Rationale

Posttraumatic stress disorder (PTSD) is a highly prevalent and chronic disorder. As a result of the high prevalence rates and associated substantial impairment, PTSD represents a significant public health problem. Although several evidence based-treatments (EBTs) for PTSD exist, there are some good reasons to develop additional EBTs for PTSD. For example, a significant minority of PTSD patients do not respond favorably to the available EBTs. Moreover, approximately one-quarter of individuals in EBTs for PTSD prematurely ends treatment (i.e., Hembree et al., 2003). Another issue concerns the lack of accessibility of EBTs for PTSD. This lack of accessibility is likely the result of geographic, economic, and time commitment barriers. Taken together, there is a strong need to develop alternative treatments for PTSD, especially treatments that are efficient. Establishment of efficient PTSD treatments would constitute a major milestone and would have substantial public health impact.

Written Exposure Therapy (WET) represents such an alternative PTSD treatment option. The investigative team has conducted prior work establishing the efficacy of WET for PTSD. This work also showed that WET is associated with remarkably low rates of treatment dropout (e.g., 8%). The proposed project represents the next step in this line of work by investigating whether WET is non inferior to Cognitive Processing Therapy (CPT), an evidence-based PTSD treatment. One hundred twenty-six ($N = 126$) men and women with a diagnosis of PTSD will be randomly assigned to either WET or CPT. We expect to conduct initial assessments on up to 220 individuals in order to enroll 126 individuals into the clinical trial. Outcome data will be collected at baseline and 6-, 12-, 24-, 36-, and 60- weeks post-baseline.

The primary specific aim is to examine whether WET results in a noninferior PTSD symptom severity outcome relative to CPT.

Hypothesis 1: Participants randomly assigned to WET will show noninferior outcome in PTSD symptom severity at the 12, 24, and 36- week post-baseline assessment, relative to participants randomly assigned to CPT.

Hypothesis 2: Participants randomly assigned to WET will show noninferior outcome in PTSD symptom severity at the 60 week post-baseline assessment, relative to participants randomly assigned to CPT.

The secondary aim is to examine differences between the two treatment conditions in dropout rate.

Hypothesis 3: WET will demonstrate a significantly lower dropout rate than CPT.

Exploratory analyses: We will also conduct several exploratory analyses to identify potential moderators and mediators of treatment outcome. These analyses will be exploratory because the empirical literature on moderators and mediators of PTSD treatment outcome is limited and does not provide guidance for specific predictions. Based on past theoretical models of cognitive behavioral therapy (e.g., Craske et al., 2008; Jaycox et al., 1998; Resick & Schnicke, 1992), we will examine initial activation and extinction of negative affect as well as improvement in cognition during the course of treatment as potential mediators of treatment outcome. Likewise, we selected potential moderator variables based upon limited empirical data as well as prior theorizing (e.g., Iverson, Resick et al., 2011; Rizvi et al., 2009). Specifically, we will examine time since index trauma event, total number of traumatic life events, type of index...
trauma event, age, gender, and racial background as potential moderators of treatment outcome. Lastly, we will examine whether reading level ability moderates treatment outcome.

**Innovation**

The proposed project is innovative in its goal to establish a treatment for PTSD that is efficient and well-tolerated. Although there are EBTs for PTSD, these treatments are associated with relatively high dropout rates and evidence indicates that a substantial subset of patients fail to respond to these treatments (Kearns & Rothbaum, 2012). Consequently, there is a great need to develop alternative treatments for PTSD. We have developed an alternative treatment for PTSD through a series of systematic studies and we have demonstrated that this treatment is efficacious. We will now examine whether WET is noninferior to CPT.

**Background**

Research has shown that PTSD is a common occurrence among those who are exposed to trauma. One of the most definitive epidemiological studies, the National Comorbidity Survey (Kessler et al., 2005), conservatively estimated that the prevalence of PTSD among the general population of United States citizens to be approximately 8%. Kessler et al. concluded that PTSD is a highly prevalent disorder that often persists for years and that exposure to events that could potentially lead to the development of PTSD is quite common. Other research has found that chronic PTSD represents a significant public health problem. More specifically, studies of rape victims (Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992; Kilpatrick et al., 1992), crime victims (Norris & Kaniasty, 1994), and motor vehicle accident and physical injury patients (e.g., Shalev, Freedman, Brandes, Peri, & Sahar, 1997; Shalev et al., 1998), all indicate that PTSD symptoms that persist beyond three to six months predict chronic psychological, medical, and occupational problems. Notably, PTSD patients manifest a variety of persistent impairments in functioning, such as unemployment and low income (e.g., Savoca & Rosenheck, 2000), problems in relationships (e.g., Riggs et al., 1998), poor problem solving capacity and aggressive behavior (e.g., McFall et al., 1999; Orth & Weiland, 2006), and poor self-care and quality of life (e.g., Buckley et al., 2004; Schnurr et al., 2006).

In response to this significant public health problem, several evidence-based treatments (EBTs) for PTSD have been identified (e.g., Institute of Medicine [IOM], 2007; Foa, Keane, Friedman, & Cohen, 2009). Evidence from many well-controlled trials with a variety of PTSD individuals indicates that these treatments are effective and that the exposure component of each of these treatment protocols is critical for clinically significant symptom change (IOM, 2007).

Although these successes are impressive, there are some good reasons to develop additional EBTs for PTSD. Most notably, a significant minority of PTSD patients do not respond favorably to the available EBTs. In their meta-analysis of randomized controlled trials (RCT) for PTSD, Bradley et al. (2005) found that approximately 33% of treatment completers continued to meet diagnostic criteria for PTSD and 46% of treatment completers did not show clinically significant symptom improvement following treatment. Moreover, approximately one-quarter of individuals in exposure-based treatments for PTSD prematurely ends treatment (i.e., dropout; Hembree et al., 2003). Another point of concern about PTSD EBTs is that they are often unavailable to those in need of treatment. This unavailability is likely the result of geographic, economic, and time commitment barriers (Sloan, Marx, & Keane, 2011).

These points suggest that there is a clear need to develop alternative PTSD treatments. In line with the IOM observation that all of the available EBTs emphasize the repeated confrontation of feared memories, images and situations by the affected individual (i.e.,...
exposure), any new treatment approach should also do the same, while simultaneously being palatable to patients and clinicians, easily disseminated and implemented, economical, and accessible. Inherently, such a treatment would only include those components that are necessary and sufficient for treatment efficacy (Cahill et al., 2009).

Written exposure (i.e., confronting the trauma memory through writing) holds promise as a treatment alternative that can fulfill all of these conditions. In one of its earliest forms, Pennebaker and Beall (1986) had individuals write repeatedly (three, 20 minute sessions) about their most traumatic or distressing experience with as much emotion and detail as possible. In this and many subsequent studies with a variety of samples, results showed that this writing procedure, referred to as written disclosure, improved both psychological and physical health (see Frattaroli, 2006, for a review).

Because of the procedural similarities between the written disclosure procedure pioneered by Pennebaker and Beall (1986) and more established exposure-based treatments for PTSD, my colleagues and I have explored the extent to which this form of written exposure could efficaciously reduce PTSD symptoms among a broad representation of trauma exposed individuals who reported at least moderate PTSD symptom severity. We conducted our early work in this area with NIMH research support (R03MH068223-1A1). In contrast to many of the other studies of written disclosure with trauma survivors, our studies have included multiple writing sessions, adequate control groups and follow-up intervals, randomized group assignments, and systematic alteration of instructional sets. We (Sloan & Marx, 2004a; Sloan et al., 2005, 2007) have found that, relative to a control writing condition, written disclosure significantly reduces PTSD symptom severity and that individuals experience significant fear activation during the initial writing session followed by significant reductions of fear activation (i.e., extinction) by the last session (Sloan & Marx, 2004a; Sloan et al., 2005, Sloan et al., 2007). Although these results suggested that Pennebaker and Beall's (1986) written disclosure procedure may potentially ameliorate PTSD symptoms among trauma survivors much like exposure-based treatments, they should be interpreted cautiously since participants were not treatment seeking and did not necessarily meet diagnostic criteria for PTSD. In fact, the mean symptom severity levels in these studies were substantially lower than what is typically reported for participants enrolled in PTSD clinical trials (e.g., Foa et al., 2005).

More recently, my colleagues and I (Sloan, Marx, & Greenberg, 2011) examined whether or not written disclosure would be beneficial to individuals meeting diagnostic criteria for PTSD. In contrast to our earlier findings, results revealed no significant PTSD symptom severity reduction for individuals randomly assigned to the written disclosure condition, relative to individuals assigned to a control writing condition. Importantly, the results also showed that participants assigned to the written disclosure condition did not experience a significant reduction in arousal and negative affect from the first to the last session. This finding suggested that the therapeutic dose (three, 20 minute writing sessions) was not sufficient to produce beneficial outcome. However, the lack of group differences might have occurred for other reasons, such as study participants were not treatment seeking. In addition, participants were not provided with any treatment rationale or psychoeducation about PTSD. Past research has suggested that these components may be necessary, but not sufficient, for successful treatment outcomes (e.g., Hamblen, Schnurr, Rosenberg & Eftekhar, 2009).

With support from NIMH (R34MH077658-02) my colleagues and I altered the written exposure protocol in several key ways. First, we added treatment rationale and psychoeducation components. Next, based on our prior work indicating the importance of directing individuals to write repeatedly about the details their index trauma, with particular
attention to felt emotions, the meaning of the traumatic event and “hot spots” (Sloan et al., 2005; 2007), we also made significant modifications to the writing instructions. To reflect these changes and distinguish the original Pennebaker and Beall (1986) written disclosure protocol from the current protocol, we refer to the current treatment protocol as written exposure therapy (WET). The WET protocol was designed to be consistent with the goal of creating a tolerable and efficient exposure-based treatment alternative for PTSD.

To conduct an initial test of the WET protocol, we conducted a RCT for individuals diagnosed with PTSD resulting from a motor vehicle accident (MVA). Findings indicated significant reductions in PTSD symptom severity for participants randomized to WET, relative to those randomized to a wait list (WL) condition, with a large between-group effect size of 3.49 (Hedge’s $g$). Notably, the between-group effect size is comparable, if not larger, to the effect sizes obtained for EBTs for PTSD, relative to a WL comparison condition (e.g., 1.10 for CPT, Resick et al., 2002; 1.91 for PE, Foa et al., 2005). Moreover, in contrast with other established PTSD treatments, the dropout rate for WET was very low (8%); client treatment satisfaction ratings were very favorable.

**Summary.** To date, research suggests that WET is an efficacious, well-received, and well-tolerated treatment for PTSD. The next step in this line of work is to investigate the efficacy of WET, relative to an established EBT for PTSD; this is the primary aim of the proposed study. Using a non-inferiority design, we will compare the efficacy of WET with the efficacy of Cognitive Processing Therapy (CPT). We have selected CPT as our comparison condition for several reasons. First, CPT is an EBT for PTSD. Second, one component of CPT is a written account of the trauma that has some similarity to WET. Third, CPT has been shown to be effective in reducing PTSD in a wide variety of civilian and military trauma survivors (e.g., Chard et al., 2010; Monson et al., 2008; Resick et al., 2002, 2008). Lastly, Dr. Resick, the developer of CPT, is located at the same site as the PI of this project; the proximity of the investigators will facilitate progress of this RCT.

**Relevance to Veterans Health.** PTSD is the leading mental health issue among veterans seeking treatment at VA medical centers. Although we have evidence-based treatments for PTSD and a large number of VA providers are trained to deliver these treatments, there is a substantial number of veterans who will not engage in these treatments, and among those who do engage in these treatments the dropout rates are larger than that observed in the civilian population (e.g., Monson et al., 2006; Resick et al., 2008). Thus, it is important to have alternate treatment options for veterans presenting for PTSD treatment.

Because all of the work that has been conducted with WET has focused on the civilian population, we conducted an unpublished, uncontrolled pilot study to examine the feasibility and tolerability of WET with veterans diagnosed with PTSD (2 were 100% service connected for PTSD). Of the 7 veterans that enrolled in the trial, one dropped out of treatment (14% treatment dropout) but this veteran returned for all subsequent assessment sessions. PTSD symptom severity was assessed using a semi-structured diagnostic interview (i.e., CAPS) administered at pre- and post-treatment, and a 3 month follow-up. Findings indicated large within group effect size at both post-treatment ($d = 1.0$) and 3 month follow-up ($d = 1.4$). In addition, five of the seven veterans no longer met PTSD diagnostic criteria following WET. Veterans reported that high treatment satisfaction as well. Although the findings from the pilot trial are encouraging, we believe it is premature to solely focus on a veteran population for this RCT. Thus, any adult with a diagnosis of PTSD will be included in the proposed RCT. We expect that some participants in
the RCT will be veterans (combat-related PTSD) and we plan to examine whether type of trauma event moderates outcome for both treatments included in this study.

Work Accomplished

Efficacy of WET with trauma survivors. As previously described, we have demonstrated the efficacy of WET for trauma survivors who reported at least moderate PTSD symptom severity as a result of a traumatic event. In these studies, trauma survivors were randomly assigned to either a WET condition or a control writing condition. Participants wrote for 20 minutes on three separate occasions. Results indicated that, at follow-up assessment, individuals assigned to the WET condition reported significantly and clinically meaningful reductions in both PTSD and depression symptom severity relative to those who were assigned to the control condition (Sloan & Marx, 2004; Sloan et al., 2005, 2007). The between-group effect size was approximately .80 (Hedge’s g) for PTSD symptom severity outcome. Notably, dropout rates were no greater than 5%.

In addition to examining the efficacy of WET, we also have investigated participants’ emotional responding during the WET sessions. We found evidence of both initial activation (via self-report, heart rate, and salivary cortisol) among participants assigned to the WET condition during the first session, relative to participants assigned to the control writing condition. We also observed a significant reduction in activation from the first session to the last session for the WET condition only (i.e., habituation) (Sloan & Marx, 2004; Sloan et al., 2005, 2007).

These findings were promising, however, we recognized that our prior studies could be improved upon. For example, in our initial studies, we did not require participants to meet criteria for PTSD and all the treatment outcomes were assessed using self-report measures. We also recognized that the WET protocol did not include any information psychoeducation or treatment rationale. We rectified this by adding these components to subsequent iterations of the WET protocol. Lastly, we found that 3 WET sessions did not promote sufficient habituation of pathological fear responding and, consequently, did not result in significant reductions in PTSD symptom severity for individuals meeting diagnostic criteria for PTSD (Sloan et al., 2011). Through additional treatment development work identified 5 sessions with a writing duration of 30 minutes resulted in adequate habituation of pathological fear and resulted in clinically significant PTSD symptom severity reductions among individuals with a PTSD diagnosis.

Although other researchers have developed PTSD treatments that include a narrative writing component (e.g., structured writing therapy; van Emmerik, Kamphuis, & Emmelkamp, 2008; narrative exposure therapy; Robjant & Fazel, 2010), those treatment protocols substantially differ from WET. Specifically, in terms of the structure of the writing session, the writing instructions and the number and duration of treatment sessions (i.e., greater number and longer duration of sessions in other treatments).

Efficacy of WET as an intervention for PTSD. After completing treatment development work on the WET protocol, we conducted an efficacy of study of WET as an intervention for MVA-related PTSD (R34MH077658-02). In this RCT, participants were randomized to either WET (n = 24) or wait-list (WL; n = 24). We enrolled 79% of those assessed over a 15 month period (average of 3 participants per month). Median time since MVA was 20 months, and all of the participants were diagnosed with chronic PTSD. Participants were recruited from the greater Boston area and were racially diverse (38% Caucasian, 35% African-American, 8% Hispanic, 6% Asian-American, 13% “other”). The average age was 40.5 years (SD = 12.9), 65% were women and 75% of the participants reported an annual household income of $35,000 or less.
Educational background of the participants was diverse with the majority of participants reporting some post-high school education (40%) and 19% reporting no more than completion of high school (see Appendix for manuscript under review).

Although participants met primary diagnosis of MVA-related PTSD, they reported extensive trauma histories, with an average of 12.8 ($SD = 10$) trauma events experienced (meeting Criterion A definition). Approximately 85% of the sample reported a history of physical assault and approximately 60% reported a history of sexual assault. Psychiatric comorbidity was also present, with 25% of the sample meeting current depression disorder diagnoses and 10% meeting current diagnostic criteria for alcohol abuse; approximately 38% of the sample met diagnostic criteria for substance use disorders, in full remission (both abuse and dependence diagnoses). To summarize, the sample was diverse in terms of age, gender, and racial background. The sample was also characterized by substantial trauma history, low socioeconomic status, and psychiatric comorbidity. As such, the sample is consistent with individuals diagnosed with chronic PTSD (Keane et al., 2010), and similar to samples recruited for RCT’s of PE (e.g., Foa et al., 1999, 2005, Schnurr et al., 2007) and CPT (e.g., Resick et al., 2002, 2008).

As illustrated in Figure 1, participants randomized to WET displayed a large and significant reduction in PTSD symptoms at post-treatment and 3 month follow-up, relative to participants in the WL. WET participants also maintained their treatment gains at the 6 month follow-up assessment. In terms of PTSD diagnosis, at the 3-month follow-up assessment only 4% of the WET participants met diagnostic criteria for PTSD, relative to 67% of the WL participants; 8% of WET participants met PTSD criteria at the 6 month assessment.

Somewhat surprisingly, although no in vivo exposures were included in the WET protocol, the WET participants reported significant reductions in driving and riding avoidance behaviors at the follow-up assessments (15 point reduction for WET compared with 3 point reduction for WL; assessed via the Driving and Riding Avoidance Scale Stewart & St. Peter, 2004).

What about treatment dropouts? Not only was WET efficacious in terms of reducing PTSD symptoms, but the treatment was also well received and tolerated. Only 2 participants (8%) dropped out of the WET condition; even though these 2 participants did not complete all treatment sessions, they did return for all of the follow-up assessments. Moreover, WET participants reported high ratings on the Client Satisfaction Questionnaire (Larsen et al., 1979), with an average score of 28 ($SD = 3.8$; maximum possible score is 32).

Does educational level or English not first language matter? We had several participants with no more than an 8th grade educational level, as well as participants for whom English was not their first language (Spanish was their first language). These individuals had no difficulty completing the written exposure sessions, and also displayed significant reductions in PTSD symptom severity.
How does WET compare with evidence-based treatments for PTSD? Figure 2 compares the reduction in PTSD symptom severity (measured via the Clinician Administered PTSD Scale, CAPS) associated with WET (data collected in our aforementioned study) with reductions in PTSD symptom severity associated with CPT, Prolonged Exposure (PE), and a minimal attention (MA) condition in a study conducted by Resick et al. (2002). Completer sample data is displayed for CPT and PE. As illustrated in Figure 2, the reductions observed for WET are comparable to those observed for both CPT and PE. The between group effect sizes (Hedge’s g) for CPT, PE (completer sample compared with MA condition) and WET (compared with WL) were 2.05, 1.76, 1.72, respectively. Although these data are encouraging, additional work is needed to directly compare the effects of WET with an EBT for PTSD.

Treatment dropout is another important consideration. The 8% dropout rate of WET compares very favorably with that of both CPT and PE, which is typically around 25-35% (e.g., Foa et al., 2005; Resick et al., 2002). In addition, the 8% dropout rate is consistent with the low dropout rates observed in our earlier work (Sloan & Marx, 2004; Sloan et al., 2005, 2007). One possible reason for the lower dropout rate is that WET involves fewer sessions than CPT and PE. In addition, a substantial number of WET participants reported a perceived sense of control over the writing sessions as a positive aspect of the treatment and this perceived control might promote better participation in the treatment.

Given the favorable findings for WET, the next step in examining the efficacy of this treatment is to compare it directly with an established EBT for PTSD. In this study, we will conduct a noninferiority RCT in which we compare WET with CPT.

Efficacy of WET with veterans. Because all of the work that has been conducted with WET has focused on the civilian population, we recently conducted an uncontrolled pilot study to examine the feasibility and tolerability of WET with veterans diagnosed with PTSD (2 were 100% service connected for PTSD). Of the 7 veterans that enrolled in the trial, one dropped out of treatment (14% treatment dropout); this veteran returned for all subsequent assessment sessions. PTSD symptom severity was assessed using a semi-structured diagnostic interview (i.e., CAPS) administered at pre- and post-treatment, and a 3 month follow-up. Findings indicated large within group effect size at both post-treatment ($d=1.0$) and 3 month follow-up ($d=1.4$). In addition, five of the seven veterans no longer met PTSD diagnostic criteria following WET. Veterans reported high treatment satisfaction as well. Although the findings from the pilot trial are encouraging, we believe it is premature to solely focus on a veteran population for this RCT. Thus, participants in the proposed study will be adults with a diagnosis of PTSD. We expect that some participants who enroll in the RCT will be veterans (combat-related PTSD). We plan to examine whether type of trauma event moderates outcome for both treatments included in this study.

Work Proposed
Recruitment Strategy & Feasibility: Our recruitment plan is based on our collective experience recruiting PTSD participants from the community. Although we used a variety of recruitment strategies in our recently completed RCT, two strategies were most effective. These strategies were 1) posting flyer announcements in the community (e.g., near public transportation stops, in community centers, public libraries, laundromats, grocery stores) and 2) posting announcements on Craigslist. Through these methods, we were able to recruit 3 participants per month, on average, who met eligibility criteria and enrolled in the RCT. We expect to recruit a greater number of participants for the proposed RCT because we will be recruiting a more diverse sample of PTSD participants in terms of the index trauma. In addition, we will recruit from community centers in the greater Boston area (e.g., Boston Rape Counseling Center) and we will use the Boston University RESPECT registry as an additional recruitment strategy.

Diagnostic Procedures, including Training and determination of reliability: The CAPS and the Structured Clinical Interview for DSM–IV (SCID) will be used to establish current PTSD diagnosis, to characterize current co-morbid psychiatric problems, and to rule out current psychosis, bipolar disorder and substance dependence. Clinical staff with at least a master’s degree will be trained in the administration of these instruments, following the procedures outlined by DiNardo et al. (1993). These procedures include successfully matching criterion diagnoses for 3 of 5 training tapes, as well as demonstrating competency in administering interviews. Training in diagnostic procedures will occur in a 1-day workshop with all assessors, to be conducted at the start of the project. The training workshop will be videotaped, allowing for consistency when adding new assessors. Additionally, all assessment staff will rate standardized diagnostic interviews (once every 3 months) to prevent rater drift. This technology will also permit standardized training of assessors who join the project after the initial training workshop. Assessors will be certified to administer the CAPS and SCID when they match criterion diagnoses and competently administer these instruments during a supervised interview. Throughout the trial, all interviews will be recorded and 10% will be selected at random for review by an Independent Reliability Evaluator. This individual will watch the taped interview and provide a diagnostic profile. S/he will remain unaware as to participants’ treatment condition assignment or the assessment time-point, in order to permit objective assessment of diagnostic reliability. Discrepancies between the Independent Reliability Evaluator’s and the independent assessor’s ratings will be resolved through consultation with the PI.

In addition to these training procedures, the assessors will present all diagnostic assessments conducted within the past week at a weekly assessment staff meeting lead by Dr. Marx.

Independent Assessors: The independent assessors will be unaware of treatment condition assignment of participants. Assessor will be housed in office space that will be located on a different floor than the floor where treatment sessions will be conducted and where study therapists will be housed (the National Center for PTSD has space on several floors of the 14 story VA Boston Healthcare System). Separating the location of the therapists and the independent assessors will help to ensure that assessors remain blinded to treatment condition. In addition, participants will be instructed to not disclose to the assessors which treatment condition they have been assigned to and the identity of their therapist. Lastly, the blinding procedures will be checked by asking the independent assessors at each assessment occasion to complete a questionnaire regarding whether any information was revealed that might indicate the treatment condition assignment of the participant. Independent assessors will be trained and supervised by Dr. Marx.

CAPS-5 The CAPS-5 is a semi-structured interview for evaluating PTSD and is the version that corresponds to PTSD diagnostic criteria that will be in DSM-5; this has been officially approved
The CAPS will be scored in two ways; presence or absence of DSM-5 PTSD and an overall symptom severity score, computed by summing the total of each symptom score (frequency + intensity).

The **Trauma Life Experience Questionnaire** (TLEQ; Kubany et al., 2000) will be completed at baseline to assess lifetime history of exposure to traumatic life events and responses to these experiences. The TLEQ has strong psychometric properties and is commonly used to assess trauma history. We will use the TLEQ to identify the frequency and type of trauma events experienced by participants for the purpose of exploring the extent to which trauma history may serve as a moderator of treatment outcome. This measure will also be used to identify the trauma index event for which the CAPS should be administered.

**SCID:** The SCID includes questions assessing each of the DSM-IV adult disorders (Spitzer, et al., 1994). Each disorder is coded as present, not present, or probable, based on structured questions that map onto the DSM-IV criteria. Additionally, each diagnosis will be given a Clinical Severity Rating (CSR) of 0 to 8, where a rating of 4 or higher represents clinical levels of interference or distress. Individuals receiving a CSR of 4 or higher for substance dependence disorders or bipolar disorder or reporting any psychotic symptoms will be excluded.

The **Mini International Neuropsychiatric Interview (MINI)** suicide module will be used to assess suicide risk during each assessment period. This measure will be used to assess high suicide risk as an exclusion criteria during the initial assessment and will be used to monitor suicidal risk throughout the trial (see Protection of Human Subjects section).

The MINI suicide module is a clinician administered interview that consists of 9 questions related to suicidal ideation and behaviors, with possible scores ranging from 0 to 53. Low suicide risk is defined as 0-8 points, moderate suicide risk is defined as 9-16 points, and high suicide risk is defined as scoring 17 or greater. We are using this measure because the MINI suicide module is clinician-administered, includes clear guidelines for determining suicide risk, and requires approximately 10 minutes to administer. The MINI demonstrates excellent inter-rater reliability, with kappa values exceeding 0.75 (Lecrubier et al., 1997; Sheehan et al., 1998); and generally good test-retest reliability, with kappa values typically exceeding 0.65 (Lecrubier et al., 1997; Sheehan et al., 1998). Individuals will be excluded from enrolling in this study if they score 17 or higher (high risk) on the MINI suicide module at the initial assessment.

**Wechsler Test of Adult Reading (WTAR)** is a pre-morbid estimate of intelligence that requires 5-10 minutes to administer. This measure consists of 50 words that a participant reads in order to estimate pre-morbid intelligence. We will administer this measure at the initial assessment in order to evaluate whether pre-morbid intelligence level moderates treatment outcome.

**PTSD Checklist** – 5 (PCL5) is a 17-item self-report measure of PTSD that corresponds to the DSM-V symptoms of PTSD. Like the CAPS, the PCL5 can be scored to yield an overall severity score (total score). The PCL will be included in the proposed study to monitor PTSD symptom severity during the treatment phase (see Protection of Human Subjects section), and will also be completed at each assessment occasion.

**The Beck Depression Inventory-II** (BDI-II; Beck et al., 1996) will be administered to assess depression symptom severity. This 21-item self-report questionnaire evaluates current depressive symptoms and has well-established reliability and validity (Dozois et al., 1998). The BDI-II will be included in the proposed study to examine changes in depression symptom
severity associated with treatment, as well as to assess any changes in suicidal ideation. The BDI-II will be completed at each assessment occasion and at each treatment session.

The Client Satisfaction Questionnaire (Larsen, et al., 1979) is a 8 item measure of participant satisfaction with treatment. This measure will be administered at the last session of treatment in order to examine whether participants are satisfied with the treatment they have received.

Treatment Credibility will be measured immediately after the first therapy session with the Treatment Expectancy Questionnaire (TEQ; Borkovec & Nau, 1972). This measure contains four items that participants rate using a 10-point Likert-type scale (0 no expectancy/credibility to 9 - very strong expectancy/credibility) according to how logical the treatment seems, their confidence in undergoing the treatment and recommending it to others, and their expectations for the treatment’s success. The TEQ has high internal consistency and good test-retest reliability (Devilly & Borkovec, 2000).

The Cognitive Emotion Regulation Questionnaire-Short (CERQ-S; Garnefski & Kraaij, 2006) is an 18-item self-report measure of conscious cognitive emotion regulation strategies. The CERQ-S has good psychometric qualities (Garnefski & Kraaij, 2006). This measure will be completed at each treatment session and will be used to examine emotion regulation strategies as a mediator of treatment outcome. The measure will also be completed at each assessment occasion. We chose this measure because of its ability to index general cognition rather than content specific cognitions (e.g., Posttraumatic Cognition Inventory). In addition, the CERQ-S is currently being used by Dr. Resick and colleagues to index cognition as a mediator of treatment change in a large, DoD-funded study examining a variety of RCTs for PTSD with active military service men and women.

The paper and pencil version of the Self-Assessment Manikin (SAM; Bradley & Lang, 1994), a valid measure of emotional responding (e.g., Lang, Greenwald, Bradley, & Hamm, 1993), will be used to obtain ratings of valence (pleasantness) and arousal in response to each treatment session. The SAM will be completed during each treatment session immediately at the start and end of each session. This measure was selected because of its ability to discriminate between valence and arousal, its ability to index valid emotional responses, and because this measure has been used in prior studies to index emotional responding to treatment sessions (Sloan & Marx, 2004a, Sloan et al., 2005). We will use participants’ SAM ratings to explore emotional responding as a mediator of outcomes.

Multidimensional Scale of Perceived Social Support (MSPPS; Zimet, Dahlem, Zimet & Farley, 1988) is a 12 item self-report measure of social support. Social support has been found to moderate outcome following a traumatic event. This measure will be included at each assessment occasion.

Peritraumatic Dissociative Experiences Questionnaire (PDEQ) is a 10 item self-report measure of dissociative experiences during and immediately following a traumatic event. We will examine whether PDEQ moderates treatment outcome. This measure will be completed at each assessment occasion.

Ruminative Style Questionnaire (RSQ; Nolen-Hoeksema & Morrow, 1991) is a 22 item self-report measure that indexes ruminative or brooding style, which has been found to be a maladaptive coping strategy. The RSQ will be administered at each assessment occasion in
order to examine whether treatment affects RSQ and whether RSQ serves as a moderator of treatment outcome.

**Posttraumatic Avoidance Behavior Questionnaire** (van Minnen & Hagenaars, 2010) is a 25 item self-report measure that indexes avoidance behaviors resulting from traumatic experiences. The PABQ will be included at each assessment occasion to measure changes in avoidance behavior as a result of treatment.

**Posttraumatic Cognitions Inventory** (PTCI; Foa, Ehlers, Clark, Tolin, & Orsillo, 1999) in a sample is a 36 item self report measure indexing cognitions following a traumatic event, such as self-blame and negative world cognitions. This measure will be completed at each assessment occasion to examine changes in posttraumatic cognitions as a result of treatment.

**Alcohol Use Identification Test** (AUDIT; Barbor et al., 2006) is a 10 item self-report measure of hazardous alcohol consumption. This measure will be completed at each assessment occasion.

The therapeutic alliance will be assessed using the 12-item therapist and client versions of the **Working Alliance Inventory** (WAI; Horvath & Greenberg, 1989; Tracey & Kokotovic, 1989). In addition to the total score, the WAI has three subscales: Goals, which reflects the agreement between therapist and patient on overall goals of treatment; Tasks, which reflects the agreement on the appropriate tasks on which to focus (to achieve goals); and Bond, the quality of the affective relationship between the therapist and the patient. The WAI will be included to examine therapeutic alliance as a potential moderator of treatment outcome, as well as to examine potential treatment condition differences. The WAI therapist version will be completed by the study therapists for each participant they treat, and the client version will be completed by each participants enrolled in the RCT at the end of treatment.

**Timing of Assessments:** The proposed study will follow each of the gold standards for treatment outcome research for PTSD (e.g., Foa & Meadows, 1997; Harvey, Bryant, & Tarrier, 2003). There is a considerable difference between WET and CPT in treatment duration (5 sessions compared with 12 sessions of treatment). If we conducted assessments at post-treatment for each treatment condition this would be problematic as assessing PTSD symptom severity at different time points might confound outcome differences due to time rather than due to treatment condition. To eliminate this possible confound, diagnostic assessments will be conducted at the same time for all participants. See **Table 1** for the Assessment Schedule. Both treatment conditions will include approximately 3-, 6- and 12 month follow-up assessment. There will be a total of 6 assessments for each participant enrolled in the study. Assessments are conducted by independent evaluators (i.e., unaware of treatment condition).

**Table 1. Assessment Schedule**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>6 weeks</th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>36 weeks</th>
<th>60 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>WET</td>
<td>Post-tx</td>
<td>6 week f/u</td>
<td>3 month f/u</td>
<td>4.5 month f/u</td>
<td>13.5 month f/u</td>
</tr>
<tr>
<td>CPT</td>
<td>Mid-tx</td>
<td>Post-tx</td>
<td>6 week f/u</td>
<td>3 month f/u</td>
<td>12 month f/u</td>
</tr>
</tbody>
</table>

**Data Management.** All study data will be entered into SPSS database, which will be housed on a secure network server accessible only by project staff. The project coordinator will check all data on the same day as entry to ensure completeness. Any incomplete data will be brought to the attention of the independent assessor and/or therapist and every effort will be made to
complete ratings. All data will be entered twice by two different staff members, in order to detect discrepancies. Field parameters will be specified such that suspect or missing values are either disallowed or flagged for the immediate attention. Prior to data analysis, all data will be cleaned and rechecked for accuracy before conducting data analysis. Three times per year, blinded data will be compiled and reviewed by the PI and Co-I’s to ascertain overall completeness and issues requiring clarification, as well as for purposes of providing information to the data safety and monitoring board.

Interventions
Treatment Conditions
Written Exposure Therapy (WET). The WET condition consists of 5 WET treatment sessions, with the first session lasting 1 hour and each subsequent session lasting approximately 40 minutes. Sessions will be spaced one week apart and will take place in a private room located within the National Center for PTSD (NC-PTSD). The first session will consist of the therapist educating the participant about common reactions to trauma and providing information regarding the rationale of WET as a treatment for PTSD. The participant will then be given general instructions for completing the trauma narratives, specific instructions for completing the first session, and will then complete the first (30 minutes) narrative writing session. Participants will be instructed to write about the same trauma experience during each session. This event will be the same event identified as the index trauma during the baseline assessment session. The importance of delving into their deepest emotions surrounding the trauma event is emphasized, as well as the importance of providing detailed information about the event. All written exposure sessions will begin with the therapist given the specific instructions for written exposure for that session and then leaving the instructions with the participant while 30 minute writing session is completed. Written exposure instructions start with a focus on describing the details of the trauma and emotions and thoughts that occurred during the trauma event and then progress to a focus on the meaning of the trauma event (e.g., what the event has meant to the person, how it has changed the way they view their life).

Cognitive Processing Therapy (CPT). CPT consists of 12, 60 minute sessions that primarily focus on challenging and changing distorted beliefs and self-blame regarding the traumatic event through Socratic questioning (Resick et al., 2002). As previously described, an exposure component is also included in the protocol; specifically, participants provide a written account of their index event. See Appendix for CPT protocol.

Therapists: Background and assignment to condition: Therapists will hold either a masters or doctoral degree. In the proposed study, we will counterbalance therapists across the two treatment condition.

Therapists Training: Dr. Patricia Resick will train the CPT therapists during a two-day training workshop. Dr. Sloan will train the WET therapists during a half-day training workshop. Both training workshops will consist of reviewing the therapy protocol, discussing challenging issues that can arise during each treatment protocol, and viewing videotaped sessions of therapists delivering the treatment. The training workshops will be followed by a certification process during which study therapists will conduct the respective treatments with pilot participants. Drs. Resick and Sloan will review and rate the therapy sessions for competency and adherence. Dr. Resick will be responsible for certifying therapists conducting CPT and Dr. Sloan will be responsible for certifying therapists conducting WET. Competency ratings will be made on the basis of skill of treatment delivery as well as adherence to the respective treatment protocol. The competency ratings will range from a score of 1 (poor) to 7 (excellent). Study therapists in
both treatment conditions must minimally score at the acceptable level (score of 4) to be deemed competent and ready to commence therapy with trial participants. In addition, therapist competency and adherence will be monitored throughout the entire trial. Study therapists must maintain the acceptable competency level in order to be able to continue as a study therapist. If a study therapist falls below the minimal level of competency, then he/she will not be allowed to provide any further treatment to participants until he/she is retrained and meets minimal competency expectations.

In addition to competency certification and monitoring, study therapists will receive weekly supervision from Dr. Resick for CPT and Dr. Sloan for WET.

**Treatment fidelity and integrity** will be assessed by two Treatment Adherence Raters who are otherwise unaffiliated with the project. These two raters will be selected on the basis of their familiarity with either WET or CPT. A randomly selected 20% of treatment sessions (equally distributed between WET and CPT) will be reviewed and rated, using adherence and competence forms.

### Sample size and Data Analysis Plan

We plan to conduct initial assessments on up to 220 participants in order to enroll 126 participants into the clinical trial. We have estimated the sample size needed to enroll 126 participants based on our collective experience conducting RCTs for PTSD interventions. Typically, 70% of the individuals screened enroll in a PTSD clinical trial. Power analyses indicated the need to enroll 126 participants, thus we will need to conduct initial assessments on up to 220 participants in order to enroll 126 participants into this RCT.

**Power analysis and sample size calculation:** We calculated power and sample size estimation using a 10 CAPS points noninferiority margin described above, and using an effect size of .30 based on the assumption that a small effect size would be expected when comparing two active treatments (Schnurr, 2007). For a noninferiority trial such a large difference can be allowed where the test treatment is favored over the standard treatment, but one needs to account for a smaller difference (margin of .05 –.20) in the other direction – where the comparator treatment is favored over the test treatment.

Using an effect size of .30 and corresponding margin effect size of at least .10, we estimate needing a total of 100 participants. To account for a 20% attrition rate, we have increased our sample size to 126. This power analysis is conservative given it does not take into consideration the longitudinal observations analyzed with random effects models. Adjusting for the longitudinal observations would increase power.

**Data analysis plan**

**Primary Aim:** Examine if WET therapy is noninferior to CPT

**Hypothesis 1:** Participants randomly assigned to WET therapy will show noninferior outcome in PTSD symptom severity at the 12, 24, and 36 week post-first treatment session relative to participants randomly assigned to CPT.

**Hypothesis 2:** Participants randomly assigned to WET therapy will show noninferior outcome in PTSD symptom severity at the 60 week post-baseline assessment relative to participants randomly assigned to CPT.

Following CONSORT guidelines for a noninferiority trial (Piaggio et al., 2006), we will conduct an intent-to-treatment (ITT) analysis, which will be defined as all randomized participants who attend at least the first therapy session. Random effects linear (hierarchical linear) models will be implemented for the primary noninferiority ITT randomized comparison of total CAPS score
as well as any secondary analyses. This ITT comparison will disregard all CPT non-adherence occurring after randomization under the ITT principal (Piaggio et al., 2006). The random effects linear models will consist of a random intercept and slope to account for within-patient correlations for the longitudinal observations across follow-up visits (baseline to 6-, 12-, 24-, and 36-weeks post-baseline assessment). Fixed effects specified separately for each post-baseline visit, the intervention, and their respective interactions will be used to obtain the ITT estimate and one-sided 95% confidence interval for the noninferiority test of change from baseline at the 24 week post-baseline assessment. The test of noninferiority will be based on showing that this upper bound of the one-sided confidence interval is less than the pre-specified margin of 10 CAPS points that is considered to show that WET is noninferior to CPT. The 12, 24, and 36-week assessment visit will be used to test noninferiority (Hypo 1). Noninferiority will be claimed if the model-based difference between the two conditions is less than this upper bound. The 60 week post-baseline assessment will be used to examine Hypo 2, which concerns long term maintenance of treatment gains.

This likelihood approach makes the most robust missing data assumption (missing at random) among assumptions not involving untestable relationships between unobserved data and missingness (Little 1995; Ten Have et al., 1998). As such, it includes CAPS data from all visits at which the subject was measured, accommodating the variation in number of observed visits per subject. We will employ residual analyses to assess normality and outliers of the CAPS and other outcome variables. If the residual distributions are skewed, we will transform the outcome to achieve more symmetric distributions. The same random effects models will be implemented for assessing the effectiveness of CPT relative to WET in terms of efficacy outcomes. However, the ITT tests will be tests of superiority rather than inferiority. Accordingly, the above model-based estimates of CPT vs. WET differences will be augmented with 95% confidence intervals and hypothesis tests of the significance of the estimates. An alpha of .01 will be used to not only guard against type I errors, but also avoid being too conservative and hence missing important exploratory findings (Michels & Rosner 1996; Savits & Olshan 1995).

**Secondary Aim:** Examine whether there are treatment condition differences in treatment dropout rate. Hypo 3: WET therapy will have a significantly lower dropout rate relative to CPT. To examine the secondary aim we will conduct Chi square analyses with dropout frequency as the dependent variable and treatment condition as the independent variable. Treatment dropout will be defined as prematurely ending treatment prior to the completion of the treatment protocol.

**Exploratory analyses**
We will conduct exploratory analyses to investigate treatment condition differences in outcome for depression symptom severity using a noninferiority approach described above. We will also examine whether there are treatment condition differences in terms of client satisfaction ratings by performing an ANOVA, with treatment as the between subject factor and client satisfaction total score as the dependent variable.

**Examination of Mediators and Moderators of Treatment Outcome.** As no consistent moderators or mediators of treatment outcome have been identified for evidence-based PTSD treatment, we will conduct exploratory analyses to examine potential mediators and moderators. We have selected potential mediators based on theoretical models and limited empirical data for exposure- based models (e.g., extinction of pathological fear responding; Craske et al., 2008; Jaycox et al., 1998) and cognitive models (e.g., cognitive changes; Resick & Schnicke, 1992). Mediators variables will include the SAM ratings (both ratings at the first treatment session and
change score from ratings at last treatment compared to first treatment), and the total score of
the CERQ-S to examine changes in cognition as a mediator. We’ve selected potential
moderators based on the limited available empirical data of moderators of PTSD treatment
outcome and speculations of possible moderators of treatment outcome (e.g., Iverson, Resick et
al., 2011; Rizvi et al., 2009). Moderators variables will include time since index trauma event,
total number of traumatic life events, type of index trauma event, age, gender, racial
background, and reading ability level as measured by the WTAR.

Guided by recent conceptual advancements in the analysis of moderator and mediators (e.g.,
Kraemer, Kiefer, Essex, & Kupfer, 2008; Mackinnon & Fairchild, 2010), we will conduct a
series of multilevel regression analyses to examine moderators and mediators of treatment. The
proposed moderators (e.g., gender, number of prior Criterion A traumatic events, time since
index) are all set prior to the beginning of treatment, meeting the temporal precedence criteria
for moderators described by Kraemer et al. (2008). A two-step analysis will be conducted to
evaluate these moderators. First, each moderator will be entered into the Level-2 (between
participants) component of the multilevel growth curve analyses to test significant time x
moderator interactions. A significant interaction would indicate moderation of treatment
response. A second, more exploratory analysis, will examine whether the influence of the
moderators varies as a function of treatment condition. Although we have no data to suggest
that moderators might vary as a function of type of treatment, we will examine this possibility in
our exploratory analyses. The Level-2 component of these models will include the main effects
of treatment condition and the moderator as well as interaction (product) terms that will test for
significant treatment condition x moderator x time interactions.

A series of lagged (i.e., PTSD will be regressed on the proposed mediator at the previous time
point) multilevel mediation analyses will be conducted to examine potential mediators. We will
explore the following possibilities: a) do changes in the proposed mediator account for changes
in PTSD, b) do changes in PTSD account for changes in the proposed mediator, c) is the
relationship between the proposed mediator and PTSD reciprocal across time, or d) are
changes in the proposed mediator and PTSD independent processes? This approach is
increasingly being applied to data from randomized controlled trials to identify mechanisms of
change and to test whether the proposed mediation model varies across different treatment
conditions (e.g., Hofmann et al., 2007; Moscovitch et al., 2005; Smits et al., 2006). In fact,
lagged multilevel mediation analyses was recently applied to data from a Prolonged Exposure
(PE) RCT and demonstrated that changes in depression that occurred during treatment were
accounted for by changes in PTSD (Aderka, Foa, Applebaum, Shafran, & Gilboa-Schectman,
2011). After evaluating the effect of the mediator across all participants, treatment condition will
be added to the Level-2 component of the analyses to test whether the mediation models vary
as a function of treatment condition (see Hofmann et al., 2007).

Resources
Each staff member working on the proposed study will have office space that will all be
located on the same wing of the medical center. Consequently, the PI and Co-l will be readily
accessible to research staff in the event of a patient crisis. All staff assigned to the proposed
project will have their own office space. All office spaces have phones with designated phone
numbers for each office. The PI’s office includes 2, four-drawer locked file cabinets, one of
which will be used to store screening forms, semi-structured interview data, data collected
during treatment sessions, and questionnaire data. As described previously, the Division has
multiple rooms that are designated as therapy/assessment rooms. These rooms will be used for
conducting assessment and therapy sessions for the proposed study. All of the equipment (e.g.,
digital recorders, computers) needed for the proposed study are already in place.

Human Subjects Section

RISKS TO THE SUBJECTS

a. Human subjects involvement and characteristics

The participant population is to be comprised of 126 men and women participants that will be
recruited on the basis of the presence of current PTSD diagnosis. These individuals will be
recruited on a volunteer basis. As indicated in the Work Proposed section, inclusion criteria are
a diagnosis of PTSD, at least 18 years of age with a diagnosis of PTSD verified with the CAPS-5,
not currently in psychotherapy for PTSD, and, if taking medication, on stable dose for at least
one month. Exclusion criteria include a substance dependence, current psychotic symptoms,
unmedicated mania or bipolar disorder, deemed high risk for current suicide or homicide,
current involvement in a violent relationship defined as more than casual contact (i.e., dating or
living with an abusive partner). See DSMP for information on assessing suicidal ideation/intent.

Only individuals who provide written informed consent will participate. A participant may
withdraw his or her consent at any time and without prejudice. A clear and detailed explanation
will precede all procedures. At the beginning of the first session participants will be fully
informed that they will be randomly assigned to one of two treatment conditions; a description of
each treatment will be provided to the participant. Participants will also be informed that they are
free to withdraw from the study at any time without any consequences. An in-depth debriefing
will explain all procedures and hypotheses, and answer any questions. The debriefing will be
conducted at the conclusion of the last follow-up assessment session. Participants will be told
that the exact nature of the study cannot be revealed to them until completion of the follow-up
visits to reduce any bias in the results. Any participant withdrawing early from the experiment
will be provided with a debriefing at time of withdrawal.

b. Sources of research materials

All information pertaining to this project (e.g., screening forms, questionnaire data, written
narratives, audio-recordings of assessment sessions and therapy sessions for both treatment
conditions) will be held in the strictest confidence and will be kept in locked files located within
the PI’s office at VA Boston Healthcare System and will be available only to individuals directly
involved with the project. Under no circumstances will individually identifiable data be released
to anyone without written consent of the participant. Results will be published as group findings
only. Experimental results will be discussed with the participant at their request.

c. Potential Risks

Treatment: Some risks are associated with the administration of psychosocial treatment. The
primary risk is the evocation of uncomfortable levels of anxiety or other emotions during the
treatment sessions. Some participants may find sessions or assignments stressful and react to
them with anxiety.

Recording: Some participants may feel uncomfortable about the assessment and treatment
sessions being recorded. However, this will be a required procedure. The purpose of the
recording will be explained, confidentiality will be respected, and both informed consent and
authorization for recording will be obtained as per requirements put forth by the Healthcare
Information Portability and Accountability Act (HIPAA). Recordings will be marked only by subject identification codes and stored in password protected computer server accessible only to staff directly involved with the project.

**Self-Report Measures and Assessor Ratings:** No risks are seen associated with these assessment procedures other than discomfort associated with the audio-recording. These will be handled as described above for recording of assessment and therapy sessions.

**ADEQUACY OF PROTECTION AGAINST RISKS**

**a. Recruitment and Consent Procedures**

Following the recruitment procedures used in our recent PTSD clinical trial, we used a variety of recruitment strategies (e.g., newspaper advertisements, sending brochures to healthcare providers in the surrounding area); two strategies were most effective. These strategies were posting flyer announcements in the community (e.g., near public transportation stops, in community centers, public libraries, laundromats, grocery stores) and posting announcements on Craigslist. We were able to recruit an average of 3 participants per month who met eligibility criteria and enrolled in the clinical. We expect to be able to recruit a greater number of participants for the proposed trial because we will be recruiting a broader sample of PTSD participants.

The study announcements will state that the free treatment is part of a research study that is available to qualified individuals. Interested individuals will be instructed to call for further information.

In accordance with HIPAA regulations, written informed consent will be obtained from each participant after a thorough explanation of procedures by a project staff person and the opportunity for the participant to ask and receive answers to questions. Participants will be informed of the nature of the investigation, the types of assessments and treatments involved, alternative treatments, and the potential risks involved in participation and will be asked to sign an informed consent statement prior to participating in the proposed study. In addition, the participant will receive an explanation of how information related to their case will be handled including all parties involved, data management, and plans to publish data in group format without identifying information.

Participants will also be informed that confidentiality may be broken under the following circumstances: disclosure of suicidal or homicidal intentions, disclosure of child abuse, disclosure of elder abuse. Confidentiality may be broken in such instances in order for protective measures to be taken.

**b. Protection against risk**

1. We will carefully screen to identify individuals whose risk for potential adverse outcomes is elevated were they to participate in the proposed research. Such individuals will be excluded from the study. As an example, a person deemed high suicidal risk (assessed using the MINI suicide module) would be excluded from study participation. These individuals will be followed by study personnel (if they give consent to be followed).
2. Clinical staff will be trained to cope with any anxiety/distress experienced by participants during the assessments and treatment.

3. Careful monitoring of participants during the initial assessment and throughout the study will be conducted by the project staff. Participants will complete the PCL and BDI at each assessment and treatment session in order to carefully monitor symptoms (and potential symptom increases). Each participant will see the same clinician for each of their treatment visits and the same assessor for each assessment occasion. Following the clinical trial policy of the VA Boston Healthcare System, all participants will be given an emergency number to call after business hours in case of an emergency. This number will be the psychiatry on call system of the VA Boston Healthcare System.

4. Participants will be instructed to contact study personnel at any time (including during the follow-up period) in the event of worsening of symptoms or relapse. Participants whose clinical condition has substantially deteriorated will be removed from study treatment and given appropriate clinical referrals will be made. These individuals will also be followed by study personnel, if they give permission to be followed. See DSMP for details.

5. Participants failing to benefit from the study treatments will be provided with a list of clinical referrals in the greater Boston area. Participants who begin treatment and experience adverse outcomes sufficient to require removal from the study will receive appropriate clinical referrals. The appropriate clinical referrals will be determined by the judgment of clinicians and supervising staff familiar with the specific participant and may include cognitive-behavioral treatment, other psychotherapy, or referral for medication treatment.

6. As in any type of treatment or clinical research program, participants’ confidentiality must be carefully guarded and respected. All data with identifying information will be stored in locked files or password-protected computer server. Data being analyzed will be identified by subject codes, and identifying information will be removed. The identity of participants will not be revealed in the presentation or publication of any results from the project. All personnel working on the project will be educated about the importance of strictly respecting participants’ rights to confidentiality and will have completed several training courses including proper practice in accordance with HIPAA regulations, protection of human subjects, and computer security.

7. Establishment of a data safety monitoring committee (see DSMP section for details and for additional information regarding protection against the risks).

**POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS**

The direct benefit to participants who enter this study will be to obtain relief from anxiety symptoms, decreased avoidance, decreased disability, and increased quality of life. For many individuals with PTSD the disorder has greatly impeded their social, vocational, and academic functioning.
IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Posttraumatic stress disorder (PTSD) is a chronic and debilitating disorder with a lifetime prevalence rate of up to 25% (Kessler et al., 2005). PTSD has been associated with substantial costs, both in terms of health care utilization and work productivity. Despite the fact that several empirically-supported psychotherapy treatments for PTSD exist, many of these individuals do not present for treatment, in part, due to the cost and time commitment required for these treatments. Establishing cost-effective, brief and readily deliverable alternatives to traditional (time intensive) psychotherapy options for individuals with PTSD has broad public health and policy implications given the high prevalence of this debilitating disorder. The proposed study seeks to establish such an alternative treatment.

DATA SAFETY AND MONITORING PLAN (DSMP)

Data Safety and Monitoring Board (DSMB)

Given the scope of the current study, a formal DSMB is not required. We will form a Data Monitoring Committee (DMC). The DMC will be comprised of 4 members who have expertise in clinical trials, preferably expertise in PTSD, and who are not affiliated in any other way with the proposed project. Each member of the DMC will work at VA Boston Healthcare System, which will eliminate the need to include individuals who are outside of VA Boston. The DMC can request unblinding of data if deemed necessary. Otherwise, group-level data will be provided to the DMC. Following each quarterly meeting, the DMC will provide the PI with a written summary of their review and recommendations. The PI will provide these quarterly summaries to the VA Boston IRB as part of the annual review process. In addition, the PI will be responsible for executing any recommended changes to the Data Safety and Monitoring Plan and complying with the reporting requirements.

Protocol for Monitoring Adverse Events

We don’t expect adverse events to occur as a result of study treatment. However, because of the psychiatric nature of the sample to be studied, there is a potential for adverse events to occur. These adverse events include suicidal ideation, homicidal ideation, and an increase in PTSD symptom severity. Although the likelihood of these adverse events occurring in response to PTSD treatment is low (e.g., Foa et al., 2002), these adverse events will be closely monitored throughout the study. Apart from these potential adverse events, we do not anticipate the occurrence of any other adverse events.

As previously described, there are two reasons suicidal risk will be assessed in the proposed study. The first reason is to determine participant eligibility and the second reason is to ensure the safety and well-being of participants throughout the study. The Mini International Neuropsychiatric Interview (MINI) suicide module will be used to assess suicide risk during the baseline assessment. The MINI suicide module is a clinician administered interview that consists of 9 questions related to suicidal ideation and behaviors, with possible scores ranging from 0 to 53. Low suicide risk is defined as 0-8 points, moderate suicide risk is defined as 9-16 points, and high suicide risk is defined as scoring 17 or greater. We are using this measure because the MINI suicide module is clinician-administered, includes clear guidelines for determining suicide risk, and requires approximately 10 minutes to administer. The MINI
demonstrates excellent inter-rater reliability, with kappa values exceeding 0.75 (Lecrubier et al., 1997; Sheehan et al., 1998); and generally good test-retest reliability, with kappa values typically exceeding 0.65 (Lecrubier et al., 1997; Sheehan et al., 1998). Individuals will be excluded from enrolling in our proposed randomized controlled trial if they score 17 or higher (high risk) on the MINI suicide module at the initial assessment. Individuals who are excluded from participating in the clinical trial will be provided with appropriate clinical referrals. The PI will follow up with each of these individuals within one week to make sure they have connected with appropriate clinical care.

To monitor suicide risk throughout the study, we will administer the BDI-II at each treatment and assessment session. If a participant endorses suicidal ideation at any level in response to question #9 (suicidal thoughts or wishes), a clinical assessor will administer the MINI suicidal module. Participants deemed to be a high risk for suicide on the MINI (i.e., score of 17 or higher) will be removed from the study treatment and appropriate actions will be taken. These actions are described below in the data monitoring section. In addition, if the participant is willing, they will continue to be followed by the PI.

Homicidal risk will be assessed using approach recommended by VA/DOD Clinical Practice Guideline for Major Depressive Disorder (2009). At the initial assessment and at the beginning of each treatment session, participants will be directly asked whether they have thoughts of harming anyone. If the participant indicates they do have thoughts of harming someone, then the clinician will ask whether the participant has an active plan or method to harm someone (e.g., weapon in their home) and whom the participant wishes to harm. Further assessment will take place for participants who indicate that they have an active plan or method. Specifically, they will be asked whether they have ever lost control and acted violently and, if so, the severity of reported past violent behavior will be assessed. If a participant indicates that they have thoughts of harming someone and they have an active plan, the participant will be considered potentially high risk and further assessment will be conducted, as described in the section on managing adverse events.

We will monitor for a substantial increase in PTSD symptom severity using the Posttraumatic Check List (PCL; Weathers et al., 1994). The PCL is a 17 item self-report measure of PTSD symptom severity. This measure will be completed at each assessment session and each treatment session. A substantial increase in symptoms is defined as at least 10 point increase in PTSD from the initial assessment and has been sustained for a three week period (Foa et al., 2002).

Protocol for Managing Adverse Events

In the event a participant is deemed high suicide and/or homicidal risk, staff will immediately locate either the PI or one of the Co-I’s (Drs. Marx and Resick), all of whom are licensed psychologists. At least one of these individuals will be on-site when assessment and treatment sessions are conducted. The PI or Co-I will intervene by a) following up with direct questions about suicidal/homicidal behaviors, b) assess mental status by asking about psychotic symptoms, mood symptoms and drug and alcohol use, c) schedule extra contacts if necessary, emphasizing problem solving, d) help the participant generate short-term objectives, and e)
negotiate an action plan. The action plan will be collaboratively generated by the investigator and the participant. The plan will address what actions need to be taken in the succeeding days to solve the problems that precipitated suicidal/homicidal behavior. The plan will also address the use of voluntary and involuntary hospitalization, if necessary. Lastly, in the case of homicidal ideation with explicit intent to harm a named individual, the PI will report the intent to the local police as required legally required to protect the named individual.

In addition to these formal assessments, all participants will be given the number of the on-call psychiatry service at VA Boston Healthcare System and informed that they should call this number after business hours in the event that they are feeling suicidal and/or distressed, or homicidal. During business hours the participants will be instructed to contact the PI. Should a participant call to indicate suicidal/homicidal risk, then the previously described intervention plan will be followed. Participants will also be informed during the informed consent process that if suicidal and/or homicidal intentions are disclosed confidentiality may be broken in order for protective measures to be taken. The suicidal risk management plan has empirical support for its efficacy (Chiles & Strosahl, 2005) and is the plan that is recommended for use by the American Psychiatric Association. Moreover, the homicidal risk assessment and management plan is recommended by VA/DoD Clinical Practice Guidelines (2009).

In the event that a participant experiences an increase in PTSD symptom severity but without suicidal/homicidal risk, the PI will intervene by asking direct questions about the nature and causes of the distress, conduct a PTSD assessment, and schedule extra contacts (assessments) if deemed necessary. Such individuals will be terminated from the protocol if they report a substantial increase in the PTSD symptom severity (i.e. at least 10 points higher than their baseline PTSD symptom severity score) that is sustained over a three week period. We have selected the 10 point increase and 3-week time frame based on Foa, Zoellner et al. (2002) in which they emphasize the importance of using a reliable index score when considering increases (and decreases) in PTSD symptoms. Importantly, Foa and colleagues (2002) have reported that only a minority of participants showed an acute substantial increase in PTSD symptom severity during Prolonged Exposure treatment, and that this acute increase was not associated with an increased risk for dropout or poor treatment outcome. Nevertheless, to protect against risk, we will monitor participants for undue distress reactions and will use a 10 point increase from baseline assessment of PTSD symptom severity that is sustained for 3 weeks as a guide for withdrawing a participant from the study treatment. If a participant is withdrawn from the study treatment, they will be followed by study personnel, if they agree to be followed. In addition, participants who are withdrawn from the study treatment or who are deemed ineligible to enroll in the trial will be provided with a list of clinical referrals that are located in the greater Boston area. The referral list will include clinics that have a sliding scale fee schedule. Study personnel will discuss with the participant which referrals are the most viable given their personal circumstances (e.g., healthcare insurance restrictions, financial restrictions, etc.). The PI will subsequently contact these participants within one week to make sure that the participant did not experience any barriers in following through with clinical referrals.

Protocol for Reporting Adverse Events
Any study-related unanticipated problem posing risk of harm to participants or others, and any type of SAE, will be reported immediately to the PI, who will then report the event to the VA Boston IRB as soon as possible and within the time period mandated by the local IRB. In addition, for SAE’s, the PI will submit a SAE form to the local IRB and NIH within 48 hours of becoming aware of the SAE. The PI will keep a copy of this SAE form on file at the study site. The information to be reported will include the subject number, a description of the event, date of onset, current status, whether or not the treatment was discontinued, the reason why the event is classified as serious, and the PI's assessment of the association between the event and the study treatment. The PI will provide any significant new information regarding ongoing SAEs promptly (i.e., within 48 hours of becoming aware of event) to the local IRB and NIH. Adverse events not designated as serious will be reported to NIH on a quarterly basis and annually to the local IRB.

**Literature Cited**


treatments for PTSD. Practice Guidelines form the International Society for Traumatic Stress Studies (pp. 139-222). New York: Guilford Press.


