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I. PROJECT SUMMARY

A. ABSTRACT:

Many Marines and Sailors return from deployment with mental health problems related to their experiences. One such problem is posttraumatic stress disorder (PTSD), which involves symptoms such as persistent unwanted memories of traumatic events, avoidance of reminders of the events, excessive watchfulness, jumpiness and irritability. Current therapies for PTSD focus chiefly on fear related to life-threat and were developed chiefly on civilians. We developed and piloted tested a psychological treatment for PTSD specifically for service members who suffer not only life-threat, but also traumatic loss and inner conflicts from morally challenging experiences. This intervention, Adaptive Disclosure (AD) is an eight-session PTSD treatment that helps Marines to identify unhelpful beliefs about a traumatic event and find ways to move forward. Preliminary clinical data suggests that AD is acceptable to Marines, feasible to implement, and safe and that it reduces PTSD and depression. The primary objective of this randomized controlled non-inferiority trial is to determine whether or not AD is as least as effective as Cognitive Processing Therapy, cognitive only version (CPT-C), which is an empirically validated and commonly used PTSD treatment.

We plan to recruit 266 Marines for this project. They will be randomly assigned to AD or CPT-C and followed during and after treatment. The groups will be compared on measures of mental health (particularly PTSD and depression), work-related functioning, trauma-related beliefs, coping and attitudes about mental health care.

B. KEY WORDS:

PTSD, psychotherapy, clinical trial

C. ABBREVIATIONS USED:

AD Adaptive Disclosure
AE: adverse event
AHLTA: Armed Forces Health Longitudinal Technology Application
AUDIT: Alcohol Use Disorders Identification Test
AUDIT-C: Alcohol Use Disorders Identification Test-consumption items
CAPS: Clinician Administered PTSD Scale
CFR: Code of Federal Regulations
CONSORT: Consolidated Standards of Reporting Trials Statement
COSI: Combat and Operational Stress Injury
CPT: Cognitive Processing Therapy
DSMB: Data Safety Monitoring Board
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EMDR: Eye Movement Desensitization and Reprocessing
HRPO: Human Research Protections Office
IPG-13: Inventory of Prolonged Grief
IRB: Institutional Review Board
NHCP: Naval Hospital Camp Pendleton
NMCSD: Naval Medical Center San Diego

OEF: Operation Enduring Freedom
OIF: Operation Iraqi Freedom
OND: Operation New Dawn
ORP: Office of Research Protections
PCL-M: PTSD Checklist, Military Version
PE: Prolonged Exposure
PHQ-9: Patient Health Questionnaire
PTCI: Posttraumatic Cognitions Inventory
PTSD: post-traumatic stress disorder
RSES: Response to Stressful Experiences Scale
SAE: serious adverse event
TAU: treatment as usual
VA: United States Department of Veterans Affairs
WHI: Work History Inventory

D. KEY PERSONNEL *[The names listed here must be identical to those names listed in Section E.]*

	• **Name, Degree & Grade/Rank** • **Phone #** • **Cell #** • **E-mail address:**	• **PI, AI, PI(A)*or RM** • **Projected Rotation Date (PRD)** • **% of time devoted to this effort**	• **Organization (e.g. NMCSD)** • **Department** • **Status (Trainee, Resident, Staff, Fellow, DoD Contractor)**
(1)	Nancy Lovell, PhD 760.719.3312 nancy.b.lovell.civ@mail.mil	NHCP site PI, PRD N/A, 5%	NHCP, Mental Health, Staff (GS employee)
(2)	Ariel Lang, PhD 858-246-0631 ajlang@ucsd.edu	Overall PI	University of California, San Diego / Veterans Medical Research Foundation
(3)			
(4)			
(5)			
(6)			
(7)			
(8)			

PI = Principal Investigator
* **PI (A)** = The local Principal Investigator for Administrative purposes (use only if PI is deployed or on extended TAD)
AI = Associate Investigator **(please see NMCSD Guidebook for information on requirements of adding associate investigators)**
RM = Research Monitor (formerly referred to as Medical Monitor)

NOTE: PLEASE COMPLETE
This is the ☐ **Original or** ☒ **Updated (check one) key personnel listing.**

Date Effective: **January 2018**

D. KEY PERSONNEL *[The names listed here must be identical to those names listed in Section E.]*

	• **Name, Degree & Grade/Rank** • **Phone #** • **Cell #** • **E-mail address:**	• **PI, AI, PI(A)* or RM** • **Projected Rotation Date (PRD)** • **% of time devoted to this effort**	• **Organization (e.g. NMCSD)** • **Department** • **Status (Trainee, Resident, Staff, Fellow, DoD Contractor)**
(1)	Ariel Lang, PhD 858-246-0631 ajlang@ucsd.edu	Overall PI	University of California, San Diego / Veterans Medical Research Foundation
(2)	Shiva Ghaed 619-524-4051 Shiva.g.Ghaed2.civ@mail.mil	NMCSD site PI, PRD N/A, 5%	NMCSD, Mental Health, Staff (GS employee)
(3)			
(4)			
(5)			
(5)	Amy Lansing, PhD 858-246-0631 alansing@ucsd.edu	AI at NHCP, NMCSD	University of California, San Diego / Veterans Medical Research Foundation
(6)	Selena Baca 858-642-2965 Selena.baca@va.gov	AI at NMCSD	Veterans Medical Research Foundation
(7)			
(8)			

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AI = Associate Investigator **(please see NMCSD Guidebook for information on requirements of adding associate investigators)**
RM = Research Monitor (formerly referred to as Medical Monitor)

NOTE: PLEASE COMPLETE
This is the ☐ **Original or** ☒ **Updated (check one) key personnel listing.**

Date Effective: **January 2018**

E. HUMAN USE ASSURANCE STATEMENT

We, the Principal Investigator and Associate Investigators on the above

noted research project, have read and understand the provisions of 32 CFR Part 219 (Protection of Human Subjects), the Belmont Report, "Ethical Principles and Guidelines for the Protection of Human Subjects of Research," and NAVMEDCEN SDIEGOINST 6500.9, Human Clinical Investigation Program, Institutional Review Board, and the Protection of Human Subjects. The DOD Multiple Project Assurance Number for this facility is DOD40005. We agree to abide by all applicable laws and regulations and agree that in all cases the most restrictive regulation related to a given aspect of research involving protection of research volunteers will be followed during the conduct of this research project. In the event that we have a question regarding our obligations during the conduct of this Navy sponsored project, we have ready access to each of these regulations, as either a personal copy or available on file from the Chairman, Institutional Review Board. We understand that the immediate resource for clarification of any issues related to the protection of research volunteers is the Chairman of that committee. We understand that failure to comply with reporting and/or review requirements will require suspension or termination of the project.

PRINT NAME, RANK / DEGREE	**POSITION OR ROLE (PI, AI, MM)**	**SIGNATURE**	**DATE**
Nancy Lovell, PhD	Local PI NHCP	**On file**	
Ariel Lang, PhD	Overall PI	**On file**	
Amy Lansing, PhD	AI	**On file**	
Shiva Ghaed, PhD	Local PI NMCSD	On file	
Selena Baca	AI	See attached	
Genelle Weits	RM	On file	
Maureen Hallett	AI	On file	

F. SUB-INVESTIGATORS

Sub-investigators are individuals who will be trained in the specifics of the protocol and on how to perform the informed consent process from prospective subjects. This does not require the submission of a curriculum vitae or listing them as investigators on the Human Use Assurance Statement. However, the Principal Investigator will be responsible for providing training to all Sub-Investigators and documenting such by listing the names below. **Prior approval must be obtained from the IRB, before Sub-Investigators can be utilized. Approval can be requested by completing this form and including it with the protocol submission.** If approved, the information must be updated at the time of continuing review.

1. Will anyone other than the Key Personnel be performing the consent process? (Check one.)

[x] **Yes** [ ] **No**

If Yes, provide justification: All work including the consent process will be performed by VMRF, UCSD and BVARI personnel, who are supported by the extramural award. **Personnel will be hired in order to minimize the impact of the study on NHCP and NMCSD mental health clinics.**

Category (Residents, Staff, Civilian):

Civilian

2. Provide Names and SSNs for all Sub-Investigators in the table below.

The following individuals will be sub-investigators on this study. All have/will participate(d) in, and satisfactorily complete(d), training in the specifics of this protocol, as well as how to appropriately obtain informed consent form prospective subjects.

PRINTED NAME	Last 4 SSN

PRINTED NAME	Last 4 SSN

G. BUDGET

Budget Summary or Payment Schedule: Not applicable. The project is funded by DoD grant entitled "Adaptive Disclosure: A Combat-Specific PTSD Treatment," awarded to Ariel Lang, PhD, MPH (Initiating PI, VMRF), Brett Litz, PhD (Partnering PI, BVARI), Amy Lansing, PhD (Partnering PI, UCSD).

H. DETAILED BUDGET LIST

This study is funded by the Congressionally Directed Medical Research Program, with execution of funding through the Veterans Medical Research Foundation. Naval Hospital Camp Pendleton and Naval Medical Center San Diego will not receive direct funding for the execution of this work; support at NHCP and NMCSD will be defined in the pending Cooperative Research and Development Agreement (which will be submitted to the IRB when finalized).

II. PROJECT DESCRIPTION

A. BACKGROUND AND SIGNIFICANCE:

As of spring 2009, more than 1.8 million U.S. troops have served in the wars in Afghanistan and Iraq, with 37% having deployed at least twice. Findings from epidemiologic studies of infantry troops in the early stages of the wars suggest that 10-18% of combat troops experience deployment-related psychological health problems, such as posttraumatic stress disorder (PTSD; e.g., Hoge et al., 2004; see Litz & Schlenger, 2009; Smith, et al., 2008). Rates of PTSD continue to increase as the wars continue (e.g., Milliken, Achterlonie, & Hoge, 2007). The negative public health impact of PTSD related to combat and operational trauma is heightened by its frequent co-occurrence with substance abuse (Jacobson et al., 2008), physical health problems (Hoge, Terhakopian, Castro, Messer, & Engel, 2007), and functional disability (Hoge, Auchterlonie, & Milliken, 2006). Thus, effective treatment of PTSD is an important priority for our military personnel and veterans. Further, the reach of effective PTSD treatment extends well beyond the individual to family members and friends, to the employer and colleagues at work, and to the society.

The primary evidence-based treatments for PTSD have limitations in the military population. Strategies such as Prolonged Exposure (PE) and Cognitive-Processing Therapy (CPT) have been shown to be effective, but they were developed and tested primarily on civilian women with sexual assault and are not specifically tailored to address the unique challenges of service members exposed to sustained combat and operational stress, trauma, loss, and other war-related adversities and conflicts. Consistent with this, effect sizes in PTSD treatment trials with Veterans are consistently smaller than those generated in civilian trials (e.g., Monson et al., 2006; Rauch et al., 2009; Ready et al., 2008; Schnurr et al., 2007). PE and CPT also are lengthy and require extensive homework, which may not fit the high operation and training tempo of the active-duty garrison-life.

AD was developed to address this need. It is an eight-session fully manualized intervention designed specifically for active duty Marines and Sailors with PTSD stemming from a variety of traumatic deployment experiences (fear-based trauma, traumatic loss, and moral injury). The first session is devoted to assessment, psychoeducation, using motivational interviewing strategies to help the service member clarify what they would like to see happen, and providing a road-map about how AD can be used in service of those goals. The middle six sessions are devoted to (1) processing the most difficult, pressing, or emblematic combat and operational experience, (2) unearthing the service member's evolved understanding of the experience as they move forward in their military careers and beyond, and (3) providing experiential opportunities for the service member to consider alternative, more helpful ways of thinking about the experience, and (4) identifying a path towards healing and recovery. The last session is devoted to articulating lessons learned, getting and giving feedback, wrapping up, and planning for future challenges. AD is based on the idea that trauma-related symptoms are sustained because of avoidance and maladaptive beliefs about traumatic experience and the post-traumatic experience (e.g., Ehlers & Clark, 2000; Resick & Schnicke, 1992). Having service members disclose and form a narrative of a traumatic event (such as is used in PE) serves two purposes. First, the narrative provides an experience to disconfirm the common fears that fully remembering and disclosing the event may lead to "going crazy," losing control, or being judged or rejected. By providing a positive and/or useful experience with disclosure, patients may be more likely to disclose difficult deployment experiences with natural support networks (family, friends, fellow service members) or, if need be, with formal support services in the military and VA, thus avoiding the negative repercussions of avoidance and withdrawal. Second, the trauma narrative is used to elicit emotions and beliefs that are linked to combat and operational trauma in order to unearth tacit or previously unacknowledged maladaptive interpretations. Once such beliefs are recognized, the therapist helps the individual to see the ways in which these beliefs might be extreme and unhelpful and to encourage the consideration of alternative, more useful and adaptive appraisals moving forward. This may be accomplished through cognitive therapy strategies or through experiential techniques. AD also includes behavioral strategies, often assigned as homework, which may include exposure to avoided stimuli to address hypervigilance, activities to honor the departed to address grief, and ways of "making amends" for guilt/shame.

Finally, because of its brevity, the goal of AD is to plant restorative and healing seeds. We assume that for service members who have been exposed to multiple deployments with multiple injurious war-zone experiences, AD is the start of a healing and recovery process that the service member will need to embrace, own, and carry-forward to be truly effective. In other words, our goal is to provide an opportunity for a course-correction, to help service members get clear about where they are and how they would like to be moving forward. AD provides a sober but hopeful, evocative and emotion-focused opportunity for service members to realize how they have changed as a result of combat and operational experiences and to think about who they want to

be moving forward (and how to get there). In AD, we reduce PTSD symptom burden and improve functioning because the service member: (a) becomes more accepting and less self-condemning; (b) begins to make choices in service of wellness and self-care; (c) shares and discloses with trusted others; (d) reclaims competence and confidence in military and social roles; and (e) is better prepared to seek support and care if they need it over time.

B. SPECIFIC OBJECTIVES:

The primary objective of this randomized controlled non-inferiority trial is to determine whether or not Adaptive Disclosure (AD), a new combat-specific psychotherapy for PTSD, is as least as effective as Cognitive Processing Therapy, cognitive only version (CPT-C), in terms of its impact on deployment-related psychological health problems (specifically PTSD and depression) and functioning.

Primary Specific Aim 1: To determine whether or not AD is as least as effective as CPT-C in terms of change in psychological health problems over the treatment period.
Primary Specific Aim 2: To determine whether or not AD is at least as effective as CPT-C in terms of change in military-relevant functioning over the treatment period.

The project has several secondary objectives. First, because AD was developed to be consonant with the Marine Corps culture, we aim to test whether AD will be better accepted by Marines than CPT-C. Second, we will examine whether AD will be superior to CPT-C in terms of changing constructs that are uniquely targeted by AD, namely traumatic grief and moral injury. Third, we examine whether AD will be superior to CPT-C in terms of increasing resilience and posttraumatic growth. Finally, we will examine trauma-related cognition as a mediator of symptom and functioning changes.

Secondary Specific Aim 1: To compare the acceptability of AD and CPT-C.
Secondary Specific Aim 2: To compare the degree of change in grief and moral injury in the two treatments.
Secondary Specific Aim 3: To compare the degree of change in resilience and posttraumatic growth in the two treatments.
Secondary Specific Aim 4: To examine posttraumatic cognition as a mediator of treatment-related changes.
Secondary Specific Aim 5: To complete a qualitative analysis of reactions to Adaptive Disclosure at the end of treatment

C. PREVIOUS WORK BY YOU RELATED TO PROPOSAL:

Fifty-six Marines have enrolled in an earlier 6-session version of Adaptive Disclosure through a clinical demonstration project at Camp Pendleton. Complete treatment data is available for 26 of these individuals. Responses to our satisfaction measure suggest that AD is well received. Out of 20 respondents: 20 agreed or strongly agreed that the intervention was helpful, 20 agreed or strongly agreed that they would recommend the intervention to other Marines, 17 agreed or

strongly agreed that they would use an intervention like this following future deployments (2 felt neutral), 17 agreed or strongly agreed that the intervention was tailored to their individual needs (3 felt neutral), 16 agreed or strongly agreed that the intervention helped them feel more in control (4 felt neutral), and 16 agreed or strongly agreed that the intervention helped resolve emotional difficulties they had been experiencing (2 felt neutral, 2 disagreed). Nine agreed or strongly agreed that the intervention was long enough to make a significant improvement on their life (5 felt neutral), but 4 disagreed, 1 disagreed strongly. This feedback was part of the reason for extending the current version of the intervention to 8 sessions. There were no serious adverse events. No Marine decompensated or needed emergency care. There were no clinically significant exacerbations in PTSD, depression or drinking behavior between the beginning and end of treatment.

Based on data from first 36 individuals who completed treatment, AD appears to significantly and positively impact mental health symptoms. The average score on the PTSD Checklist – Military Version (PCL-M) dropped from 62.3 at pre-treatment to 50.2 after six sessions [effect size (Cohen's d) = 0.80, 90% CI 0.53-1.07]. The average score on the Patient Health Questionnaire – 9 (PHQ-9), our measure of depression severity, dropped from 14.6 at pre-treatment to 11.4 at post-treatment [effect size (Cohen's d) = 0.6, 90% CI 0.35-0.85]. The total score on the Posttraumatic Cognitions Inventory (PTCI) reduced from 11.2 to 9.3 [effect size (Cohen's d) = 0.45, 90% CI 0.19-0.71], with the most pronounced differences on the scales assessing negative cognitions about the self and world. Finally, the total score on the Response to Stressful Experiences Scale (RSES), a measure of resiliency after stressful events, increased from 9.7 to 10.9, suggesting improved ability to cope with stress in an adaptive way.

D. RESEARCH DESIGN

1. General Approach:

This project is a randomized noninferiority trial comparing AD to CPT-C.

2. Methods:

Potential participants will be referred by Naval Hospital Camp Pendleton and Naval Medical Center San Diego mental health providers (refer to Recruitment of Subjects). A partial HIPAA waiver is being requested so that providers can give names and contact information to study personnel to facilitate scheduling. Individuals who are referred will be contacted by telephone by study personnel, who will explain the project and offer an initial appointment. If the individual is willing to be evaluated for the study, the staff member will set a time for the initial evaluation, in which consent will be obtained and inclusionary and exclusionary criteria will be assessed. For eligible individuals who choose to participate, the baseline self-report measures will be completed in this visit as well. During the visit (or within the next week if necessary), the individual will be introduced by telephone (Boston VA), or in person (San Diego VA), to an assessor who will complete a clinician-rated assessment of their PTSD symptoms [using the

CAPS, see Assessment]. This interview will be completed by telephone or in person to provide an independent clinical assessment by a mental health professional who can remain blind to treatment condition; the CAPS retains good psychometric properties when administered in this way (Aziz & Kenford, 2004).

Once eligibility is established, participants will be randomly assigned to one of two treatment conditions: AD or CPT-C. The Boston site will provide randomization materials ahead of time so that staff biases cannot influence group assignment. The participant will begin treatment with a study therapist immediately. The therapist will contact the participant by phone, email or text message to arrange appointments, but no clinical information will be sent by email or text. He/she will receive 720 minutes of individual psychotherapy delivered as 8 weekly 90-minute sessions of AD or 12 60-minute sessions of CPT-C over 8 weeks (ideally scheduled twice a week for the first 4 weeks and once a week for the second 4 weeks nut some variation is permitted); sessions may extend over an additional 2 weeks if needed. A brief symptom assessment will be used weekly during treatment. The full assessment battery will be repeated at the end of treatment and 3 and 6 months after treatment (see Assessment). We will contact the participant by telephone, email or text to arrange these appointments.

An effort will be made to retain subjects in the study. Therapists will call patients after missed sessions to explore the reasons for nonattendance and encourage continuation. In the event that a patient does discontinue the treatment (either by dropping out being discontinued for clinical reasons), we will attempt to perform a full assessment within one week of exit from the trial. Following the protocol recommended by the CONSORT statement (Moher, et al., 2001), we will keep track of: how many people are referred to the study; how many of those participate in screening for the study; how many of those screened meet inclusion criteria and how many are excluded by exclusion criteria; how many are invited to participate in the study; and of those who we invite to participate, how many actually enroll. This information will provide an empirical basis for assessing pre-inclusion attrition rates and identifying any potential enrollment bias. In addition to assessing possible differential refusal and the impact it might have on generalizability of findings, we will record the reasons patients are excluded from or refuse to participate in the study. This will permit us to examine potential differences in rates and reasons for study refusal or exclusion.

Assessment

Initial eligibility will be determined by use PCL-M (total score > 34; Weathers, Litz, Huska, & Keane, 1991) immediately after consent. In addition, sections A, B, C, K and I of the Mini International Neuropsychiatric Interview (MINI; Sheehan et al 1998) and a brief neuropsychological battery will be administered to assess for exclusionary criteria, and the potential participant will be queried about homicidality and current mental health utilization. The Boston or San Diego site then will determine final eligibility by telephone or in-person, using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1990).

Should the Boston site interview someone who is off site, a prepared sheet of contact information with Dr. Ghaeds' and other designated NMC staff members phone numbers to intervene in case of emergency, will be in possession by the the San Diego assessor.Once determined to be eligible, participants will complete the full assessment battery, which will be repeated at the end of the initial treatment period, 3 months after the end of treatment and 6 months after the end of treatment except as indicated below. Assessments may be completed within 2 weeks of these time points. The full battery, the entirely to which is administered to both experimental groups, will consist of the following measures. All instruments are well-established and frequently used.

Descriptives and Covariates

Demographic information will be collected, including age, gender, race/ethnicity, marital status, education, branch of service, rank, military occupational specialty (MOS), length of service, deployment history and items which are in standard use in the NHCP Mental Health Clinic to help us to characterize the individual's baseline level of impairment. (Administered at baseline)

The INTRuST TBI Screening Instrument is a 3-item tool to identify probable exposure to head injury, modified to include age at which endorsed events occurred.

The Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1988) is a brief self-report measure of problematic alcohol use.

A short neuropsychological battery will be administered to assess cognitive processes that may have been impacted by head injury or psychopathology. These measures include: WAIS-IV Digit Span (~5-10 minutes), California Verbal Learning Test - 2 (CVLT-2; 15 minutes total), DKEFS Trails (~6 minutes), WAIS-IV Letter-Number Span (~5 minutes). (Administered at screening)

The mental health service history – Interview supplement will be used to detail mental health treatment received prior to study entry (at baseline) and since the last assessment.

Primary Aims

Psychological Health

The CAPS is the primary outcome measure. This 45–60 minute interview yields PTSD diagnostic status as well as a continuous total severity score. The scale also assesses social and occupational functioning, guilt, and the validity of symptom reports. A question will be added in the format of the interview to ask about shame. It will be administered by telephone or in person by a trained clinician in Boston or San Diego, who is blind to treatment status at the beginning and end of the intervention. (Administered before and after treatment)

The PTSD Checklist, Military Version (PCL-M; Weathers, Litz, Huska, & Keane, 1994) is a 17-item self-report measure of DSM-IV PTSD symptoms.

The nine depression items from the Patient Health Questionnaire (PHQ-9; Spitzer, Kroenke & Williams, 1999) make up a brief self-report measure of the severity of depressive symptoms.

The Buss-Perry Aggression Questionnaire (Buss & Perry, 1992) is a 27-item questionnaire assessing physical and verbal aggression, anger and hostility.

Military-Relevant Functioning

The brief version of the Inventory of Functional Impairment (IFI; Marx) is 14-item self-report measure of multiple dimensions of functional impairment in active duty service members and veterans. The measure will be supplemented with additional questions about military-specific work functioning.

The SF-12 is an abbreviated version of the Short Form 36 Health Survey (SF-36), which is a measure of health-related quality of life. The Physical and Mental Component Summary scales (PCS and MCS) from the SF-12 are virtually identical to those derived from the SF-36, and the SF-12 has good validity for detecting ill health (Jenkinson et al., 1997).

Secondary Aims

Acceptability

Credibility measure adapted from Borkovec & Nau, 1972. (Administered after session 1.)

Client Satisfaction Questionnaire (CSQ-8; Attkisson & Greenfield, 1994), an 8-item measure of satisfaction with services received. (Administered after the final therapy session)

The Working Alliance Inventory (WAI; Busseri & Tyler, 2003), a 12-item measure of rapport/alliance with the therapist. (Administered at the treatment mid-point).

AD-Specific Constructs

The Inventory of Prolonged Grief (IPG-13; Prigerson et al., in press) is a 13-item measure of bereavement-related distress.

The Moral Injury Events Scale (MIES; Nash et al., in submission) is a 9-item measure of perceived transgressions by the self or others and perceived betrayal.

The short form of the Posttraumatic Growth Inventory (PTGI-SF; Cann et al., 2010) is a 10-item measure of five domains of posttraumatic growth.

Mechanism

The Posttraumatic Cognitions Inventory (PTCI; Foa, Ehlers, Clark, Tolin, Orsillo, 1999) will be used to assess changes in trauma related cognitions. The PTCI assesses 3 broad categories of posttraumatic beliefs known to be associated with poorer posttraumatic adjustment – negative beliefs about self, negative beliefs about the world, and self-blame.

Before treatment sessions 2-8, both conditions will also complete an abbreviated assessment battery [PCL-M, PHQ-9 and AUDIT-C (consisting of the first 3 items of the AUDIT)] to monitor weekly symptom changes.

Assessor Training and Adherence: Dr. Gray will train the assessors prior to beginning enrollment unless they can demonstrate prior appropriate training. Training will include reading and viewing training materials, observation of CAPS administration, and supervised administration of at least three CAPS. Each assessor will be considered trained on CAPS when he or she "matches" Dr. Gray on three interviews. To establish matching, Dr. Gray will co-rate an interview conducted by

the assessor. A match occurs when the assessor and Dr. Gray agree on the diagnosis and are within 2 points of severity (frequency + intensity) on all of the symptom clusters (PTSD criteria B, C, and D). If the assessor does not match on three interviews after five attempts, Dr. Gray will determine whether additional training is necessary or if the assessor needs to be replaced.

Dr. Lansing will train the personnel who will be administering the neuropsychological battery. Training will include didactics about the administration and scoring of the instruments, observation of administration and scoring, observed administration and scoring, and periodic monitoring.

Intervention

Both AD and CPT-C are manualized interventions. Weekly feedback about progress in treatment will be provided to the patient's mental health clinic provider, but details of the approach being used will be excluded so that providers remain blind to the randomization. The blind can be broken if necessary for crisis management. Providers will receive a summary of progress after the post-treatment assessment has been completed. AD is outlined in the table below.

Adaptive Disclosure: Treatment Outline

Session 1: Assessment and Introduction to AD

Welcome, introductions
Assess current functioning, desired change (hopeful and/or realistic?), how we can help, what Marine was like before deployment, how Marine is now
Discuss change due to trauma and reclaiming old self
Introduce "adaptive disclosure"
Psychoeducation: Combat and Operational Stress Injury (COSI)
Give instructions for impact statement

Sessions 2-7: Exposure-Based Activation, Identification and Processing of Deployment-Related Difficulties

Review week and impact statement
Trauma narrative
Process appraisals and meaning and implications of event. Go to Supplements as appropriate.
Review session and grounding/relaxation (if needed)

Grief Supplement	*Moral Injury Supplement*
3a. Education about grief	3a. Education about moral injury
3b. "Empty Chair" for grief	3b. "Empty Chair" for moral injury
3c. Discuss ways to honor the dead	3c. Discuss ways to make amends or move on

Session 8: Wrap-up and Planning for the Long Haul

Review progress
Identify/discuss areas to continue to work on, including triggers, self-

care, social reattachment/reengagement
Wrap-up

Therapist Training and Adherence: Therapists will have a doctoral degree in clinical psychology and some experience treating PTSD, preferably with active duty military or Veterans. There will be a primary AD therapist who delivers only AD and a primary CPT-C therapist who delivers only that approach. One additional staff position is available for treatment delivery; if a single full-time clinician is hired, it will be necessary for this person to delivery both approaches. Therapists will be trained in San Diego by Drs. Litz, Nash and Rodgers. Training will involve review of the AD or CPT manual and supporting materials, intensive supervision of the first two cases and weekly group supervision.

All sessions will be audiotaped and reviewed to ensure sustained fidelity to the treatment approach (provided that the participant consents). Dr. Litz will review AD cases and Dr. Rodgers will review CPT-C cases for adherence. They will review audio recordings of 100% of the first 2 cases, 50% of the subsequent 3 cases, and 25% of the next 5 and 10% thereafter. Drs. Litz and Rodgers can at their discretion increase the proportion reviewed for difficult patients or therapists needing additional monitoring. Therapists will be provided with prompt feedback about their performance. All recordings will be transported to the VMRF facility and stored in a locked cabinet in an office in the VMRF building. Selected sessions will be transported to Dr. Litz via Federal Express or another carrier that allows for tracking. All recordings will be destroyed when the participant completes or drops out of treatment.

3. Retrovirology Research: N/A

4. Investigational Drugs/Devices/Biologics Research: N/A

5. Statistical Analysis:

Statistical Plan
Data analysis will be completed by the Boston site and will involve the following

Data screening and missing data: Given the assumptions underlying some of the analyses described below, tests of normality will be conducted and transformation applied where appropriate. In addition, outliers will be identified, and corrective action (deletion, adjustment, or retention) will be taken depending on the source of the deviation, as per Tabachnick and Fidell (1996). Missing data will not be imputed; instead, the maximum likelihood estimation in Mplus will be used to estimate the models. This method derives the parameter estimates from the data that is available.

Pre-treatment equivalence: In order to determine pretreatment equivalence, a one-way ANOVA (with treatment condition as the between subjects factor) will be conducted on the primary outcome measure, the CAPS (indexed as symptom severity, defined as the mean of the sum of

the 17 Frequency and Intensity Ratings). For descriptive purposes, this analysis will also be conducted on the other outcome and moderator variables. In addition, t-tests and chi-square analyses will be conducted on demographic variables to determine equivalence across groups. Similar analyses will be conducted to compare dropouts and completers on pre-treatment and demographic variables in order to determine if these groups differ on relevant variables.

Primary Outcome Analysis: We will calculate the mean difference in CAPS scores by subtracting the average change in scores for CPT from the average change in scores for AD. Then, we will create a 95% confidence interval around that difference. If the interval is above a non-inferiority margin of -10 points, we will reject the null hypothesis (that CPT is superior) and accept the research hypothesis (that AD is non-inferior). The non-inferiority margin is based on a calculation of a reliable difference in CAPS scores (Monson et al., 2006). We will follow a similar procedure for the other primary outcome measures (i.e., the PCL-M, the PHQ-9, the IFI, and the SF-12).

Analyses of Clinical Significance: Clinically significant change will be calculated by the Jacobson-Truax (Jacobson & Truax, 1991) method, as recommended in recent reviews of clinical change indices (e.g., Bauer, Lambert, & Neilson, 2004). This method suggests a two-step criterion. First, a reasonable cutoff between the patient/dysfunctional and non-patient/functional populations is established. Jacobson and Traux's suggested cutoff A, defined as the point 2 SDs beyond the range of the pre-therapy mean for the CAPS (i.e., cutoff A = Mclinical - 2 SDclinical), will be used. Second, a reliable change index (RC) for each participant will be calculated to ensure that changes are not due to an artifact of measurement error. The RC is computed according to the following formula: RC = (x2 – x1)/Sdiff where x1 represents the participant's pretreatment CAPS total score, x2 represents the participant's posttreatment or follow-up CAPS total score, and Sdiff is the standard error of difference between the two test scores. Sdiff will be calculated from the internal consistency of the CAPS at each time point, as suggested by Martinovich, Saunders, and Howard (1996). An RC larger than 1.96 reflects real change (Jacobson & Truax, 1991). Based on the two-step criterion, individuals will be classified as recovered (passed both cutoff A and RC criteria), improved (pass RC criterion but not cutoff A), unchanged (did not pass RC criteria), or deteriorated (passed RC criterion but symptom scores increased).

We will also calculate three other indices of change based on the percentage of PTSD cases in each group, the number of treatment responders, and the number of participants who exhibit high-end state functioning (see Ehlers et al., 2003). Participants will be considered responders on a measure if they demonstrate at least a 20% improvement from pre-therapy levels (e.g., Ladouceur et al., 2000), and participants exhibiting high end-stage functioning will be defined as those with total CAPS scores at or below 30 and PHQ-9 scores at or below 5. Chi-square analyses between treatment conditions will be conducted to compare the proportion within each condition meeting PTSD

diagnosis, responder status, and high end-state functioning at post-treatment and follow-up assessment.

Secondary inferential analyses: The longitudinal nature of the design will produce a multilevel or nested data structure (Raudenbush & Bryk, 2001; Kenny, Kashy, & Bolger, 1998). The lower level, or level-1 data, will consist of the repeated measures that will be collected for each individual at multiple time points (e.g., pre, post, follow-up, and session-by-session outcome data). The level-1 data is nested within upper level, level-2, or person-level variables (e.g., individual difference variables including treatment group membership, minority status, posttraumatic cognitions, etc.). This data structure is appropriate for contemporary growth curve modeling techniques (see Collins & Sayer, 2001; Singer & Willett, 2003). With these techniques (e.g., growth-curve analysis), we will be able to estimate initial status and change over time in the outcome variables (i.e., level-1 or within-subjects component of the analyses), and examine how these coefficients vary as a function of individual difference variables (the level-2 or between-participants component of the analyses; e.g., gender). In terms of measurement of specific aims:

Primary Specific Aim 1: To determine whether or not AD is as least as effective as CPT-C in terms of change in psychological health problems over the treatment period.

As mentioned above, we will chiefly be interested in the results of the non-inferiority tests. These results will show whether or not AD is as least as effective as CPT-C, in terms of its impact on deployment-related psychological health problems (specifically PTSD and depression).

Primary Specific Aim 2: To determine whether or not AD is as least as effective as CPT-C in terms of change in military-relevant functioning over the treatment period.

The results will also show whether or not AD is as least as effective as CPT-C, in terms of its impact on functioning.

Secondary Specific Aim 1: To compare the acceptability of AD and CPT-C.

We will use an independent sample t test to compare the acceptability of the two treatments.

Secondary Specific Aim 2: To compare the degree of change in grief and moral injury in the two treatments.

We will use a mixed model repeated measures ANOVA to determine whether the groups differ in terms of change in grief and moral injury over time. A mixed model analysis is advantageous because it uses all of the available data; no adjustment is needed for missing data. Also, a mixed model analysis does not require sphericity or compound symmetry.

Secondary Specific Aim 3: To compare the degree of change in resilience and posttraumatic growth in the two treatments.

Analyses for this aim are similar to those described in Secondary Specific Aim 2.

Secondary Specific Aim 4: To examine posttraumatic cognition as a mediator of treatment-related changes.

We will use two methods to evaluate whether PTCI mediates the relationship between treatment and PTSD symptom severity. The first method is the casual step approach (Baron & Kenny, 1986). With this method, we hope to show that treatment predicts PTCI scores and PTCI scores predict PTSD symptom severity. Also, we hope to show that the relationship between treatment and PTSD symptom severity score is reduced with the introduction of PTCI scores. Because this method infers an indirect effect but does not test for it specifically, we will also employ a bootstrapping procedure. Mplus will be used to generate 5000 samples of the data set in order to produce 5000 estimates of path coefficients between treatment and PTCI scores and between PTCI scores and symptom severity scores. Multiplication of these two path coefficients will produce a sampling distribution of the indirect effect. Thus, there is no need to make an assumption about the shape of the sampling distribution (and the standard error of the indirect effect; Hayes, 2009), unlike the Sobel test (Sobel, 1982, 1986).

Secondary Specific Aim 5: To complete a qualitative analysis of reactions to Adaptive Disclosure at the end of treatment

As part of the treatment protocol, the therapist queries participants about their subjective impressions of the intervention and what changes, if any, they attribute to it. We will use qualitative methodology to code these responses so that we may describe subjective reactions.

6. Military Relevance / Operational Use, if any:

As of spring 2009, more than 1.8 million U.S. troops have served in the wars in Afghanistan and Iraq, with 37% having deployed at least twice. Findings from epidemiologic studies in the early stages of the wars suggest that 10-18% of combat troops experience deployment-related psychological health problems, such as posttraumatic stress disorder, and rates of PTSD continue to increase as the wars continue. PTSD itself is impairing, but the burden of the disorder is heightened by its frequent co-occurrence with other mental and physical health problems.

The impact of PTSD does not stop with the affected service member. Forty four percent of active duty military in the USA have children under the age of eighteen. PTSD symptoms have a substantial impact on spousal well-being and the overall functioning of the family, leading to problems such as poor parenting, family violence, divorce, sexual problems, aggression, caregiver burden and child behavioral problems. PTSD also impacts the communities in which the service member lives. PTSD is associated with work impairment, including increased unemployment, missed work and work inefficiencies, homelessness, increased medical costs for treatment of PTSD and secondary problems. Thus, advancing research and clinical care for

PTSD has the potential to have a cascading positive affect beyond the service member to their family and communities.

This study has the potential to impact research on the treatment of PTSD in service members because it is based on a sophisticated and dimensional understanding of the phenomenology and unique impact of combat and operational trauma, loss, and inner conflict in active duty service members across the deployment cycle. We anticipate that our results will foster more innovative, military-culture sensitive, and ecologically valid treatments for mental health problems related to combat and operational trauma, traumatic loss, and various sources of lasting inner conflict, utilizing evidence-informed and theory-driven cognitive-behavioral strategies.

The results of this study also have the potential to greatly impact patient care for service members. At present, the DoD and the VA are participating in large scale roll outs of cognitive-behavioral therapies. Yet, in our opinion, because these approaches have not been tested specifically on active-duty service members (or new veterans), their acceptance and feasibility with patients and care providers, and their efficacy all remain empirical questions. In contrast, AD was developed from clinical experience and observations about the psychological, biological, spiritual, and social challenges that stem a wide variety of combat and operational experiences (such as grief, guilt and moral injury). In our experience thus far, clinicians in our early demonstration project setting (Marine Corps Base Camp Pendleton) have requested training in AD and greatly appreciate our manual, which has extensive information not only about the how-to's but also the justification for the approach in terms of the phenomenology and unique clinical presentations of service members with combat and operational trauma. Thus, AD holds the promise of not only helping warriors to find better ways of healing and recovering from their experiences but provides a model of care that can build confidence and self-efficacy among caregivers. Because it is brief and culturally sensitive, AD may also be more attractive to service members, their leaders, and care-providers.

E. APPLICATION TO USE HUMAN SUBJECTS

1. Subject Population:

Participants will be 266 active duty Marine Corps or Navy personnel. They will be referred to the study by their mental health provider (see Recruitment). Participating individuals must: (1) have experienced at least one traumatic event as defined by DSM-IV during deployment during OIF, Operation New Dawn (OND), and/or OEF; (2) have current PTSD or subsyndromal PTSD with clinically significant distress/impairment and be able to recount the event that led to the PTSD symptoms; and (3) have received an initial mental evaluation from a military provider.

The sample size of 266 was established based on the following sample size calculation. We used the *Study Size* program, Version 2.0.4 (Olofsson, 2001-2007) and a standard deviation of 25, based on Monson et al. (2008). If the true difference between AD and CPT is 0 points,

then we need 99.1 participants per group, or roughly 200 participants, to ensure that power=.80. Estimating an attrition rate of approximately 25%, we anticipate a need to recruit 266 (200/.75) participants to achieve an adequate sample.

Subject Inclusion Criteria:

1. Age 18 or older
2. Current PTSD as diagnosed by the CAPS or subsyndromal PTSD (at least meeting criteria A and B) with distress and/or functional impairment as determined by the CAPS and review by study senior clinicians. Co-occurring disorders such as depression, anxiety, or treated substance abuse or dependence problems are permitted.
3. Individuals expected to deploy two or more months from the time of referral and/or assessment are eligible. Anyone deploying sooner than that would be unable to complete the entire intervention and thus are ineligible. Potential enrollees need not be presently deployable.
4. Prospective enrollees must be willing to commit to all treatment sessions and to complete assessment materials.

Subject Exclusion Criteria:

1. Serious suicidality or homicidality that has required urgent or emergent evaluation or treatment within the past three months.
2. A known, untreated substance abuse or dependence problem. Inclusion is possible if there is evidence that the individual has been afforded and is complying with treatment for the substance problem. Inclusion is possible if the treating clinician and study supervisor concur that participation is not contraindicated.
3. Serious Axis I mental disorders (those that are normally incompatible with active military service), such as psychotic disorders or bipolar type I, are not eligible.
4. Cognitive impairment that would interfere with one's ability to complete the intervention. If a potential participant performs below the mildly impaired range on the neuropsychological battery, the study neuropsychologist (Dr. Lansing) will review the case and make a clinical judgment based on review of testing and, in some cases, additional evaluation as to ability to participate.
5. Concurrent enrollment in any cognitive-behavioral treatment, group therapy, or any other treatment that involves systematic disclosure of troubling deployment-related memories. Participants can continue current pharmacological treatment, marital counseling, or any supportive therapy.
6. People will be excluded if they received CPT in the past, unless a clinician believes that additional CPT could be clinically useful because of the amount of time that has passed, the number of sessions received or another circumstance.

We expect sample demographics to approximately represent the demographic composition of the Marines at Camp Pendleton, which is 94% male, mostly Caucasian (66% white, 15% Hispanic, 8% black) and

relatively young (48% age 22-30, 38% age 17-21, 11% age 31-40) (Marine Corps demographics, December 2008).

2. Protected Population (i.e., children, women of childbearing age, and 3rd party subjects):

Women of childbearing age are eligible for participation as there is no risk based on this psychotherapeutic intervention to potential offspring.

Prisoners are eligible for participation provided that (a) consent was provided prior to incarceration, (b) continued participation is in the best interest of the participant based on the judgment of the PI and IRB Chair, (c) privacy can be provided for study activities, and (d) the participant demonstrates continued understanding of the voluntary nature of his/her participation and his/her rights as a research subject.

3. Method of Subject Indentification and Recruitment:

This project will rely on referrals from Naval Hospital Camp Pendleton and Naval Medical Center San Diego mental health providers. We will meet regularly with clinic leadership to maintain support for the project. Mental health providers educated about the study in the following ways: (a)provide materials describing the nature of the intervention and the target population, (b) attend weekly staff meetings, (c) give talks to describe the interventions in staff grand rounds, and (d) provide feedback to staff about referred patients. If a mental health provider identifies a patient who may be eligible, he/she will briefly explain the nature of the study and ask for oral permission (based on the requested partial HIPAA waiver)to give the patient's name and phone number to study staff, who will then call the patient to explain the study in more detail and, if the patient is willing, to schedule a screening visit.

a. Consent Process:

This study will be conducted in compliance with Title 45 Part 46 of the CFR pertaining to informed consent. At the first visit, prior to initiation of any study procedures, subjects will give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, risks, and potential benefits.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants. Consent forms describing in detail the intervention, study procedures and risks are given to the participant and written documentation of informed consent is required prior to starting the intervention. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants will have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The participants may withdraw consent at any

time throughout the course of the study. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The informed consent form for the Naval Medical Center San Diego Clinical Investigation Department has been used for this study because all subjects will be recruited and all activities will take place at Naval Hospital Camp Pendleton or Naval Medical Center San Diego. A VA HIPAA Authorization will be required because the grant supporting this project was awarded to the Veterans Medical Research Foundation. In addition, the Boston VA will obtain a verbal consent to conduct their portion of the assessment interview.

4. Experimental Procedure(s):

AD is an experimental psychotherapy. CPT is a well established psychotherapy for PTSD, but its use in active duty Marines and Sailors remains experimental.

5. Research Material Collected:

Research materials consist of assessments, questionnaires and audio recordings of therapy sessions.

6. Protection of Patient Privacy:

Patient confidentiality will be maintained through the assignment of patient identification numbers. These numbers will be used in keeping of all research records. The key linking identification numbers to identifying information will be kept in a locked cabinet separate from other study data. All hard copy research materials will be securely transported by authorized study personnel from Naval Hospital Camp Pendleton and Naval Medical Center San Diego to the VMRF building. Hard copies of the data will be kept in locked file cabinets in a locked office with keys available only to research personnel participating directly in this protocol. Hard copies of the data with all HIPAA identifiers removed will be faxed securely from VA to VA, or transported using Federal Express oranother service that adequately tracks shipments to the Boston site for data entry and analysis. Electronic data will be managed with all current security provisions. Patients will be informed during the consent process about the limits of confidentiality.

7. Risks:

The risks or discomforts which are possibly related to participation in this study are as follows: the interview questions, questionnaires, and discussions during psychotherapy may produce discomfort or anxiety from the discussion of personal or emotional topics.

Individuals who are part of a vulnerable population may feel additional pressure to comply with study procedures based on their status.

8. Radiation or Laser Exposure: N/A

9. Justification of Risks:

Preliminary evidence suggests that AD may be useful for reducing distress in this sample, and CPT-C is an empirically supported PTSD treatment. Some patients may also feel that they are making a useful contribution by furthering our understanding of how to treat other Marines with deployment-related symptoms.

There is benefit to the Marine Corps and to society in evaluating the efficacy of this intervention, which has the potential to be a better PTSD intervention for military trauma.

We believe that the benefits from this study outweigh its risks.

10. Minimization of Risks:

The therapists will have 24-hour access (via cell phone or pager) to Dr. Lovell and Dr. Lang or a designated clinical supervisor in case of any clinical emergencies. Any potential serious adverse events will be immediately reported to the principal investigators. All serious (i.e., severe and undesirable event with significant symptoms or more serious), unexpected (i.e., not anticipated based on the literature and as discussed in the MSP and/or consent forms) adverse events (AEs), regardless of their relationship to study treatment or procedure (causality), and those SAEs judged to be associated with the study treatment or procedure must be reported to the DSMB, IRBs and the Army's Human Research Protections Office (HRPO). All life-threatening SAEs or lethal reactions must be reported regardless of attribution.

Subjects will be informed about all potential study risks during the informed consent process. They will be informed that they can refuse to answer any question or terminate their assessments at any time if they so desire. The assessors and therapists will be specifically trained to respond effectively to subjects who experience anxiety and/or other distress during assessments or treatment and will be under the supervision of senior clinicians.

The risk associated with treatment-related discomfort is mitigated because patients can titrate the way in which they talk about the trauma and the activities in which they engage. Therapists will be carefully trained to encourage full engagement in imaginal exposure but to allow the patient to set limits where needed. Subjects can contact their therapist at any time if they are not able to cope with their anxiety independently. The therapist's contact information will be provided in the initial therapy session. Subjects will also have 24-hour access to mental health services at Naval Hospital Camp Pendleton and Naval Medical Center San Diego.

There may be a concern that study participation would delay subjects from seeking other forms of treatment for their symptoms. First, pros and cons of available treatment options will be reviewed during the initial evaluation, so potential participants will have chosen to participate will full knowledge of their other options. Second, there is reason to believe that AD will be a potent intervention for these conditions based on preliminary data and the efficacy of CPT-C has been established for PTSD. Third, if at any time

the therapist and supervisors judges that a subject requires a different approach or higher intensity care, the subject will be provided with referrals for outpatient or inpatient care, as appropriate.

Consistent with consent being a process, individuals who are part of a vulnerable population will be reminded that the terms of the consent form are unchanged based on their new status and that participation/non-participation has no bearing on legal proceedings. For prisoners, an individual will be identified in the detention facility in the event that safety monitoring becomes indicated.

A Data Safety Monitoring Board (DSMB) will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support those purposes, the DSMB will review the initial protocol and any proposed amendments, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.

11. Medical Monitor (signature form attached separately)

III. DATA COLLECTION SHEET(S) AND QUESTIONNAIRES:

Included in this submission are data collection sheets and questionnaires for the proposed study.

IV. CONSENT FORM, INFORMATION SHEET, OR WAIVER

Included in this submission is a 1st party consent with HIPAA Patient Authorization form.

V. BIBLIOGRAPHY

Attkisson, C. C., & Greenfield, T. K. (1994). The Client Satisfaction Questionnaire – 8 and the Service Satisfaction Questionnaire – 30. In M. E. Maruish (Ed.) *The Use of Psychological Testing for Treatment Planning and Outcome Assessment.* Hillsdale, NJ: Lawrence Erlbaum Associates.

Aziz, M. A., & Kenford, S. (2004). Comparability of telephone and face-to-face interviews in assessing patients with posttraumatic stress disorder. *Journal of Psychiatric Practice, 10*, 307-313.

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51,* 1173-1182.

Bauer, S., Lambert, M., & Neilson, S. L. (2004). Clinical significance methods: A comparison of techniques. *Journal of Personality Assessment, 82(1),* 60-70.

Blake, D. D., Weathers, F., Nagy, L. M., Kaloupek, D. G., Klauminzer, G., & Charney, D. S. (1990). A clinician rating scale for assessing current and lifetime PTSD: The CAPS-1. *Behavior Therapist, 13*, 187-188.http://www3.interscience.wiley.com/cgi-bin/reflink?object=TYPE%3DJCIT%26BIBID%3D5%26SNM%3DBlake%26FNM%3DD.%20D.%26SNM%3DWeathers%26FNM%3DF.%26SNM%3DNagy%26FNM%3DL.%20M.%26SNM%3DKaloupek%26FNM%3DD.%20G.%26SNM%3DKlauminzer%26FNM%3DG.%26SNM%3DChar%20

Borkovec, T. D., & Nau, S. D. (1972). Credibility of analogue therapy rationales. *Journal of Behavior Therapy & Experimental Psychiatry, 3*, 257-260.

Buss, A. H. & Perry, M. (1992). The Aggression Questionnaire. *Journal of Personality and Social Psychology, 63*, 452-459.

Cann, A., Calhoun, L. G., Tedeschi, R. G., Taku, K., Vishnevsky, T., Triplett, K. N., Danhauer, S. C. (2010). A short form of the Posttraumatic Growth Inventory. *Anxiety, Stress & Coping, 23*, 127 – 137.

Collins, L. M., & Sayer, A. G. (Eds.). (2001). *New methods for the analysis of change*. Washington, D.C.: American Psychological Association.

Ehlers, A., & Clark, D. O. (2000). A cognitive model of posttraumatic stress disorder. *Behavior Research and Therapy*, 38, 310-45.

Ehlers, A., Clark, D. M., Hackmann, A., McManus, F., Fennell, M., Herbert, C., & Mayou, R. (2003). A randomized controlled trial of cognitive therapy, a self-help booklet, and repeated assessments as early interventions for posttraumatic stress disorder. *Archives of General Psychiatry, 60,* 1024-1032.

Foa, E., Ehlers, A., Clark, D., Tolin, D., & Orsillo, S. (1999). The Posttraumatic Cognitions Inventory (PTCI): Development and validation. *Psychological Assessment, 11,* 303-314.

Hayes, A. F. (2009). Beyond Baron and Kenny: Statistical mediation analysis in the new millennium. *Communication Monographs, 76(4),* 408-420.

Hoge, C. W., Castro, C. A., Messer, S. C., McGurk, D., Cotting, D. I., & Koffman, R. L. (2004). Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *New England Journal of Medicine, 351,* 13-22.

Hoge, C. W., Auchterlonie, J. L., & Milliken, C. S. (2006). Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. *Journal of the American Medical Association, 295*, 1023-1032.

Hoge, C. W., Terhakopian, A., Castro, C. A., Messer, S. C., & Engel, C. C. (2007). Association of posttraumatic stress disorder with somatic symptoms, health care visits, and absenteeism among Iraq War veterans. *American Journal of Psychiatry, 164*, 150-153.

Jacobson, I. G., Ryan, M. A. K., Hooper, T. J., Smith, T. C., Amoroso, P. J., Boyko, E. J., Gackstetter, G. D., Wells, T. S., & Bell, N. S. (2008). Alcohol use and alcohol-related problems before and after military combat deployment. *Journal of the American Medical Association, 300,* 663-675.

Jacobson, N. S. & Truax, P. (1991). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology, 59(1),* 12-19.

Jenkinson, C., Layte, R., Jenkinson, D., Lawrence, K., Petersen, S., Paice, C., & Stradling, J. (1997). A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *Journal of Public Health Medicine, 19*, 179-186.

Johnson, D., Polusny, M., Erbes, C., King, D., King, L., Litz, B., Schnurr, P., Friedman, M. & Southwick, S. (2008). The Response to Stressful Experience Scale (RSES). VA National Center for PTSD. This is a government document in the public domain.

Kenny, D., Kashy, D. A., & Bolger, N. (1998). Data analysis in social psychology. In D. T. Gilbert, T. Daniel, & S. T. Fiske (Eds.), *The handbook of social psychology, Vols. 1 and 2* (4th ed., pp. 233-265). New York: McGraw-Hill.

Ladouceur, R., Dugas, M. J., & Freeston, M. H. (2000). Efficacy of a cognitive-behavioral treatment for generalized anxiety disorder: Evaluation in a controlled clinical trial. *Journal of Consulting and Clinical Psychology, 68*, 957-964.

Litz, B. T., & Schlenger, W. E (2009). Posttraumatic stress disorder in service members and new veterans of the Iraq and Afghanistan wars: A bibliography and critique. *PTSD Research Quarterly, 20,* 1-7.

Milliken, C. S., Auchterlonie, J. L., & Hoge, C. W. (2007). Longitudinal assessment of mental health problems among active and reserve component soldier returning from the Iraq War. *Journal of the American Medical Association, 298,* 2141-2148.

Moher, D., Schulz, K., Altman, D., for the CONSORT Group (2001). The CONSORT statement: Revised recommendations for improving the quality of reports of parallel group randomized trials. *Journal of the American Medical Association, 285*, 1987-1991.

Monson, C. M., Fredman, S. J., & Adair, K. C. (2008). Cognitive-behavioral conjoint therapy for posttraumatic stress disorder: Application to Operation Enduring and Iraqi Freedom veterans. *Journal of Clinical Psychology, 64*, 958-971.

Monson, C. M., Schnurr, P. P., Resick, P. A., Friedman, M. J., Young-Xu, Y., & Stevens, S. P. (2006). Cognitive processing therapy for

veterans with military-related posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology, 74,* 898-907.

Prigerson H, Horowitz M, Jacobs S, Parkes C, Aslan M, Raphael B, Marwit S, Wortman C, Goodkin K, Neimeyer R, Bonanno G, Block S, Kissane D, Boelen P, Maercker A, Litz B, Johnson J, First M, Maciejewski P. (in press). Field trial of consensus criteria for Prolonged Grief Disorder proposed for DSM-V. *Public Library of Science (PloS) Medicine.*

Rauch, S. A., Defever, E., Favorite, R., Duroe, A., Garrity, C., Martis, B., & Liberzon, I. (2009). Prolonged exposure for PTSD in a Veterans Health Administration PTSD clinic. *Journal of Traumatic Stress, 22,* 60-64.

Raudenbush, S.W., & Bryk, A.S. (2001). *Hierarchical Linear Models: Applications and Data Analysis Methods* (2nd ed.). Thousand Oaks, CA: Sage.

Ready, D. J., Thomas, K. P., Worley, V., Backscheider, A. G., Harvey, L. A. C., Baltzell, D., & Rothbaum, B. O. (2008). A field test of group exposure therapy with 102 veterans with war-related posttraumatic stress disorder. *Journal of Traumatic Stress, 21,* 150-157.

Resick, P. A., & Schnicke, M. K. (1992). Cognitive Processing Therapy for sexual assault victims. *Journal of Consulting and Clinical Psychology, 60,* 748-756.

Saunders, J., Aasland, O., Babor, T., de la Fuente, J. & Grant, M. (1988). Development of the Alcohol Use Disorder Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addictions, 88,* 791-804.

Schnurr, P. P., Friedman, M. J., Engel, C. C., Foa, E. B., Shea, M. T., Chow, B. T., Resick, P. A., Thurston, V., Orsillo, S. M., Haug, R., Turner, C., & Bernardy, N. (2007). Cognitive behavioral therapy for posttraumatic stress disorder in women: A randomized controlled trial. *Journal of the American Medical Association, 8,* 820-830.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, .P, Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59 (suppl 20)*, 22-33.

Singer, J., & Willett, J. (2003). *Applied longitudinal data analysis: Modeling change and event occurrence.* New York: Oxford University Press.

Smith, T. C., Ryan, M. A. K., Wingard, D. L., Slymen, D. J., Sallis, J. F., Kritz-Silverstein, D. & the Millennium Cohort Study Team (2008). New and persistent symptoms of post-traumatic stress disorder self reported after deployment and combat exposures: Prospective population based US military cohort study. *British Medical Journal, 336*, 366-371.

Sobel, M. E. (1982). Asymptotic confidence intervals for indirect effects in structural equation models. In S. Leinhardt (Ed.), Sociological methodology (pp. 290-312). San Francisco: Jossey-Bass.

Sobel, M. E. (1986). Some new results indirect effects and their standard errors in covariance structure models. In N. Tuma (Ed.), Sociological methodology (pp. 159-186). Washington, DC: American Sociological Association.

Spitzer, R., Kroenke, K., Williams, J. (1999). Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. *Journal of the American Medical Association, 282,* 1737-1744.

Tabachnick, B. G., & Fidell, L. S. (1996). *Using Multivariate Statistics* (4th ed.). Needham Heights, MA: Allyn and Bacon.

Weathers, F., Huska, J., Keane, T. (1991). *PCL-M for DSM-IV.* Boston: National Center for PTSD – Behavioral Science Division. This is a Government document in the public domain.

Weathers, F. W., Litz, B. T., Huska, J. A., & Keane, T. M. (1994). *PTSD Checklist*. Boston, MA: National Center for PTSD.

IX. APPENDIX

A. REVIEW SIGNATURES

The proposed research involves reviews and/or approvals by the committees and organizations noted below.

	YES	NO		APPROVAL DATES:		INITIAL
				PENDING	APPROVED	
1. HUMAN SUBJECTS			IRB			
2. RETROVIRUS			MED-O2H			
3. INVESTIGATIONAL AGENT			FDA			
4. RADIATION/LASER			RSC/LUC			
5. COLLABORATION			CRADA/MOU			

(CID will complete approval dates.)

The following signatures indicate the documentation has been reviewed and has been completed appropriately according to the best knowledge of the signees.

CID Program Administrator

(Signature)	**Date**

B. DEPARTMENT SUPPORT STATEMENT

- **There is no support anticipated to be required from, or impact on, any other department at Naval Hospital Camp Pendleton and Naval Medical Center San Diego.**

- **Any support from VMRF/UCSD to NHCP and NMCSD will be outlined in the pending CRADA.**

C. INSERT: COMMITTEE MINUTES signed by Chairman, IRB, and Commander

SUPPLEMENT: Power Calculation and Data Analysis Plan

Sample size. Our initial sample size was planned for 266. Due to unanticipated and uncontrollable delays, we established an interim analysis plan with our DSMB to determine whether additional accrual would likely change the results. On this basis, the study was halted prior to achieving the intended sample size.

Data analysis plan: Non-inferiority. To assess NI, we examined the predicted difference in mean change between AD and CPT-C. If the 95% confidence interval (CI) around the estimate does not contain the NI margin, we can reject the null hypothesis (that AD is inferior to CPT) and accept the research hypothesis (that AD is non-inferior to CPT-C). The NI margin for CAPS-IV scores was established *a priori*, based on a calculation of a reliable difference from baseline to posttreatment CAPS-IV scores from a previous trial (10 points). The margins for other outcomes were generated using the Reliable Change Index (RCI). Although the RCI threshold for CAPS-IV in this trial was 22 points; we adhered to the pre-specified 10-point differential as a more conservative NI test.

We conducted linear regression analyses (SAS Software version 9.4) to predict the effects of treatment on mean change score (at a one-tailed 0.05 alpha), controlling for the influences of baseline scores. We also controlled for time (days) since the start of the trial. Although the study was powered for pre- to posttreatment change, we conducted exploratory analyses of the available follow-up data.

Because a significant proportion of participants did not complete the posttreatment evaluation, we performed a series of sensitivity analyses to test the robustness of the results. The sensitivity analyses varied slightly for each outcome. For the CAPS-IV, the first analysis multiply imputed CAPS-IV scores based on the last recorded PCL-M score of each participant

that attended at least half of the therapy sessions. The second analysis also used PCL-M scores, employing a series of preemptive imputations of all missing within treatment PCL-M scores. In the third analysis, multiple imputation was used to simulate posttreatment CAPS-IV scores based on a rational set of baseline covariates (age, race, CEQ scores, highest level of education, and baseline CAPS-IV scores). The above analyses were contingent upon the Missing-At-Random assumption. Because there is no definitive way to determine the cause of missing data, we interrogated potential differences between completers and non-completers and found that completers in the CPT-C arm had lower mean baseline CAPS-IV scores than non-completers (72 vs. 81, Cohen's d = .49). This led us to perform a fourth imputation analysis under the Missing-Not-At-Random assumption; we imputed conditional posttreatment CAPS-IV scores for the CPT-C arm to reflect the higher propensity for dropout given higher baseline scores by generating proportionately higher posttreatment scores.

Data analysis plan: Describing the clinical significance of the results. To benchmark the clinical significance of the primary endpoint, consistent with recent PTSD trials of service members, we categorized the clinical significance of change scores and end-point state *for each participant* in each arm. Participants that exceeded the RCI threshold ($\geq$ 22-point change) were categorized as "improved." Participants who exceeded the RCI *and* whose posttreatment endpoint score was two SD below the mean baseline score for the trial were categorized as "recovered". If individuals' change did not exceed the RCI, they were categorized as "no-change." Individuals whose post-test scores were higher than their baseline scores and outside the RCI were categorized as "deteriorated." A second set of benchmarks were created, which we labeled *intent-to-treat*; these were the same as the completers, except that patients who had missing posttreatment scores were added to the "no-change" category.