Evaluation of Web-Based CBT for Women Veterans with PTSD

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STUDY PROTOCOL WITH STATISTICAL ANALYSIS PLAN

Recruitment. Women Veterans with PTSD (target $N = 100$) were recruited for this RCT. Veterans who met the following criteria were identified by national VA electronic medical records: (1) age 18 or older, (2) female, (3) Veteran, (4) lives in a state with a Pacific or Mountain time zone (i.e., New Mexico, Arizona, Montana, Wyoming, Colorado, Utah, Washington, Idaho, Oregon, California, Nevada), (5) has an ICD code for PTSD or a positive VA mandated PTSD screen, (6) no mental health stop code (reflecting VA-based visits) in the last two months, and (7) not on the high risk list of imminent danger to self or others. Approximately 30,000 women met these criteria. Because the study aimed to enroll women who were not actively engaged in current mental health care (defined as prior two months), this criterion was applied when identifying potential participants via medical records. Randomly selected women were mailed letters approximately every other week in batches of 100-200 letters inviting them to potentially participate in the study. The invitation letter included an overview of the study and directed women to contact the study office for more information. Each individual may have received up to two invitation letters and up to three follow-up phone calls to assess her interest and eligibility.

Inclusion criteria for the RCT included: (1) age 18 or older, (2) female, (3) Veteran, (4) current PTSD as assessed by the CAPS-5 interview, (5) reports routine access to computer and Internet, and (6) provides written research informed consent using IRB-approved form, including willingness to be audio-taped during the eligibility interview and study coach calls, willingness to be left voice messages, and availability of at least one collateral contact.

Exclusion criteria included: (1) on VA "high risk" list for imminent danger to self or others, (2) currently at imminent danger of harm to self, according to the M.I.N.I. International

Neuropsychiatric Interview – Suicidality instrument, (3) actively engaged in individual therapy in the past two months, and/or receiving couple's or group therapy in the past two months if that therapy focuses on PTSD at a frequency of once per month or more, (4) scheduled to receive a future individual therapy appointment, or a future couples' or group therapy appointment if that therapy focuses on PTSD, at a frequency of once per month or more, (5) moderate or severe alcohol use disorder or any non-alcohol substance use disorder in the past year excluding mild cannabis or any nicotine abuse, (6) acute psychosis, psychotic episode, or psychotic disorder diagnosis within the past year, (7) homicidality, and (8) unstable administration schedule or dosing of any antidepressant, anxiolytic, or sedative-hypnotic (i.e., will exclude for any related medication changes in the four weeks prior to the eligibility interview). Furthermore, women who participated in earlier phases of the research (qualitative interviews and the pilot study) were not included. These criteria are consistent with PTSD RCTs and PTSD telehealth research (Morland et al., 2009; Schnurr et al., 2003).

Study procedure. The study involved three assessment phases: eligibility, baseline, and follow-up (post-treatment and 3- and 6-month follow-ups). The eligibility interview was conducted by a study assessor via telephone. Baseline and follow-up assessments were conducted online. Participants were randomized to condition following the baseline assessment.

Eligibility screener and interview. When interested women Veterans contacted the study office, study staff conducted a pre-consent eligibility screening, which consisted of questions corresponding to inclusion/exclusion criteria. The purpose of the pre-consent eligibility screening was to quickly determine which candidates are most likely to qualify, thus eliminating the need to conduct consent and full eligibility interviews for all potential participants. If patients were found to be eligible following the pre-consent eligibility screening, study staff reviewed the

consent, answered any questions, and mailed the consent form to the participant to obtain written consent. The full eligibility interview was scheduled at this time and conducted only when written, signed consent had been received in the study office. The full eligibility interview included a collection of demographic information as well as the Mini International Neuropsychiatric Interview (MINI) to assess substance use disorders (Lecubrier et al., 1997) and the CAPS-5 (Weathers et al., 2013). PTSD diagnosis on the gold-standard CAPS was required for study eligibility. The staff member who conducted the eligibility interview in the role of study assessor did not serve as the participant's study coach to avoid potential bias during the assessment. If the interval between the eligibility interview and baseline assessments was longer than four weeks, we required re-administration of CAPS via telephone to ensure PTSD status.

Baseline and follow-up assessments. The baseline and follow-up assessments (at post-treatment and 3- and 6-month follow-ups) consisted of an online survey hosted by SurveyMonkey (SurveyMonkey Inc., Palo Alto, CA). Information collected during the online baseline assessment served as a baseline from which to evaluate the efficacy of the study intervention on the primary outcome (PTSD symptom severity) and secondary outcomes (depression and quality of life). Information about concurrent treatment that might moderate the efficacy of the study intervention ("co-therapies") was also gathered at the baseline assessment (e.g., mental health specialty visits, PTSD-related pharmacotherapy use, and chaplain or similar community support resources) and throughout the course of the study. Following the baseline assessment, patients were randomly assigned to one of the study conditions. Participants received $25 for the baseline assessment, $30 for each of the three follow-up assessments, and a $35 bonus for completing all assessments (for a total maximum of $150).

Randomization. We used the Sealed Envelope™ program (Sealed Envelope Ltd., 2016) to generate a randomization table to condition (1:1 allocation ratio) using a permuted block design with block sizes of two and four to maximize the likelihood of a balanced sample size across arms (Schulz & Grimes, 2002), and stratifying by rural status to facilitate exploratory analyses of the impact of this variable on trial outcomes and to maximize the likelihood of balance across arms on this potential characteristic (Kernan et al., 1999). We defined rural status as living more than 40 miles away from the closest VA medical facility, in line with eligibility criteria used by the Veterans Access, Choice, and Accountability Act and shown to be a marker indicating decreased likelihood of receiving psychotherapy (Pfeiffer et al., 2010).

DESTRESS-WV intervention. For the DESTRESS-WV condition, the initial telephone session with the study coach served to 1) provide brief psychoeducation regarding PTSD; 2) complete a safety plan that is individualized to the patient for times when she is distressed; 3) introduce the intervention model, the study coach role, and the participant's role; 4) introduce the patient to the website's structure; and 5) problem-solve any obstacles to using the website. Participants were asked to log on the website twice a week each week for eight weeks and complete different homework activities. Nonetheless, up to 12 weeks of access was provided. The coach called the participants once a week at an agreed upon time while they were completing the program to monitor symptoms and safety, review progress through the website, provide encouragement, review a particular skill or strategy when applicable, review barriers to treatment compliance, and address barriers to treatment (target call time is 15 minutes). The coach had access to a back-end of the DESTRESS-WV website where she monitored participants' progress, and this was monitored weekly between every study coach call.

Before completing each session, participants were encouraged to plan 30-60 minutes free from interruption, during which they can review that session's content. Sessions covered basic coping skills (deep breathing, progressive muscle relaxation, and reaching out for support); cognitive strategies to identify and challenge unhelpful thoughts; in-vivo exposures; writing about stressful, daily life events; and writing about and processing a traumatic experience. Sessions could only be accessed at a minimum of 24 hours apart to promote appropriate pacing and provide opportunity to complete homework assignments.

DESTRESS-WV homework. After the first session, each time participants logged on to the DESTRESS-WV site, they were prompted to enter responses from the previous session's homework assignment. Broken up into units, these assignments promoted stress-reduction skills, self-monitoring, application of stress management techniques to each in vivo exercise, processing and coping with a particularly salient or intense traumatic memory as well as significant current-day stressors, and relapse prevention. Participants were required to complete a given homework assignment before proceeding to the next session, otherwise the sessions did not progress. Participants were also reminded of the study coach's phone number and could call the coach at any time with questions or concerns. Study coach voicemails were monitored daily during regular business hours.

Phone monitoring only. The purpose of the phone monitoring condition was to assess participants' safety and symptoms, similar to the DESTRESS-WV condition, while providing general support in a safe atmosphere where participants were actively being listened to and empathized with by the coach. The aim of using this approach was to provide an alternative and to control for nonspecific therapeutic factors, including regular supportive contact with study staff.

The initial telephone session served to: (1) provide brief psychoeducation regarding PTSD; (2) complete a safety plan that is individualized to the participant for times when she is distressed; and (3) introduce the study coach and the participant's roles. Participants were expected to attend calls weekly and, in addition to answering questions regarding their weekly symptoms, were encouraged to discuss any issues from the week they would like. The coach used active listening and reflective statements but did not actively encourage the use of CBT strategies, as in the DESTRESS-WV condition. Calls were expected to last an average of 15 minutes, similar to the length of calls in the DESTRESS-WV condition.

Outcome measures. Baseline, post-treatment, and 3- and 6-month surveys all assessed outcome measures and were conducted online, thus eliminating the need for a blind assessor.

Primary outcome. The PTSD Symptom-Checklist –Version 5 (PCL-5) was used to assess symptoms of PTSD at baseline and follow-up assessments (Weathers et al., 2013). This is a 20-item, self-report instrument that assesses the presence and severity of DSM-V PTSD symptoms in the last month. It can be summed for a total severity score, ranging from 0-80. PCL-5 test scores have demonstrated good internal consistency ($\alpha = .96$), test–retest reliability ($r = .84$), and convergent and discriminant validity with samples of Veterans (Bovin et al., 2015).

Secondary outcomes. The Patient Health Questionnaire (PHQ) is a brief self-report assessment of common mental disorders and was used to assess symptoms of depression (PHQ-8; Kroenke et al., 2009). The eight items specifically correspond to symptom-based diagnostic criteria in DSM-IV, and demonstrate good validity, reliability, and sensitivity to change (Kroenke & Spitzer, 2002). The Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) was used to assess quality of life (Endicott et al., 1993). It consists of

16 items and has been shown to have good internal consistency, test-retest reliability, validity, and sensitivity in clinical settings (Stevanovic, 2011).

Process outcomes. Feasibility of DESTRESS-WV was examined by completion of intervention sessions and retention of participants through the duration of the intervention. For the DESTRESS-WV treatment arm, we defined a "treatment completer" as someone who completed at least nine of the 16 intervention sessions, and for the phone monitoring only arm we defined a treatment completer as someone who completes at least five of the nine coaching calls. We hypothesized that no more than 30% of the women in this study will dropout from the study (withdraw or be lost-to-follow-up), similar to overall dropout rates for PTSD trials (Imel et al., 2013). Of the women who do not dropout, we hypothesized that at least 70% will be treatment completers as per the above definitions, similar to participation rates found by Engel et al. (2015).

Acceptability was evaluated by participants in both study groups using the Client Satisfaction Questionnaire-8 (CSQ-8; Larsen et al., 1979), an 8-item measure on a 4-point Likert scale that assesses general satisfaction with treatment. For example, participants rate the quality of the service they received, the extent to which the program met their needs, the extent to which they were satisfied with the amount of help received, and whether services helped them deal more effectively with their problems. The measure has good internal consistency, construct validity, and criterion-related validity (Attkisson & Zwick, 1982). An additional item assessed how satisfied participants were with receiving treatment through the phone or Internet (based on assigned condition), from 0 (*not at all*) to 4 (*very much*). Finally, seven items created for the study assessed satisfaction with the study coach, ranging from 0 (*not at all*) to 4 (*very much*). Items included how much the participant liked the coach, how helpful the coach was, and how

much the participant felt the coach listened and understood them. We hypothesized that overall mean satisfaction will be greater than the mid-point of the scale.

Participant safeguards. As noted above, during the first phone call with the study coach, participants in both conditions created a personalized safety plan. This included identifying healthy coping strategies that could be done alone (e.g., going for a walk, engaging in a pleasurable activity) as well as identifying individuals in their support network they can call. The safety plan also included the Veterans Crisis Line number and the study coach's contact information.

Participants were carefully monitored for signs of clinical deterioration that may jeopardize their health or warrant removal from the study. During the treatment phase, at each call (nine calls for a total of eight weeks), the study coach assessed PTSD symptoms using an abbreviated PTSD Checklist (PCL) that consisted of seven items (three re-experiencing symptoms, two avoidance symptoms, two hyperarousal symptoms). Participants rated each symptom from 1 (*not at all*) to 5 (*extremely*). If there were an increase of seven or more points on this abbreviated PCL (i.e., 20% of the maximum possible score) from the baseline score (i.e., score on first coach call before initiation of treatment), the study coach discussed with the participant whether it appears that the exacerbation was related to study participation or was likely situational (e.g., life stressors or changes in circumstances often precipitate PTSD exacerbations, as do trauma anniversaries). If it appeared to be the former, the possibility of withdrawing from the treatment aspects of the study were discussed with the participant and PI and a decision reached mutually.

Any patient who became actively suicidal was assessed by the study coach using the study's Safety Protocol. The Safety Protocol assessed and identified whether current risk was

minimal (hopelessness or ideation only), moderate (ideation and plan but no intent), or imminent (ideation, plan and intent). Clear guidelines were offered in accordance with each risk level (e.g., moderate risk entailed providing the participant with the Veterans Crisis line and local resources and recommending follow-up mental health care in 24 hours).

All participants who withdrew from the treatment protocol were given the option of continuing to provide information at the follow-up assessments for intent-to-treat analyses of outcomes. Additionally, participants randomized to DESTRESS-WV were reminded of the study office phone number and the Veterans Crisis Line during each logon. Participants were also reminded of these phone numbers and other resources after each follow-up assessment.

Power. This is a pilot RCT designed to provide estimates of feasibility of the treatment approach, dropout rates, acceptability, and initial effect sizes. The study's budget and timeline allows us to plan to randomize 100 participants. For the primary outcome, Litz et al. (2007) observed a differential effect size of 0.41 at 8 weeks (n = 33), 0.10 at 3 months (n = 24), and 0.95 at 6 months (n = 18) when comparing change from baseline in PTSD symptoms for participants randomized to DESTRESS (n = 24) versus supportive counseling (n = 21), with an overall dropout rate of 27% prior to the end of 8 weeks of therapy. In a second trial of DESTRESS by Engel et al. (2015) where participants were randomized to optimized usual care (n = 37) or DESTRESS (n = 43), the 6-week effect size was 0.23 (n = 64), the 12-week effect size was 0.47 (n = 62), and the 18-week effect size was 0.08 (n = 66), with an overall dropout rate of 18%.

As noted above, we hypothesized no more than 30% of participants will dropout prior to the end of the study. Thus, with the goal of randomizing 100 participants and assuming a sample size of at least n = 35 participants per group, we have 80% power to detect an effect size of 0.68 using a two-sided Type I error rate of 5%.

Following the recommendation of Bacchetti (2010), Table 1 presents a sensitivity analysis of possible results from this study in terms of 95% confidence intervals for the difference in change from baseline in PCL-5 for the DESTRESS-WV versus the phone monitoring only group. Engel et al. (2015) state that for their study of DESTRESS versus optimized usual care (OUC), for PCL-4 the observed 12-week change from baseline (Mean ± SD) was 12.6 ± 16.6 for the DESTRESS group and 5.7 ± 12.5 for the OUC group. In our table the pooled standard deviation of change from baseline varies from 8 to 22, while the possible difference in change from baseline between groups varies from 0 to 14. The numbers in parentheses after the confidence intervals are the effect sizes.

Table 1. Sensitivity Analysis of Possible Results for Difference in Change from Baseline Between Groups (95% Confidence Intervals and Effect Sizes)

	Difference = 14	Difference = 7	Difference = 0
SD = 8	[10.2, 17.8] (1.8)	[3.2, 10.8] (0.9)	[-3.8, 3.8] (0)
SD = 15	[6.8, 21.2] (0.9)	[-0.2, 14.2] (0.5)	[-7.2, 7.2] (0)
SD = 22	[3.5, 24.5] (0.6)	[-3.5, 17.5] (0.3)	[-10.5, 10.5] (0)

RCT data analytic strategy. We used summary statistics (e.g., means, standard deviations, percentages) and graphs (e.g., strip charts, box plots, bar charts, scatter plots) to compare participant demographics at baseline by assigned treatment group (DESTRESS-WV vs. phone monitoring only), and to initially compare outcomes by treatment group. Analyses followed the intent-to-treat principle, so that all participants who had at least a baseline assessment and were randomized were included in the analyses. For descriptive purposes, analyses were conducted to determine group comparability on baseline participant characteristics and potential moderator variables. Because differential attrition can compromise inference about treatment effectiveness, we compared study dropouts versus non-dropouts and treatment non-completers versus treatment completers on demographic and outcome variables. Dropouts

included those who withdrew from the study or were lost-to-follow-up; treatment non-completers may or may not be study dropouts as treatment non-completers were invited to continue participating in study assessments. Treatment completers include those completing nine or more sessions of DESTRESS-WV or, for those in the phone monitoring condition, five of the nine coaching calls.

To account for repeated measures within subjects, we used a linear mixed effects model for the analysis of the primary outcome, PCL-5, with the subject treated as a random effect. We have PCL-5 measures at four times during the course of the study: at baseline, 8 weeks (the first post-treatment assessment), and 3 and 6 months post-treatment. The response (dependent) variable was PCL-5 score, and the predictor (explanatory) variables included treatment group, assessment visit (treated as categorical), and a treatment group by assessment visit interaction term, along with the covariates trauma category and rural status. A significant treatment group by visit interaction term indicates a significant difference in change from baseline between treatment groups. Results include adjusted means, standard errors, and 95% confidence intervals for each group at each time, confidence intervals for change from baseline at each time within each group, confidence intervals for differences in change from baseline between the two groups at each time, p-values, and effect sizes. We also used linear mixed effects models for the two secondary outcomes, depression and quality of life.

Linear mixed effects models easily accommodate missing values. We compared the rate and timing of dropouts between treatment groups, and also baseline demographics and outcome scores between treatment completers and non-completers. If necessary, we will perform sensitivity analyses by using only participants who were treatment completers and using multiple imputation to deal with missing values.