMSE is an 11-question, personnel rated measure that covers patient orientation, registration, attention/calculation, recall, and language skills.

Psychophysiological Patient Report: This is a brief self-report administered following each psychophysiological assessment. Using a likert scale (Not at all to Very/Severe) participants rate the assessment VE as to 1. How closely the video matched their experience and 2. How distressing they found the video.

Intent to Attend (Leon et al., 2007) is a short, two question survey asking participants how likely they are to complete all of the study and how likely they are to attend the next session.

Psychophysiological Reactivity Assessment: Acoustic startle response, skin conductance, and heart rate will be assessed during a viewing of three VR scenes. The VR scenes will be presented through a head-mount display for a duration of 15 minutes. Psychophysiological data collection is described below.

Cortisol Reactivity Assessment: Saliva cortisol will be sampled at four intervals relative to the 15-min viewing of VR scenes: prior to, immediately after, 15 min, and 45 min after VR. Cortisol sampling methods are described below.

The Emory Treatment Resistance Interview for PTSD (E-TRIP) is a structured interview that assesses prior trials of pharmacology and psychotherapy PTSD treatments and provides a quantitative indicator of PTSD treatment resistance.

Posttraumatic Stress Disorder Checklist (PCL): The PCL is a 17-item self-report checklist of PTSD symptoms based closely on the DSM-IV criteria. Respondents rate each item

from 1 ("not at all") to 5 ("extremely") to indicate the degree to which they have been bothered by that particular symptom over the past month.

Measures at each Therapy Session

Expectancy of Therapeutic Outcome Questionnaire (ETOQ*)* assesses how logical the treatment appears, and the expectancy of success for the patient and for others. This measure is administered after session 1 only.

Clinical Global Impressions Scale, Severity of Illness (CGI-Severity; Guy & Bonato, 1970). This is a study personnel rated measure of severity of illness ranging from 0 (not assessed) to 7 (among the most extremely ill patients). This measure is administered after sessions 1–6.

Clinical Global Impression – Improvement (CGI-Improvement; Guy & Bonato, 1970). This is a study personnel rated measure of patient's improvement since start of study ranging from 1 (very much improved) to 7 (very much worse). This measure is administered after sessions 2-6.

Clinical Global Improvement Scale, Patient Report (CGI - Self Report; Guy & Bonato, 1970). This is a self-reported global measure of change in severity of symptoms, ranging from 1 (*very much improved*) to 4 (*unchanged*) to 7 (*very much worse*). This measure is administered after sessions 1-6.

The PTSD Symptom Scale is a 17-item interview used to aid in the detection and diagnosis of PTSD (described above), administered before sessions 2-6.

Subjective Units of Discomfort (SUDs) will be gathered during each exposure session (sessions 2-6). Participants will be asked to rate their level of discomfort on a scale of 0 (no anxiety) to 100 (panic levels of anxiety) every 5 minutes during the VR exposure.

Intent to Attend (Leon et al., 2007) is a short, two question survey asking participants how likely they are to complete all of the study and how likely they are to attend the next session.

Blinded Medication Check is a one-question measure to asses which medication the participant believes they took.

Cortisol Sampling will be obtained from saliva in order to measure post-dexamethasone cortisol levels and detect the presence of dexamethasone in saliva. Cortisol sampling methods are described below.

Post treatment and 3, 6 and 12-month Follow-up Assessments

The Clinician Administered PTSD Scale (CAPS) (see above).

The Beck Depression Inventory (BDI) as above.

The PTSD Symptom Scale as above.

The Clinical Global Improvement Scale (Severity, Improvement, and Patient Report) as described above.

The Quality of Life Inventory as above.

The State Trait Inventory as above.

Patient Update Interview: This a brief study personnel-interview administered to obtain general patient follow-up data, i.e. between-assessment treatment, medication changes, substance use status/changes, and patient report on relationship/employment/health changes.

Psychophysiological Patient Report as above.

Psychophysiological and Cortisol Reactivity (as described above) to the VR scenes will be assessed at each follow-up point.

Posttraumatic Stress Disorder Checklist (PCL) as above.

Psychophysiological Data Collection:

Psychophysiological data will be acquired at a sampling rate of 1kHz, amplified and digitized using the EMG module of the Biopac MP150 for Windows (Biopac Systems, Inc., Aero Camino, CA).

1. The acoustic startle response (eyeblink component) will be measured via electromyographic (EMG) recordings of the right *orbicularis oculi* muscle. Two 5 mm Ag/AgCl pre-gelled disposable electrodes will be positioned approximately 1 cm under the pupil and 1 cm below the lateral canthus. The startle probe (noise burst) will be a 108-dB (A) SPL, 40-ms burst of broadband noise with a near instantaneous rise time.

2. Skin conductance level and skin conductance response will be acquired at a sampling rate of 1 kHz using the GSR module of the Biopac system. Two 5 mm Ag/AgCl disposable electrodes filled with isotonic paste will be attached to middle phalanges of the second and fourth finger of the non-dominant hand.

3. Heart-rate and heart-rate variability (HRV) will be measured using the ECG module of the Biopac system at a sampling rate of 1 kHz. One 5mm Ag/AgCl electrode will be placed on the chest above the right clavicle, another electrode will be placed on the chest under the left side of the ribcage.

Collection of Salivary Samples:

Salivary samples will be collected in prior to the beginning of the VR assessment, immediately after viewing VR scenes and 15 and 45 min after VR scenes using saliva collection tubes. The saliva samples will be assayed for cortisol levels on assessment days. On intervention days, saliva samples will be collected in the morning when the patient arrives for the session and will be assayed for cortisol and presence of dexamethasone to confirm compliance. Assays will be completed in the Yerkes Endocrinology Core Laboratory at Emory using commercial radioimmunoassay kits (DiaSorin, Stillwater, Minn.). The inter- and intra-assay coefficients of variation will be determined and is expected to be between 4-7%. Radioimmunoassay kits from IgG Corporation (Nashville, Tenn.) will be used to determine dexamethasone concentrations to confirm that subjects have detectable dexamethasone levels for the post-dex cortisol sample.

Interventions:

VRE. The VRE treatment program will consist of 90-minute individual treatment sessions. Procedures include education about common reactions to trauma, breathing retraining, prolonged (repeated) virtual exposure to trauma, and discussion of thoughts and feelings related to exposure exercises. The discussion addresses unrealistic beliefs about the self and the world, attempting to “process” material that came up during the exposure and make new associations explicit (e.g., “You see, by staying with the image long enough, your anxiety decreases.”) Session 1 is devoted to information gathering, education about common reactions to trauma, elaboration of the index trauma, breathing retraining, and fostering a therapeutic alliance. The remaining 5-10 sessions consist of VRE interventions and discussion of these experiences.

The patient will be encouraged to expose him or herself to traumatic memories triggered by the virtual environments, following guidelines for standard exposure therapy. As the number of sessions is limited, we are limiting exposure to the identified index trauma, and in some cases, a second traumatic event. The therapist asks the patient to give a SUDs (Subjective Units of Discomfort, 0= no anxiety and 100=maximum anxiety) rating approximately every five

minutes during all exposures as an indication of his level of anxiety. The therapist makes appropriate comments and encourages continued exposure until anxiety has decreased. The therapist simultaneously views on a video monitor all of the virtual environments in which patients are interacting and therefore is able to comment appropriately and is attempting to match stimuli that the patient is describing to the virtual stimuli, as much as possible, for example by landing the helicopter at the appropriate time in the memory, or by having gunfire, bombs, fog, or night time to match the memory. The 90-minute session will consist of 15 minutes of checking in with the patient about their functioning and anxiety since the last session, up to 45 minutes of exposure to their traumatic memories and the virtual stimuli, followed by processing and discussion about the material from the exposure. Information is gathered each session on any other exposure the patient may have conducted, although no homework will be assigned, as patients will only be on study medication for office visits.

Medication. Beginning with session 2 (the first session where VRE is used), the patients will take either the dexamethasone medication (0.5 mg) or placebo 8-10 hours prior to the VRE session. A study staff member will call the patient to remind them to take their medication at the appropriate time. As the study will be double-blind, neither the patients, the study staff nor clinicians will know which pill the patient took. However, as a check for compliance, saliva samples will be tested for the presence of dexamethasone. These results will be available to investigators once the study is completed and unblinded. This approach has been used in our previous IRB protocols (IRB #51911, PI: Jovanovic), with high compliance rates.

8.1 Procedure

Study staff will conduct extensive phone screening to determine appropriateness of this project for each patient and will provide information on project design and procedures. Upon medical history review and a physical exam performed by the study physician, a pre-assessment visit will be scheduled at which time patients will be thoroughly evaluated as to inclusion and exclusion criteria (detailed above) and explained the procedures of the project in detail. Informed consent will be obtained at this pre-assessment visit. The consent form, CAPS and M.I.N.I. will be completed prior to official study entry. If eligible and willing to participate, individuals will officially be enrolled in the study and will complete the pre-treatment assessment questionnaires. During the pre-assessment visit we will collect a one-time saliva sample to be used for the purpose of DNA extraction. DNA extraction is optional and will be presented to participants under a separate consent. Following consent, initial diagnostic interviews, self-reports, and DNA extraction (if consented), psychophysiological data will be collected (described above), including 3 cortisol samples at each assessment, and the first of the therapy visits will be scheduled. Following randomization, the participant will receive a pill and be instructed to take it at 11pm before every VRE therapy session. During any visit after taking dexamethasone, the participants will be assessed for adverse effects of the drug by the study staff. Significant adverse effects will be reviewed by the study physician; if the study physician determines that the study puts the participant at undue risk, their participation will be stopped.

All treatment will be free of charge to the participant and no funding is available to compensate for these visits (treatment sessions 1-6 or 11). Post treatment and follow-up visits, however, (post, 3, 6, and 12-month follow-up) will be compensated $20 for time and travel.

If the treating therapist makes a clinical judgment at the conclusion of treatment sessions that a participant requires additional follow-up treatment sessions for stabilization, these may be offered as compassionate care. The participant will also continue with scheduled post-treatment assessments as per the study protocol.

Independent Assessor Reliability Monitoring. All MINI and CAPS interviews will be videotaped and rated for reliability. Ten percent of the baseline MINI and CAPS interviews will

be randomly selected in an ongoing way in order to monitor the reliability of the interview process.

8.2. Risks to participation:

- As a guard against *risk of breach of confidentiality*, all information will be stored in locked files in a locked research area that can only be accessed by research personnel. No names or identifying information will be used in publications that result from this research. Under no circumstances will identifying information be released to any outside party (beyond those immediately connected with the study) without written consent from the subject. In cases where data are stored on computers, no data containing identifiers or PHI will be stored on hard drives—only on removable media, which will be removed from the computer when not in use. All databases will be password protected.
- With regard to *risk of distress associated with interviews*, the participants will be told that they can stop the process at any point if they become overwhelmed or fatigued. Following their participation in the research, participants will be debriefed and have an opportunity to discuss their participation in the research and ask any questions they may have for the interviewer. If the patients are currently in psychiatric treatment, they will be encouraged to discuss any distress with their clinician (and with their permission we will provide feedback on the assessment to the treating clinician). If they are no longer in treatment, or if they request it, a list of resources (local mental health services) will be provided to them after participation. All subjects completing interviews and questionnaires will be provided with phone numbers so that they can have any questions answered that they feel have not been satisfactorily addressed. The investigative team has extensive experience, and they will determine if there is a need for clinical intervention; if necessary, arrangements for appropriate clinical services will be made.
- With regard to *risks associated with the acoustic startle response, electrodermal activity*, *and electrocardiogram recording*, if skin cleansing becomes uncomfortable for a given subject, the researcher will end the skin preparation at that point and apply the electrodes without further cleansing. The decibel levels and duration of the auditory stimuli are not sufficient to cause any damage to the ear. If a subject finds the noises too uncomfortable, the researcher will stop the experimental session immediately.
- With regard to *risk of dexamethasone administration,* no significant side effects have been observed in response to intermittent administration of dexamethasone (Decadron; Merck & Co., Inc., Whitehouse Station, NJ, http://www.merck.com). Decadron can cause anaphylactic shock in allergic patients and there are a wide range of side effects associated with prolonged administration. Participants will be carefully prescreened for allergies, pregnancy and other medical problems such as osteoporosis, diabetes, narrow-angle glaucoma, immunosuppressed state (e.g. HIV infection), and current infection that this medicine might affect before drug administration and a review of medical history and a physical exam will be performed by the study physician prior to study randomization

8.3 Benefits of Therapy:

The benefit of this project to individual subjects is the potential for clinical improvement, which far outweighs the risks. This project's potential to contribute knowledge regarding this application and the ability of acute dosing with DEX to facilitate treatment of PTSD are considered significant benefits with no foreseen global risks. Participants have the opportunity to complete the entire, full package of PE, (12 sessions), thereby increasing the odds that each patient should benefit from participating in this study.

9.0 Data Collection:

The sources of research material collected from patients will include paper and pencil self-report questionnaires, information from structured interviews, psychophysiological measures (including heart rate, skin conductance, salivary cortisol, and startle), and clinician ratings of symptomatology. Assessment and treatment sessions will be videotaped to calculate inter-rater reliability of assessments and treatment compliance. All of the above will become part of each patient's research file. This data will be collected specifically for this research program. Data will be entered and stored electronically using REDCap, a secure, online database capture application (Harris et al., 2009). All information about individual participants, including the questionnaires, videotapes, assessment results, and therapy notes will be kept private, to the extent allowed by law. All information about participants (including videotapes) will be stored in locked file cabinets in locked offices. Videotapes will only be shared with other study staff to make sure treatment is being conducted correctly. Videotapes will contain initials rather than full names. Videotapes will be erased or destroyed 3 years after completion of the study.

10.0 Statistical Considerations

10.1 Preliminary Analyses

Premature Termination. Patients will be considered dropouts (a) if they miss two or more sessions or (b) if serious adverse reactions or clinical complications (e.g., suicidal intention) develop. Initial data analyses will be conducted on treatment completers. This will address relative efficacy among treatment completers. A second analysis will be conducted including all patients who initiate treatment using an intent-to-treat analysis. This will address relative efficacy in the population intended for treatment, thus incorporating issues related to potential differential dropouts in the treatment groups. Finally, analyses will be conducted to see if treatment completers differ from drop-outs on demographic variables and pre-treatment measures.

Group Equivalence: We will evaluate the effectiveness of random assignment to two treatment groups by comparing the groups on demographics, baseline measures of key outcome variables, and other important theoretical covariates. We will characterize differences between study dropouts and completers, and between dropouts from the VRE+DEX and VRE+placebo groups. We will compare dropouts to completers on the same set of baseline variables that will be used to examine initial group equivalence. Differences between conditions will be assessed using one way ANOVA for continuous variables and chi-square analyses for categorical variables (Fleiss et al., 2013). Any observed differences that approach statistical significance ($P \leq 0.15$), and which are theoretically or empirically identified as potential confounders will be included as covariates in subsequent cross sectional and longitudinal analyses.

10.2 Statistical Analyses

Power and Sample Size

Power calculations are based on Cohen (1992). We set the Type I Error rate at 0.05 (two-tailed) for all computations. We first calculated the number of participants needed to test the effect of VRE augmentation with DEX at immediate post-treatment assessment (Hypothesis 1 above). Then, knowing how many participants would be needed at the end of this phase, we worked backward to calculate how many participants would need to be enrolled initially. We will continue to collect data from all participants, including those who drop out of treatment or are discontinued. Thus, loss to the study represents a failure to participate in measurement, and not merely dropout from treatment. We assumed that: (1) 10% of participants will be lost to the

study by the end of treatment; an additional 15% of participants will drop out of treatment, resulting in 25% of participants randomized to placebo or 0.5mg DEX groups that would not complete treatment. We anticipate that 10% of completers will be lost to the study prior to the 3 month follow-up visits.

The effect size measure used, *d*, represents the standardized difference between sample means. Cohen (1988) has proposed that d = .30, .50, and .80 be categorized as "small," "medium," and "large," respectively. We assume that a medium effect size—half a standard deviation—is the smallest clinically meaningful difference between DEX-augmented VRE vs. placebo-augmented VRE at the end of treatment.

For a two-group study design, 100 participants (*n*=50 in each group) would be needed to achieve a minimum desired power of 85% to detect an effect size of .65 with a 2-sided test at a significance level of 0.05.

Hypothesis 1: Patients who receive VRE+DEX will evidence more improvement on within-session measures (SUDs), on immediate post-treatment symptoms measures and on startle, SCR and HR, than the group who receives placebo.

To analyze pre-treatment and immediate post-treatment differences, the first analysis will compare the VRE+DEX condition to the VRE+placebo condition on the following outcome measures: 1) symptom measures (continuous variables); 2) psychophysiological measures (startle responses, cortisol levels, heart-rate, skin conductance) (continuous variables). It is expected that VRE+DEX participants will show significant improvement on all outcome measures immediately post-treatment compared to VRE+ placebo participants.

Continuous variables will be analyzed using multivariate repeated measures ANCOVA with treatment condition being the between subjects factor, the pre-treatment vs. post-treatment condition being the within subjects factor, and the scale scores as the multiple measures accounting for appropriate covariates as determined through preliminary analyses discussed above. Adjusted means and mean differences as well as interaction terms will be obtained and evaluated. Categorical variables will be analyzed using logistic regression and controlling for appropriate covariates resulting in adjusted odd ratios.

An additional approach to testing this hypothesis will involve using two categorical measures of clinically significant improvement: 1) a 30% decrease in the CAPs, and 2) a rating of "much improved" or "very much improved" by the therapist and participant on the CGI inventory at the end of active treatment. These data will be analyzed using logistic regression with the inclusion of appropriate terms for the covariates and treatment-by-covariate interactions.

Furthermore, we will look at the number of sessions required to reach 70% improvement or maximum treatment response and the number of dropouts, predicting fewer sessions to reach 70% improvement or maximum treatment response and fewer dropouts in the VRE + DEX group.

Within-subject measures will also be obtained to assess improvement within sessions. SUDS and psychophysiological measures (heart rate and skin conductance) will be used to measure within session anxiety levels. Average and peak values of these continuous variables will also be analyzed using a repeated measures ANCOVA.

Hypothesis 2: Patients who receive VRE+DEX will evidence more improvement on follow-up assessments (symptom measures and psychophysiological responses) gathered 3, 6 and 12 months post-treatment compared to the patients who receive the placebo.

Interval specific analyses: First, the effectiveness of the VRE+DEX treatment will be analyzed for the two interval periods separately: from immediately post-treatment to the 3, 6 and 12 -month assessment. To test these time interval specific treatment effects, logistic regression will be used to compute adjusted odd ratios for dichotomous outcomes and multivariate

repeated measures ANCOVA will be used to obtain adjusted means, mean differences and interaction terms for continuous outcomes. For each of these analyses, the baseline measure for each specific outcome will be included as a covariate in the analysis.

GEE Modeling for analysis of entire 12-month assessment period: Additionally, to evaluate treatment effects for the entire 12-month follow up period, logistic and linear generalized estimating equation (GEE) regression models will be used for dichotomous and continuous variables respectively. GEE modeling is an appropriate analytic tool for longitudinal, repeated measures data as it is designed to adjust for within-subject correlations over time (Liang & Zeger, 1986; Kleinbaum et al., 1998; Hardin & Hilbe, 2003). By using the GEE method, the relationship between outcome variables obtained at different assessment time points and predictor variables are analyzed simultaneously. GEE models are comprised of a time independent variable (i.e. treatment condition) and a time-dependent variable (i.e. key outcomes variables and covariates). The estimated coefficients reflect the relationship between the time-independent and time-dependent using all available longitudinal data. Since repeated observations within one subject are not independent of each other, a correction must be implemented to account for within-subject correlations. This correction is achieved by assuming an a priori correlation structure for the repeated measurements of the outcome variables. It is proposed that the autoregressive correlation structure will be utilized. The assumption behind the autoregressive correlation structure is that the correlation between responses is dependent on the interval of time between responses. The resulting GEE parameters can be interpreted as the odds or the mean difference for logistic and linear regression models respectively, over the entire 12-month period for an average participant. GEE analyses will be performed using STATA, version 8.0 (Stata Press, College Station, Texas) using the xtgee command with corr(ar1).

Security. A participant will be identified throughout the central database by his or her unique subject identification number (SID). Information which could identify a subject, such as name, address or social security number, will either not be stored electronically or will be kept in files on a separate machine and network from the database files containing study data. All subject paper files will be stored in locked cabinets at all times. All computer systems and programs will be password protected. All network-based communications of study and other confidential information will be encrypted. Good computer security practice (shutting down of computer after work hours, restricting physical access to machines, prohibition of password sharing) will be required of all study personnel. Virus protection software will be installed on each study machine. The virus detection tools will be used, maintained, audited and, if necessary, updated on all computers and pathways into the system. Redundant backups will allow for quick restoration of data in the unlikely event that a hardware failure or security breach should occur. Periodically, database files will be archived onto compact discs and stored offsite.

Archiving. All study raw data, forms, documents, software programs, software applications and computer data files will be indexed and archived routinely. Strict version control of documents and software applications will be instituted. At the completion of the study, primary study documentation will be consolidated and retained in filing cabinets in an organized fashion, with a clear index to organization.

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