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CONTRACTING ORGANIZATION: Boston VA Research Institute, Inc. (BVARI)

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14. ABSTRACT
Many service members exposed to combat and operational stressors develop posttraumatic stress disorder (PTSD). Evidence-based interventions for treating PTSD, however, were not developed for military trauma and thus may be suboptimal for this population. This study compares Adaptive Disclosure, an intervention for Marines and Sailors with PTSD stemming from deployment experiences, to an empirically supported PTSD treatment. The report details the complete work on this trial.

15. SUBJECT TERMS
Active-duty, Marine Corps, Posttraumatic stress disorder (PTSD), Psychotherapy for service members

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1. INTRODUCTION:

More than 2 million U.S. troops have served in the wars in Afghanistan and Iraq. 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). Once service members and new Veterans develop sustained mental health problems related to combat and operational stress, many are at risk to remain chronic across the lifespan (e.g., Kessler et al., 1995; Kulka et al., 1990; Prigerson et al., 2001). Thus, primary and secondary prevention of PTSD is a critical challenge for the military and the VA (e.g., Litz & Bryant, 2009). We have developed a novel intervention, Adaptive Disclosure (AD), to address these needs. AD is a hybrid and extension of evidence-informed cognitive-behavioral therapy strategies packaged and sequenced to target the three-high base-rate combat and operational traumas, namely, life-threat trauma, loss (principally traumatic loss), and experiences that produce inner moral conflict (Steenkamp et al., 2011). AD employs a Prolonged Exposure (PE) strategy (imaginal emotional processing of an event) and cognitive-therapy-based techniques used in Cognitive Processing Therapy (CPT), but also includes gestalt-therapy techniques designed to target loss and moral injury. In our open pilot trial, we demonstrated treatment acceptability among Marines and large reductions in PTSD and comorbid symptoms. The primary objective of the current randomized controlled non-inferiority trial is to determine whether AD is no less effective than CPT, cognitive only version (CPT-C), in terms of its impact on deployment-related psychological health problems (specifically PTSD and depression) and functioning.

2. KEYWORDS:

Posttraumatic Stress Disorder (PTSD), Psychotherapy for service members, active-duty, Marine Corps

3. ACCOMPLISHMENTS:

- Goal: Hire and credential new study staff (Months 1-36)
  - % Completion: 100%
  - Postdocs at the Boston site were hired and credentialed
  - Postdocs were trained as an independent evaluator
- Goal: Establish weekly meetings with PIs (Months 1-36)
  - % Completiosssn: 100%
  - PIs held monthly conference call meetings to discuss study progress and adjudicate cases
- Goal: Train and certify study personnel on all study procedures (Months 1-36)
  - % Completion: 100%
  - All staff at the Boston site are trained on all study procedures
  - All regulatory requirements for the Boston site are completed
- Goal: Train independent evaluators in CAPS administration (Months 1-36)
  - % Completion: 100%
  - Postdocs were trained in CAPS administration

- Goal: Identify and recruit potential participants; monitor enrollment progress at clinics; provide ongoing supervision for therapists; collect data from study participation (Months 7-24)
    - % Completion: 100%
    - We assessed 148 military personnel for eligibility
    - We randomized 122 military personnel
    - Actual timeline for enrollment shifted from Q1-Q3 due to recruitment difficulties at San Diego site
- Goal: Collect CAPS data from study participants over the phone (pre- and post-treatment) (Months 7-30)
    - % Completion: 100%
    - We collected pre-treatment CAPS data for all randomized participants (N=122).
    - We collected post-treatment CAPS data for all participants who completed treatment and were still enrolled in the study (N=70).
- Goal: Conduct audio recording for on-going adherence and provide prompt feedback to assessors and therapists (Months 7-30)
    - % Completion: 100%
    - After receiving consent from the participant, CAPS assessments are recorded using Phillips DPM8000 recorders
    - One participant did not consent to audio recording in 2017, so their assessment was not recorded.
- Goal: Collect and report adverse events (Months 7-30)
    - % Completion: 100%
    - There was a total of 21 adverse events during the course of the trial, three of which were serious adverse events. Serious adverse events were fairly split between the two treatment arms (AD = 2; CPT-C = 1).
- Goal: San Diego will send de-identified data to Boston for entry and secure storage (Months 7-30)
    - % Completion: 100% (148 out of target 266 participants)
    - San Diego has sent 148 deidentified data packets to Boston.
    - They are stored securely in locked file cabinets behind a locked door.
    - We will not enter or collect any further data. We have closed the triall to data collection and will use these 148 participants for all data analysis.
- Goal: Ongoing data entry and data quality monitoring (Months 7-30)
    - % Completion: 100%
    - Due to delay in enrollment, the actual timeline for data entry had to shift accordingly, from Q2 to Q3
    - All CAPS collected during the reporting period were entered on an ongoing basis, and have been double entered and cross-checked to ensure data integrity
    - All participants' data has been double entered. Our data entry infrastructure was designed to double enter all data in order to conduct data integrity checks.
    - An unpaid student volunteer was hired and helped double-enter data.
- Goal: Conduct data analysis according to proposed plans; summarize study results, prepare manuscripts and present findings at conferences; prepare and submit final report to DoD (Months 30-36)
    - % Completion: 100%

- An initial non-inferiority analysis revealed the following: Performing a linear regression analysis (predicting the change in CAPs between AD and CPT over the two time points) yielded a predicted estimated difference in mean CAP scores (AD-CPT) of 0.33, with a 95% CI of [-10.10, 9.44].
    - This preliminary analysis was based on the smaller than expected (N=122; expected N=266). The fact that we were able to detect the effect (of non-inferiority) from the smaller sample – and that it is a robust statistically significant result means that there is no evidence that N=122 vs. N=266 de-legitimatizes the results.
    - Since 10 points falls outside of that confidence interval, we can safely reject the null hypothesis that AD is intolerably worse than CPT in reducing CAPs scores = non-inferiority is met.
- The results confirmed that AD is not less effective than CPT-C. For the primary endpoint (PTSD) and two secondary endpoints (depression and functioning), the confidence intervals for the mean differences between AD and CPT-C did not contain the various NI margins.
- Dr. Litz presented an overview of and findings from the trial to the Department of Defense and to the Army in September 2019.
- A manuscript describing the trial and our primary findings has been drafted and is currently under review at a scientific journal.
- A final report has been prepared and submitted to the DoD.

What opportunities for training and professional development has the project provided?
Nothing to Report.

How were the results disseminated to communities of interest?
Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?
Nothing to Report.

4. **IMPACT:**

What was the impact on the development of the principal discipline(s) of the project?
Findings from this project suggest that AD is no less effective than one of the first-line treatments for PTSD, CPT-C. Based on these non-inferiority results, whether AD is attractive as a treatment option will depend on clinician and patient judgment about the approach and scope of the treatment (e.g., the goodness of fit for certain service members). Further research should be conducted to determine which cases may benefit from AD, compared to first-line PTSD psychotherapies. A randomized controlled superiority trial is currently underway with a modified and extended version of AD, Adaptive Disclosure – Enhanced (AD-E). This veteran trial is to solely treat moral injury and loss by targeting psychological and behavioral obstacles to occupational, relationship, and family functioning, as well as quality of life.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?
Nothing to Report.

What was the impact on society beyond science and technology?
Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

1. Actual timeline for enrollment shifted from Q1 to Q2 due to recruitment difficulties at the San Diego site.
    - Associate Investigator at Naval Medical Center increased referrals in order to resolve these difficulties
    - Due to the delay in enrollment, the actual timeline for data entry had to shift accordingly, from Q2 to Q3
    - These delays did not impact our expenditures

2. Recruitment ended with an N=122 (compared to the original N=266).
    - A preliminary non-inferiority analysis revealed that we were able to detect non-inferiority from a smaller sample, indicating that increasing the sample size further does not de-legitimatize the results
    - For further statistical details, please see the last goal under "Accomplishments"

Significant changes in use or care of human subjects
Nothing to Report.

Significant changes in use or care of vertebrate animals
Nothing to Report.

Significant changes in use of biohazards and/or select agents
Nothing to Report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

    Journal publications.
    Nothing to Report.
    Books or other non-periodical, one-time publications.
    Nothing to Report.
    Other publications, conference papers and presentations.
    Litz, B. T., Lang, A., Nash, W., Gray, M., Lebowitz, L., Doros, G., & Rusowicz-Orazem, L. (2019, September 24). *Adaptive disclosure: A combat-specific PTSD treatment*

[Presentation to the Department of Defense and Army]. PTSD Treatment Research IPR, Fort Detrick, MD, United States.

- **Website(s) or other Internet site(s)**
  Nothing to Report.

- **Technologies or techniques**
  Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Nothing to Report.

- **Other Products**
  Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	*Brett Litz*
Project Role:	*Principal Investigator*
Nearest person months worked:	*1*
Contribution:	*Dr. Litz has engaged in study design and study management.*

Name:	*Julie Yeterian*
Project Role:	*Postdoctoral Fellow*
Nearest person months worked:	*1*
Contribution:	*Dr. Yeterian has engaged in project coordination, study management, and CAPS assessment administration.*

Name:	*Danielle Berke*
Project Role:	*Postdoctoral Fellow*
Nearest person months worked:	*1*
Contribution:	*Dr. Berke has engaged in project coordination, study management, and CAPS assessment administration.*

Name:	*Stephanie Larew*
Project Role:	*Postdoctoral Fellow*
Nearest person months worked:	*1*
Contribution:	*Dr. Larew has engaged in project coordination and study management.*

Name:	*Charla Rhodes*
Project Role:	*Research Technician*
Nearest person months worked:	*1*
Contribution:	*Ms. Rhodes has engaged in project coordination and data entry.*

Name:	*Alanna Coady*

Project Role: *Research Technician*
Nearest person months worked: *1*
Contribution: *Ms. Coady has engaged in project coordination and data entry.*

Name: *Jessica Carney*
Project Role: *Research Technician*
Nearest person months worked: *1*
Contribution: *Ms. Carney has engaged in project coordination and data entry.*

Name: *Casey Anasoulis*
Project Role: *Undergraduate volunteer*
Nearest person months worked: *1*
Contribution: *Ms. Anasoulis has engaged in data entry.*

Name: *Breanna Grunthal*
Project Role: *Research Technician*
Nearest person months worked: *2*
Contribution: *Ms. Grunthal has engaged in project coordination, data entry and management, and manuscript preparation.*

Name: *Luke Rusowicz-Orazem*
Project Role: *Biostatistical Consultant*
Nearest person months worked: *2*
Contribution: *Mr. Rusowicz-Orazem has engaged in data management, data analysis, and manuscript preparation.*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to Report.

What other organizations were involved as partners?

University of Wyoming
- Matthew Gray, PhD; independent contractor supervising treatment fidelity

San Diego Veterans Medical Research Foundation (VMRF)
- Ariel Lang, Ph.D., site PI
- Carrie Rogers, Ph.D., Treatment Supervisor
- Shiva Ghaed, Ph.D., Associate Investigator
- Amy Lansing, Ph.D., Study Therapist
- Selena Baca, B.A., Research Coordinator

8. SPECIAL REPORTING REQUIREMENTS
QUAD CHART:

Adaptive Disclosure: A Combat-Specific PTSD Treatment
Contract No. W81XWH-17-1-0041/ BA160047

PI: Brett Litz, PhD
Partnering PI: Ariel Lang (VMRF)
Org: Veterans Medical Research Foundation
Award Amount: $499,732

Study/Product Aim(s)

- Determine if AD is at least as effective as CPT-C in terms of change in PTSD and Depression symptoms over an 8-week treatment period.
- Determine if AD is at least as effective as CPT-C in terms of change in in military-relevant functioning over 8 weeks of treatment.

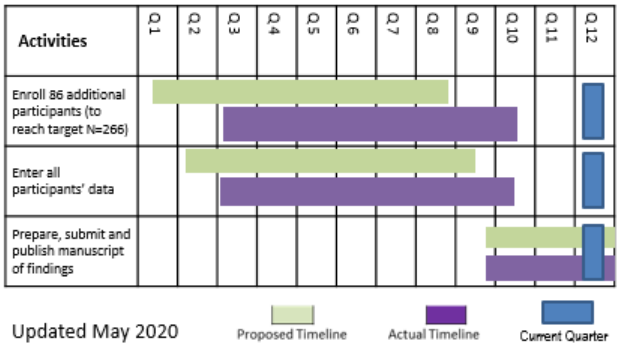
Approach

- Randomized, controlled non-inferiority trial (n=266) comparing Adaptive Disclosure to Cognitive Processing Therapy, cognitive only version.
- Marines/Sailors with PTSD will be followed during the intervention and for 6 months after treatment.
- Primary outcomes include PTSD severity, depression and military-relevant functioning.

New Accomplishments

- Data analysis has completed.
- A manuscript has been drafted and submitted to a scientific journal.

Timeline



Goals/Milestones

☑ Conduct audio recording for on-going adherence and provide prompt feedback to assessors and therapists
☑ Collect and report adverse events
☑ San Diego site sent de-identified data to Boston for entry and secure storage
☑ Finished data entry and data quality monitoring
☑ Finished conducting data analysis according to proposed plans
☑ Prepared and submitted manuscript of primary findings to a scientific journal

Budget Expenditure to Date
Projected Expenditure: $499,732
Actual Expenditure: $292,646.23

9. APPENDICES:

- Appendix 1: Primary Outcomes Manuscript Draft (pages 11-36)
- Appendix 2: Primary Outcomes Manuscript Draft, Supplemental Content (pages 37-41)

Appendix 1: Primary Outcomes Manuscript Draft

Adaptive Disclosure, a Combat-Specific PTSD Treatment, Versus Cognitive-Processing Therapy, in Deployed Marines and Sailors: A Randomized Controlled Non-Inferiority Trial

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Key Points

Question: Is a new therapy geared toward combat trauma, *Adaptive Disclosure* (AD), comparable to a first-line psychotherapy for PTSD?

Findings: 122 Marines and Sailors were randomized to receive AD or Cognitive-processing Therapy – Cognitive Therapy (CPT-C), using a parallel randomized controlled non-inferiority design; blind independent PTSD interviews was our primary endpoint. We found that that AD was no-less effective to CPT-C, as predicted.

Meaning: Based on these non-inferiority results, whether AD is attractive as a treatment option will depend on clinician and patient judgment about the approach and scope of the treatment (e.g., the goodness of fit for certain service members).

Abstract

Importance: First-line psychotherapies for PTSD are less efficacious for war-trauma. Therapies geared towards the military culture/context need to be tested. **Objective**: We conducted a non-inferiority (NI) trial of *Adaptive Disclosure* (AD) to determine if AD was not less effective than a first-line psychotherapy. **Design:** A two-arm parallel randomized NI trial. Eligibility was current PTSD, active-duty status, and willingness to be treated for 8 or 12 weeks. **Setting**: The treatments occurred in specialty care at the Naval Hospital, Camp Pendleton or the Naval Hospital, San Diego. **Participants**: 122 U.S. Marines and Sailors were randomized. **Interventions**: AD is a manualized experiential approach that flexibly individualizes treatment by employing different gestalt therapy strategies to target threat-, loss-, and moral injury-related trauma/PTSD. *Cognitive Processing Therapy – Cognitive Therapy* version (CPT-C) is an established first-line evidence-based cognitive therapy. **Main Outcomes and Measures**: The primary endpoint was PTSD symptom severity change from pre to posttreatment, using the Clinician Administered PTSD Scale for DSM-IV (the PCL-M was also administered). Secondary endpoints were depression (PHQ-9) and functioning (RAND VR-12). **Results**: The initial test of NI with participants with available post-treatment data showed that AD was NI to CPT-C for all measures. A series of sensitivity analyses supported the NI results for each measure. The mean difference in CAPS-IV change scores between AD and CPT-C was 0.33 [-10.10, 9.44]. The mean difference in PHQ-9 scores was -1.01 [-3.31, 1.28]. The mean difference in VR-12 Physical Sub-Component change scores was -0.27 [-4.50, 3.95] and -2.10 [-7.03, 2.83] for the Mental Sub-Component change scores. The differential effect size for CAPS-IV was Cohen's *d* = 0.01 [-0.46, 0.48]; the mean effect size for the sample was Cohen's *d* = 0.91. **Conclusions and Relevance**: Because AD is a new treatment, a NI test was an appropriate first step. As predicted,

AD was found to be no less effective than an established first-line psychotherapy for PTSD. Whether AD is attractive as a treatment option based on these findings will depend on clinician and patient judgment about the approach and scope of the treatment (e.g., the goodness of fit for certain service members). **Clinicaltrials.gov registration**: https://clinicaltrials.gov/ct2/show/record/NCT01628718

First-line exposure and cognitive psychotherapies are less efficacious for war-related PTSD compared to civilian trauma,[1-2] arguably because war trauma occurs in a unique occupational/cultural context. The military attracts people who want to serve and fosters an ethical and intensely interdependent code of conduct.[3] In the military, personal threats are occupational hazards and may be less harming than traumatic losses and transgressive acts, otherwise known as *moral injury*.[4] Failures to be responsible for others' safety and moral transgressions frequently evoke guilt and shame.[5] Grief over fallen comrades is akin to losing a close family member and often leads to survivor guilt and complicated grief.[6]

In collaboration with the Navy/Marine Corps, we developed and piloted *Adaptive Disclosure (AD),*[7] treating Marines/Sailors at Camp Pendleton. AD is a psychotherapy that trains clinicians about the military culture and the warrior ethos and uses different strategies to target danger- loss- and moral injury-related PTSD. AD was designed to be very brief (six-sessions) to accommodate operational time-constraints and an open trial showed that it was well-received and well-tolerated and led to large effect size reductions in PTSD.[8-9]

In this first controlled study, we conducted a randomized non-inferiority (NI) trial of AD compared to *Cognitive Processing Therapy*[10] – *Cognitive Therapy* version (CPT-C).[11] The primary endpoint was PTSD symptom change, pre to posttreatment. Secondary endpoints were depression and functioning. The prediction was that AD would not be less efficacious than a first-line treatment (CPT-C).

Methods

Participants

122 U.S. Marines/Sailors were randomized to receive AD/CPT-C (Figure 1). Eligibility criteria were current DSM-IV PTSD, active-duty status, and willingness to be treated for 8 or 12

weeks. Exclusion criteria were serious suicidality/homicidality, substance use disorder, cognitive impairment, current trauma-focused therapy, and past CPT. All participants provided informed consent. Randomization/assignment (via 1:1 sequences generated a priori by blocks of 6; 3 per arm) was generated by a technician and concealed from investigators.

Procedure

We followed consensus guidelines for PTSD trials.[12] A study therapist provided the therapies and received weekly hourly clinical supervision by experts in the two therapies (see eMethods supplemental document for fidelity ratings).

Participants were referred by mental health providers, and following consent, completed a battery of questionnaires to determine eligibility. Eligible participants completed the baseline assessment and a clinician-rated assessment of their PTSD symptoms with an independent evaluator. To equilibrate the number of treatment hours, we expanded AD from six to eight 90-minute weekly sessions; CPT-C was delivered in 12 hour-long weekly sessions. The assessment battery was repeated at the end of treatment. Participants completed an abbreviated assessment before each session to monitor symptoms. Three- and six-month follow-ups were attempted, but too few service members were available for follow-up.

Treatments

AD employs emotion-focused, experiential change-agents designed to target the unique sequelae of life-threat, traumatic loss, and moral injury. The manual includes sections on the military culture and warrior ethos, and how and why traumatic loss and moral injury are uniquely harmful. AD uses an imaginal narrative of a focal trauma as a vehicle to uncover and disclose previously unacknowledged aspects of a trauma and its meaning and implication. AD employs Gestalt therapy techniques[13] to help service members process traumatic loss and moral injury and

find paths to healing and repair. For traumatic loss, the patient has evocative real-time dialogues (in imagination) with the lost service member. Emphasis is placed on moving forward or carrying on in a manner that honors and commemorates the fallen. For moral injury, patients engage in an imaginal dialogue with a compassionate and forgiving moral authority. Patients are also asked to share what the other's reaction is to what they just heard. In subsequent sessions, the experiential dialogue is used as an opportunity for the patient to articulate what the other would say if they could about how the patient should proceed in their life. A typical theme that arises for loss is the mandate to live a good life is the best way to honor the lost person. For personal moral transgressions, a common theme is the expression of alarm and disappointment but a mandate to make amends, repair damage done, and contextualize the event in the scope of a life that includes goodness. For betrayal-based moral injury, a common theme entails expressions of anger and solidarity but also a wish for the patient to move on by allowing goodness to occur around him or her. These experiential dialogues are akin to secular confessions, aiming to challenge guilt, shame, and self and other condemnation. Homework is assigned to engage in corrective life experiences (e.g., amends-making).

CPT-C omits the written trauma narrative utilized in CPT. CPT-C helps patients identify how their trauma has changed their thoughts and beliefs, particularly about safety, trust, intimacy, power and self-esteem. CPT-C addresses ways of thinking that keep individuals "stuck" and interfere with recovery. In addition to Socratic dialogues, CPT-C uses homework to help patients learn the connection between thoughts and emotions and to work on modifying appraisals.[11]

Measures

Demographic and military service characteristics information was collected with a standardized self-report form.

Primary endpoint: PTSD. This trial occurred before DSM-5. The Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV)[14] is the gold standard semi-structured interview that assesses frequency and intensity of the 17 PTSD symptoms over the past month. The CAPS-IV yields a diagnostic and a total severity score (the sum of frequency and intensity ratings). The CAPS-IV has demonstrated strong psychometric properties.[15] The internal consistency reliability in our sample was .85.

The PTSD Checklist, Military Version (PCL-M;)[16] was used to cross-validate the interview findings. It is a 17-item self-report measure of DSM-IV PTSD symptoms over the past month. The PCL-M was administered at baseline, every session, and follow-up. The PCL-M has excellent psychometric characteristics.[17] The internal consistency reliability in our sample was .89.

Secondary endpoint: Depression. The Patient Health Questionnaire (PHQ-9)[18] is a 9-item self-report measure of the severity of depressive symptoms over the past 2 weeks, with higher scores indicating greater depression severity. Items were rated on a 4-point Likert scale from 0 to 3, and the PHQ-9 was administered at baseline, every session, and follow-up. The PHQ-9 has excellent test-retest reliability, internal consistency, and construct validity.[18] The internal consistency reliability in our sample was .86.

Secondary endpoint: Functioning. The Veterans RAND 12-Item Health Survey (VR-12)[19] was used to index the impact of physical and mental health on functioning. The VR-12 consists of Physical Component (PC) and Mental Component (MC) subscales. Of the 12 items, 10 are rated on a 5-point Likert scale, and two are rated on a 3-point Likert scale. It includes

fewer items for seven of the eight scales, relative to the SF-36 but provides 90% of the reliable variance in the two component summary measures.[20]

Credibility and Expectancy. We used a modified version of the Credibility and Expectancy Questionnaire (CEQ; we shortened it to 4-items and we modified the language to fit the military culture).[21] The internal consistency reliability in our sample was .91.

Power Calculation and Data Analysis Plan

Sample size. For the sample size calculation, we used the Study Size program, Version 2.0.4 and a standard deviation of 25, based on a CPT trial with veterans.[22] If the true difference between AD and CPT is 0 points, then we needed 99 participants per group, or roughly 200 participants, to ensure power = .80.

Non-inferiority tests. 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 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[22]; the same margin was used in a recent NI trial[23]). The margins for other outcomes were generated using the *Reliable Change Index* (RCI; see eMethods).[24] Although the RCI threshold for CAPS-IV in this trial was 22 points, we used the 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 (one-tailed 0.05 alpha), controlling for 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 available follow-up data.

Because a significant proportion of participants did not complete the posttreatment evaluation (see Figure 1), 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 participants' last PCL-M score if they attended at least half of the sessions (*Final PCL-M Score* in Figure 2). The second analysis employed a series of preemptive imputations of all missing within treatment PCL-M scores (*Sequential PCL-M Score*). In the third analysis, multiple imputation was used to simulate posttreatment CAPS-IV scores based on baseline covariates (age, race, CEQ scores, highest level of education, and baseline CAPS-IV scores; *Full Imputation*). Because completers in the CPT-C arm had lower mean baseline CAPS-IV scores than non-completers (72 vs. 81, Cohen's d = .49), a fourth imputation analysis imputed conditional posttreatment CAPS-IV scores for the CPT-C arm to reflect the higher propensity for dropout (*CPT-C Conditioned*).

The NI margin for the PCL-M was 12 points, determined by the RCI. We first calculated the change score as the final PCL-M score minus the baseline assessment score for the subset of participants that attended at least half the therapy sessions. The first sensitivity analysis used multiple imputation to obtain a plausible set of values for participants missing final PCL-M scores that did not attend at least half the sessions. We also predicted the missing final PCL-M change scores with baseline PCL-M scores, using the same set of variables described above. Because there is inherent variability in creating a change value from the final recorded PCL-M score of each participant given differing number of total sessions attended, we also performed a multiple imputation analysis that incorporated sequential imputations of missing PCL-M scores

prior to imputing a score. We performed a series of regressions that predicted missing PCL-M scores at each session as a function of the scores of the previous two measurements, as well as the baseline characteristics used in the previous model. The final regression produced an imputed change score using the intent-to-treat sample.

The NI margin for the PHQ-9 was 7 points, determined by the RCI. The completer analysis used the final PHQ-9 score as the final session's measurement for those participants that attended at least half of their respective cohort's total sessions. The sensitivity analyses mirrored those of the PCL-M. The VR-12 subscales were analyzed separately; the NI margin for the PC was 12 points and the MC was 8 points. Completer analyses used participants with posttreatment scores. A multiple imputation sensitivity analysis simulated missing posttreatment PC and MC scores from the same set of variables described above.

Benchmarking clinical significance. Consistent with recent PTSD trials of service members,[25] we categorized the clinical significance of CAPS-IV change and endpoint scores *for each participant* in each arm.[24] Participants that exceeded the RCI threshold ($\geq$ 22-point change from baseline) were categorized as "improved." Participants who exceeded the RCI *and* whose posttreatment score was two SD below the mean baseline score for the trial were categorized as "recovered" (see eMethods). If change did not exceed the RCI, participants were categorized as "no-change." Posttreatment scores that were higher and outside the RCI were categorized as "deteriorated." We also generated *intent-to-treat* benchmarks; patients who had missing posttreatment scores were added to the "no-change" category.

Results

Participant Characteristics

Table 1 shows the demographic characteristics of the study group. Participants were mostly male (91.7%) and Caucasian (63.11%) with a mean age of 29.80 (SD = 6.39). There were no differences between the arms on any demographic characteristic (see Table 1), nor baseline CAPS-IV scores (t_{120} = -1.96, p = .57; see Table 2).

Non-inferiority Findings

Figure 2 shows the results of the NI analyses of CAPS-IV change scores from pre- to posttreatment. Each sensitivity analysis confirmed the robustness of the completer analysis, which showed that AD was non-inferior to CPT-C. Moreover, the PCL-M findings replicated the CAPS-IV finding. The estimated mean difference in PCL-M score change between AD and CPT-C was 3.88 [-1.56, 8.32]. The imputation of posttreatment PCL-M scores resulted in an estimated mean difference of 3.79 [-1.37, 8.95]. The estimated mean difference in PCL-M change scores based on sequential PCL-M imputations of missing session values (in addition to baseline score and demographic characteristics) was 2.85 [-2.62, 8.31].

The estimated mean difference in PHQ-9 scores was -1.01 [-3.31, 1.28]. The imputation of posttreatment PHQ-9 scores resulted in an estimated mean difference of -0.41 [-2.61, 1.79]. Imputing posttreatment PHQ-9 scores from sequential imputations of missing session values (in addition to baseline score and demographic characteristics) resulted in an estimated mean difference of -1.23 [-3.70, 1.24]. Each result satisfied the conditions of NI.

The estimated mean difference in VR-12 PC change scores was -0.27 [-4.50, 3.95]. The imputation of posttreatment VR-12 PC from baseline score and demographic characteristics resulted in an estimated mean difference of 0.18 [-3.74, 4.10]. The estimated mean difference in VR-12 MC was -2.10 [-7.03, 2.83]. The imputation of posttreatment VR-12 MC from baseline

scores and demographic characteristics resulted in an estimated mean difference of 0.31 [-4.36, 4.97]. Each result satisfied the conditions of NI.

Exploratory follow-up results. Attempts were made to follow-up with service members once per month (with questionnaires) for six months until it became clear that this was untenable due to compliance and availability. Using the PCL-M, we examined NI for the three- and six-month follow-up sessions to attempt to replicate the pre-post results with the service members who could be followed. The estimated difference in mean PCL-M change from baseline to the three-month follow-up was approximately -1.63 [-14.7188, 11.4587]. The estimated difference from baseline to the six-month follow-up was approximately 1.55 [-8.8970, 11.9896], each supporting NI. Given the small sample size at each follow-up, sensitivity analyses could not be conducted.

Clinical significance. The mean effect size for CAPS-IV change between the two arms was Cohen's $d = 0.01$ [-0.46, 0.48] (for the overall sample, Cohen's $d = 0.91$). The rates of recovered, improved, no-change, and worsened are presented in Table 3. For the intent-to-treat sample, 24% of participants in the AD arm and 25% of the participants in the CPT-C arm improved or recovered. For completers, these rates were 41% and 45%, for AD and CPT-C, respectively.

Attendance and dropout. We defined dropout as missing the last treatment session.[26] 37% of patients in the AD arm and 40% of patients in the CPT-C arm dropped out (Chi-square test p-value = 0.7418). Patients in the AD arm attended a mean of 75% of the eight sessions and patients in the CPT-C arm attended a mean of 71% of the twelve sessions (t-test p-value = 0.5430).

Adverse events. Serious adverse events were rare and due to psychiatric emergencies (AD=2; CPT-C=1). There were 18 adverse events (11 in the AD arm and 7 in the CPT-C arm). Of these, increased psychiatric symptoms appeared to be study related (AD=7; CPT-C=2; see eResults for more detailed information).

Discussion

The trial results confirmed that AD is not less effective than CPT-C, an established first-line psychotherapy for PTSD. Across the primary endpoint (PTSD, as assessed by CAPS-IV and PCL-M severity scores) and two secondary endpoints (depression and functioning), the confidence intervals for the mean differences between AD and CPT-C from baseline to posttreatment did not contain the various NI margins. Because of periodic unprecedented regulatory delays and logistical constraints, the trial's effective recruitment phase was considerably shortened. Consequently, this trial was somewhat underpowered, risking Type-II error. Thankfully, we avoided Type-II error by consistently finding results supporting NI and no differential effect size between arms.

The trial was powered to test differences between AD and CPT-C over the course of treatment because we assumed that a variety of logistical and motivational limitations would make it difficult for service members to attend follow-ups. As anticipated, only a small percentage of Marines/Sailors were available for follow-up. We also encountered a problem with missing posttreatment data. Yet, all the sensitivity analyses validated the completer findings.

Recent clinical trials testing PTSD therapies among service members treated in garrison have also struggled with dropout and low follow-up rates. In the three STRONG STAR trials, 31% of soldiers dropped out of treatment (81% of therapy sessions were attended)[27]; the percentages of soldiers with missing posttreatment data were: 9%, 27%, and 29%, and the

percentages missing six-month follow-up data in the three trials were 30%, 47%, and 50%. It appears that treating service members with demanding multisession psychotherapies entails difficulties getting service members to commit to or to be available for follow-ups. Future trials should account for the reasons for dropout and generate solutions (e.g., telehealth) that will increase the validity of results.

The benchmark analyses showed that the percentage of completers that recovered or improved in AD and CPT-C were impressive and higher than the percent improved or recovered in the STRONG STAR trials combined (which was 31%).[25] The percent of the intent-to-treat samples in each arm in this trial was also slightly higher than the STRONG STAR trials (which was 21%).[25] Our completer-based indices of clinically significant change were comparable to a VA cooperative study[28] of prolonged exposure (which was 39%), yet, our rates of recovery or improvement for the intent to treat samples was lower than the VA cooperative study (which was 32%).

These results may not be applicable to other service branches and veterans. Whether AD is attractive as a treatment option based on these findings will depend on clinician and patient judgment about the approach and scope of the treatment. A superiority trial of AD is underway[29]; future research is also needed to determine which cases may benefit from AD, relative to other treatments.

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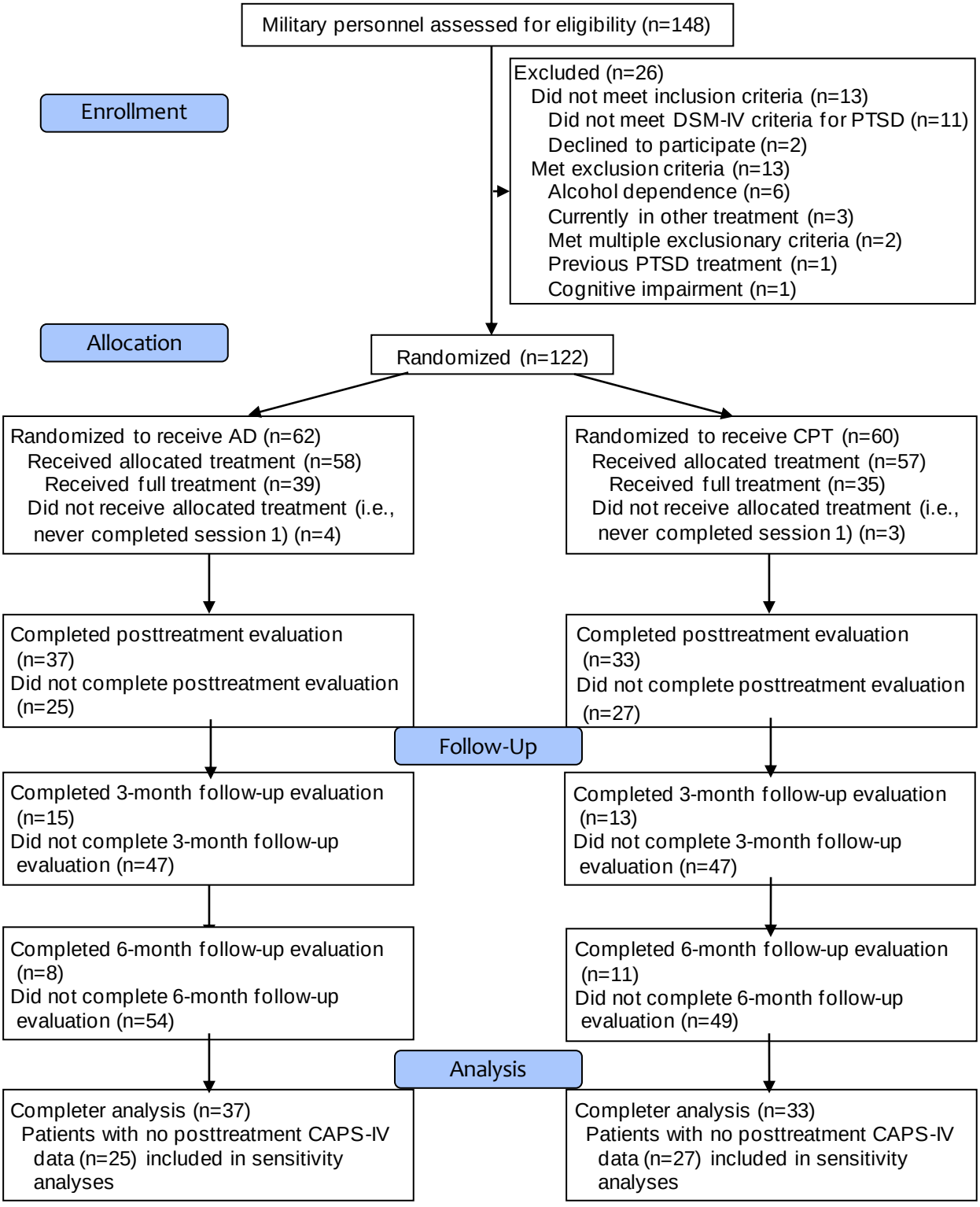
Figure 1. *Patient Flow Through Enrollment, Randomization, and Treatment*



Note. We were not able to contact participants who have dropped out to determine reasons for doing so.

Table 1. *Comparison of Demographic Characteristics Between Therapy Arms (N = 122)*

Demographic Characteristic	Total Sample	AD (*N* = 62)	CPT-C (*N* = 60)	
	% (*n*)	% (*n*)	% (*n*)	*p value*
Gender				1.00[a]
Male	91.7 (110)	91.8 (56)	91.5 (54)	
Age[b]				.39
	29.80 (6.39)	30.30 (6.43)	29.29 (6.38)	
Education				.97[a]
Some High School/High School Diploma/GED	38.52 (47)	38.71 (24)	38.33 (23)	
Some Higher Education	61.48 (75)	61.29 (38)	61.67 (37)	
Race				.48[a]
White	63.11 (77)	66.13 (41)	60.00 (36)	
Nonwhite	36.89 (45)	33.87 (21)	40.00 (24)	
Marital Status				.09[a]
Currently/Previously Married	71.31 (87)	64.52 (40)	78.33 (47)	
Never Married	28.69 (35)	35.48 (22)	21.67 (13)	
Income				.81[a]
<$50,000	63.93 (78)	62.90 (39)	65.00 (39)	
$50,000+	36.07 (44)	37.10 (23)	35.00 (21)	
Military Rank				.24[a]
Enlisted	98.36 (120)	100 (62)	96.67 (58)	
Officer	1.64 (2)	0 (0)	3.33 (2)	
Number of previous deployments				.83[a]
0-2	59.02 (72)	58.06 (36)	60.00 (36)	
3+	40.98 (50)	41.94 (26)	40.00 (24)	

Note. AD = Adaptive Disclosure. CPT-C = Cognitive Processing Therapy, Cognitive Only.
[a]P value represents the result from chi-square tests.
[b]Values reported are means and standard deviations (instead of percentages and n's, respectively). P value represents the result from independent samples t-test.

Aim	Measure	AD		CPT-C		Independent Samples t-test	
		M	SD	M	SD	*Est.*	*p*
Primary Endpoints							
	CAPS-IV	74.58	19.25	76.53	18.43	-1.96	0.57
	PCL-M	63.00	11.45	62.47	11.06	0.53	0.79
Secondary Endpoints							
	PHQ-9	15.42	5.86	16.16	7.11	-0.73	0.54
	VR-12 Mental Health Scale	28.61	11.45	30.63	12.23	-2.01	0.37
	VR-12 Physical Health Scale	48.05	12.49	46.36	12.07	1.70	0.46
Covariates							
	CEQ	23.72	5.35	22.74	7.67	0.98	0.44

Table 2. *Treatment Arm Comparisons for Baseline Measures*

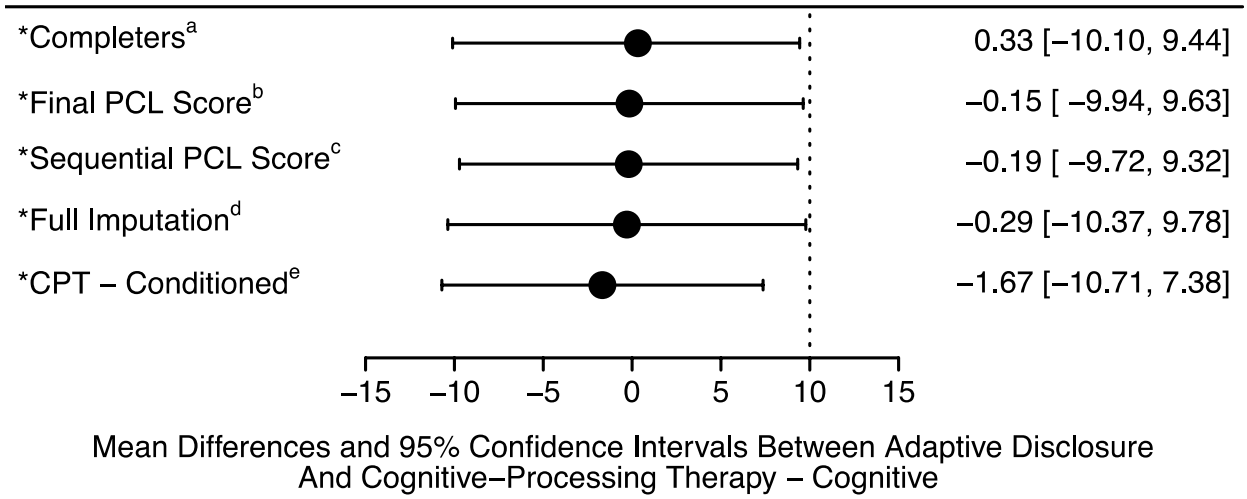
Note. M = mean. SD = standard deviation. AD = Adaptive Disclosure. CPT-C = Cognitive Processing Therapy, Cognitive only. CAPS = Clinician Administered PTSD Scale. PCL-M = PTSD Checklist Military Version. PHQ = Patient Health Questionnaire. VR-12 = Veterans RAND 12-item Health Survey. CEQ = Credibility and Expectancy Questionnaire.

Table 3. *Benchmarks for Clinical Significance of CAPS Scores*
Note: See eMethods Supplemental document that describes the Reliable Change Index (RCI; which

	Intent to treat (*N*=122)			
	Recovered % (*n*)	Improved % (*n*)	No Change % (*n*)	Deteriorated % (*n*)
AD (*N* =62)	17.74 (11)	6.45 (4)	75.80 (47)	0 (0)
CPT (*N* =60)	13.33 (8)	11.67 (7)	75.00 (45)	0 (0)
	Completers (*N*=70)			
	Recovered % (*n*)	Improved % (*n*)	No Change % (*n*)	Deteriorated % (*n*)
AD (*N* =37)	29.73 (11)	10.80 (4)	59.45 (22)	0 (0)
CPT (*N* =33)	24.24 (8)	21.21 (7)	54.54 (18)	0 (0)

if met, defines *Improved*), the 2SD threshold for endpoint scores, which if met along with the RCI, defines *Recovered*. *No-change* is defined as not meeting the RCI threshold. *Deteriorated* is defined as change scores that show worsening, exceeding measurement error (the absolute value of RCI).

Figure 2. Non-inferiority Results Between Adaptive Disclosure and Cognitive-Processing Therapy-Cognitive Results for CAPS-IV Change Scores from Baseline and Posttreatment



[a] The analysis results comprised of study completers with non-missing baseline and posttreatment CAPS-IV scores. [b]The analysis results inferred from posttreatment CAPS-IV imputation based on the Final PCL-M scores of subjects who attended at least half of total therapy sessions. [c]The analysis results inferred from posttreatment CAPS-IV imputation based on final PCL-M scores sequentially imputed from the previous session scores. [d]The analysis results inferred from posttreatment CAPS-IV imputation based on baseline CAPS-IV scores, Expectancy and Credibility score, age, educational attainment, and race. [e]The analysis results inferred from posttreatment CAPS-IV imputation from the baseline and demographic characteristics conditioned upon the scores of the CPT-C cohort. *Indicates the analyses that comprise the sensitivity analysis testing the robustness of the results of the completers analysis. **Indicates the non-inferiority margin of 10-point difference in the mean change in CAPS-IV between Adaptive Disclosure and Cognitive-Processing Therapy-Cognitive.

Appendix 2: Primary Outcomes Manuscript Draft, Supplemental Content

Supplemental Content

eMethods
- **Treatment Fidelity**
  - **Adaptive Disclosure**
  - **Cognitive Processing Therapy – Cognitive Only**
- **Methods for Indexing Clinically Significant Change**
  - **Reliable Change Index**
  - **Clinically Significant End-state**
  - **Categorizing Each Participant's Clinical End State**

eTable 1
eTable 2
eResults
- **Adverse Events**
- **Tertiary Superiority Tests**

eCONSORT Checklist Information
eTable 3

eMethods

Treatment Fidelity.

Adaptive Disclosure

An independent Adaptive Disclosure clinician and original AD treatment developer rated random samples of treatment sessions using independently developed adherence and competency forms. Ratings were blind as the evaluator had no knowledge of symptom status, trajectory or outcomes. Forty individual AD sessions were rated including all 8 sessions for each of the first 2 AD patients. An additional 24 randomly selected sessions were reviewed. Ratings were provided for 244 treatment adherence elements and these were almost invariably present (98.7%). Overall session quality was rated on a 7-point Likert-type scale (1 = *unacceptable*, 7 = *excellent*, with *moderate* at the midpoint). The average overall session quality rating was 6.08 (*SD* = 1.14) and no sessions were rated below midpoint (*moderate*). In all, 95% of competency session ratings were "*very good*" or "excellent" with the remaining sessions being rated "*moderate*" to "*good*".

Cognitive Processing Therapy – Cognitive Therapy

All were deemed delivered per protocol. Proscribed elements occurred in 0% of rated instances. A CPT and CPT-C expert provided competence and fidelity ratings of all cases, using a 5-point scale (1 = poor, 5 = excellent, with satisfactory as the midpoint). The average therapist competence score was 4.09. Across all sessions, 98.5% of competence elements were "good" or "excellent" and none were below "satisfactory."

Methods for Indexing Clinically Significant Change

Reliable Change Index.

The method described by Jacobson and Truax (1991) for CAPS-IV scores entails obtaining a ratio of each subject's individual change score, from baseline to posttreatment assessment, to the sample's standard difference, calculated from the standard error of the difference score, incorporating the baseline measure's reliability. This ratio is each participant's RCI value. If an RCI value exceeds 1.96, then the change in an outcome from baseline to post-treatment exceeds measurement error at a 95% confidence interval. The change score in CAPS that resulted in an RCI greater than 1.96 when divided by the sample baseline standard difference was 22 points.

Clinically Significant End-state.

Jacobson and Truax also recommended a method for determining the degree to which an individual's end-state score (independent of his or her baseline score) suggests that the patient is no longer dysfunctional once treated. In cases where there are no standards available that would otherwise determine a threshold score on a given test that corresponds to a non-dysfunctional state, which is the case for traumatized patients with former PTSD, Jacobson and Truax recommended an end-state score that is at least 2SD below the mean of a reference group. In most cases, the reference group should be individuals randomized into a give trial. In the PTSD field, there is no consensus about end-point scores or status that suggests no longer being dysfunctional, consequently, the 2SD threshold is a good enough proxy that can be used to benchmark endpoints across trials. It is of note that loss of PTSD diagnosis after treatment is problematic because the caseness criteria are arbitrary and cases without the diagnosis can have greater symptom burden than those with PTSD, and posttreatment and partial PTSD is associated with equal comorbidity and distress as PTSD in veterans.

Categorizing Each Participant's Clinically Significant Change.

Following Jacobson and Truax (1991), and consistent with a recent publication that benchmarked the combined results of three high quality randomized controlled trials of first-line psychotherapies for PTSD conducted at Ft. Hood with active-duty service members with PTSD*, we classified participants as *recovered* if they passed the 2SD end-state criterion and the RCI criterion, *improved* if they passed the RCI criterion but not the 2SD end-state criterion, *unchanged* if they did not pass the RCI criterion, and *deteriorated* if

worsened scores passed the RCI criterion. We reported the rates of these categories in two ways: (1) using participants who had posttreatment data (completers), and (2) adding participants with missing follow-up data to the *unchanged* category, consistent with an intent-to-treat analysis. In the manuscript, we compared these rates with those reported in Litz et al.* and a VA cooperative study comparing prolonged exposure and present-centered therapy with veterans with PTSD.**

* Litz BT, Berke DS, Kline NK, et al. Patterns and predictors of change in trauma-focused treatments for war-related posttraumatic stress disorder. *J Consult Clin Psychol*. 2019 Nov;87(11):1019-1029.
**Schnurr PP, Friedman MJ, Engel CC, et al. Cognitive behavioral therapy for posttraumatic stress disorder in women: A randomized controlled trial. JAMA. 2007 Feb;297(8):820-830.

eTable 1. Participants' Clinically Significant Change from Combined STRONG STAR Trials

	Clinical Change Categories (all pre- to post-treatment)			
	Recovered	**Improved**	**Unchanged**	**Deteriorated**
Combined STRONG STAR trials				
Completers % (*n*)	20.6% (98)	10.5% (50)	66.5% (316)	2.3% (11)
Intent to treat % (*n*)	13.96% (98)	7.12% (50)	77.35% (543)	1.57% (11)

eTable 2. Participants' Clinically Significant Change from Schnurr et al., 2007

	Clinical Change Categories (all pre- to post-treatment)			
	Recovered	**Improved**	**Unchanged**	**Deteriorated**
Schnurr et al., 2007				
Completers % (*n*)	28% (65)	11% (27)	59% (138)	2% (5)
Intent to treat % (*n*)	22.9% (65)	9.51% (27)	65.8% (187)	1.8% (5)

eResults

Adverse Events. The proportion of participants experiencing a serious adverse event was small and similar between the two trial arms. AD was associated with two serious adverse events and CPT-C was associated with one. These were each psychiatric: alcohol poisoning; dissociative episode; and suicide attempt. There were 18 adverse events (11 in the AD arm and 7 in the CPT-C arm). Two types of adverse events appeared to be study related, namely increased psychiatric symptoms (5 in the AD arm and 1 in the CPT-C arm) and increased suicidal ideation (2 in the AD-E arm and 1 in the CPT-C arm). It appears that AD was associated with a greater number of psychiatric symptom exacerbations.

Tertiary Superiority Tests. Objectives secondary to the non-inferiority analyses included assessing the potential superiority of AD to CPT-C with respect to the constructs of credibility and acceptability, grief symptoms, reports of exposure to and the impact of potentially moral injurious events, and posttraumatic growth. We performed linear regressions using SAS Software 9.4 at the 0.05 level of significance to estimate the mean differences in measures between treatment groups. We used multiple imputation to test the robustness of the results for the measures containing missing values. The predictors used in the imputation model included age, education, race, baseline score of measure, and Acceptable and Credibility score. Each estimated mean difference represents the mean difference of (AD-CPT) for values of the change in the score of a measure between baseline and posttreatment (excepting the acceptability measures, which were administered at a single time point).

We examined the potential superiority of AD to CPT-C regarding the construct of "acceptability" of therapy by Marines, given that AD was developed to be consonant with Marine Corps culture. The first measure used to examine acceptability was the Acceptance and Credibility (AD-CRED) measure adapted from Borkovec & Nau, 1972, completed after the first session of therapy. The estimated difference in mean AD-CRED between AD and CPT-C was approximately 0.74 [-1.5234, 2.998], p-value = 0.52. The second

measure used to examine acceptability was the Client Satisfaction Questionnaire (CSQ-8). The estimated mean difference in CSQ-8 between AD and CPT-C was approximately -0.25 [-2.039, 1.547], p-value = 0.79. We assessed potential superiority of AD to CPT-C with respect to traumatic grief by analyzing mean differences in the change of Inventory of Prolonged-Grief (IPG-13). The estimated difference in mean change of IPG-13 was approximately 1.44 [-1.999, 4.838], p-value = 0.49. The imputation analysis resulted in a mean difference of approximately 1.96 [-2.3447, 6.2716], p-value = 0.37. We do not see evidence of AD's superiority to CPT-C with respect to traumatic grief.

We assessed the superiority of AD to CPT-C with respect to reports of exposure to and the impact of potentially moral injurious events by analyzing the mean differences in the change in scores of the Moral Injury Events Scale (MIES). We examined the mean difference in total MIES – representing the total symptom burden of moral injury -, as well as the two subscales: moral injury to self and moral injury to others, representing internal and external manifestations of the construct. The estimated mean difference in total MIES was approximately 0.99 [-2.089, 4.074], p-value = 0.60. The imputation analysis resulted in a mean difference of approximately 1.23 [-2.7069, 5.1763], p-value = 0.54. The estimated mean difference in MIES-self was approximately 0.20 [-2.1026, 2.499], p-value = 0.88. The imputation analysis mean difference for MIES-self was approximately 0.99 [-2.0290, 4.0033], p-value = 0.52. The estimated mean difference in MIES-other was approximately 1.31 [-1.0454, 3.6604], p-value = 0.36; the imputation analysis resulted in a mean difference of approximately 0.92 [-1.9321, 3.7690], p-value = 0.53.

We assessed the superiority of AD to CPT-C with respect to posttraumatic growth by analyzing the mean differences in the change in score of Posttraumatic Growth Inventory (PTGI). The estimated mean difference in PTGI was approximately 2.95 [-1.3054, 7.1922], p-value = 0.18. The imputation analysis produced an estimated mean difference of 2.55 [-1.2598, 6.3554], p-value = 0.19.

eCONSORT Checklist Information

CONSORT Checklist Items Not Mentioned in the Manuscript

7b. When applicable, explanation of interim analyses and stopping guidelines

Based on changes for our military partners (reduction in deployments, drawdown), we were asked to move from the Naval Hospital at Camp Pendleton (NHCP) to the Naval Medical Center at San Diego (NMCSD), and the approval process for this was lengthy. After reopening, we agreed with the funding agency to do an interim analysis to determine if there was a superiority effect and to estimate the number of additional cases needed given for the non-inferiority tests at the new treatment site. On the basis of that analysis, the DSMB determined that there was no superiority affect and recruitment of the original sample size would not change the result. Thus, the decision was made to end the trial, in conjunction with the funder.

14a. Dates defining the periods of recruitment and follow-up

We were open from March 2013 to May 2015 at NHCP. We then reopened from September 2018 to December 2019 at the NMCSD. These periods began with the start of recruitment and ended with the final follow-up.

14b. Why the trial ended/was stopped

Based on changes for our military partners (reduction in deployments, drawdown), we were asked to move from NHCP to the NMCSD, and the approval process for this was lengthy. After reopening, we agreed with the funding agency to do an interim analysis to determine the number of additional cases needed given this addition of a new site at this later point. On the basis of this analysis, the DSMB determined that recruitment of the original sample size would not change the result, and the decision was made to end the trial.

19. All important harms or unintended effects in each group.

The proportion of participants experiencing a serious adverse event was small and similar between AD (2) and CPT-C (1) arms. These were each psychiatric: alcohol poisoning; dissociative episode; and suicide attempt. There were 18 adverse events (11 in the AD arm and 7 in the CPT-C arm). Two types of adverse events appeared to be study related, namely increased psychiatric symptoms (5 in AD arm and 1 in the CPT-C arm) and increased suicidal ideation (2 in the AD-E arm and 1 in the CPT-C arm). It appears that AD was associated with a greater raw number of psychiatric symptom exacerbations.

eTable 3. All Recorded Adverse Events

AE/SAE	Event	Total # Pts	# AD Pts (N=62)	# CPT Pts (N=60)
SAE	Psychiatric - alcohol poisoning	1	0	1
SAE	Psychiatric - dissociative episode	1	1	0
SAE	Psychiatric - suicide attempt	1	1	0
AE	Psychiatric - increased psychiatric symptoms	6	5	1
AE	Psychiatric disorders - suicidal ideation	3	2	1
AE	GI disorders - upset stomach	1	0	1
AE	Neoplasms - tumor	1	1	0
AE	Nervous system - lightheaded	1	0	1
AE	Nervous system - migraine	3	2	1
AE	Renal and Urinary - urinary tract infection	1	1	0
AE	Skin and Tissue - allergic reaction	2	0	2