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STATISTICAL ANALYSIS PLAN FOR CSP #591 (CERV-PTSD)

I. SUMMARY OF STUDY

A. Objective

The primary objective is to compare the effectiveness of Prolonged Exposure and Cognitive Processing Therapy for reducing the severity of PTSD symptoms. The secondary objective is to compare the effectiveness of Prolonged Exposure and Cognitive Processing Therapy for reducing the severity of comorbid mental health problems and service utilization and improving functioning and quality of life. The tertiary objective is to examine whether discrepancy between patient preferences and treatment assignment reduces the effectiveness of each treatment.

B. Target population

Participants will be male and female Veterans with PTSD due to any military event.

C. Randomization

Participants will be randomly assigned in a 1:1 ratio to receiving PE or CPT. Randomization will be based on permuted blocks within each study center.

D. Length of study

Recruitment is 2.5 years. Each participant will be treated and followed for up to 12 months and, therefore, the total duration of active recruitment, treatment and follow-up is 3.5 years. Table I.1 summarizes the assessment schedule for a participant who completes the study.

E. Target sample size

Estimate to randomize 900 participants (450 per group).

Table I.1: Assessment Schedule

Measure	Baseline	During treatment	Post-treatment	3-month	6-month
Demographic information	X				
VA TBI Screen	X				
VA MST Screen	X				
Life Events Checklist	X	(X)			
Suicide Screen	X, A		A	A	A
Homicide Screen	X, A				
MoCA	X				
Treatment preference	A				
Structured Clinical Interview for DSM-5	A				
Expectancy of Therapeutic Outcome		X (session #1)			
PTSD Checklist [2]		X (weekly)			
Patient Health Questionnaire-9 [2]		X (weekly)			
Concomitant Medications	A		A		A
Psychotherapy	A		A		A
Clinician-Administered PTSD Scale [1]	A	A (session #6)	A	A	A
Posttraumatic Diagnostic Scale [2]	X		X	X	X
Beck Depression Inventory-II [2]	X		X	X	X
Spielberger State Anger Inventory [2]	X		X	X	X
Brief Addiction Monitor (2 items) [2]	X		X	X	X
Short Inventory of Problems-Revised [2]	X		X	X	X
WHO-DAS-II [2]	X		X	X	X
WHOQOL-BREF [2]	X		X	X	X
VA and non-VA Utilization [2]	X (6 months prior)		X (time since baseline)		X (time since posttreatment)
Client Satisfaction Questionnaire [2]			X		

[1] Primary Outcome
[2] Secondary Outcomes
X required (completed at the site by participant, SC, therapist or PI)
A required (completed by assessment lab)
(X) conditional

II. PLAN DETAILS

A. Type of primary analysis

Intention to treat

B. Methods for handling multi-center data

Aggregated by intervention group for comparison

C. Analysis of subgroups

See Section II.H.5 for subgroup analyses.

D. Interim or sequential analyses

In the conduct of clinical trials, there is an ethical obligation to review the data on safety, study conduct and progress, study feasibility, and efficacy over the course of the study. At its first meeting, the DMC discussed and decided how it would conduct interim monitoring for CSP #591. The second DMC meeting will be held one year after recruitment starts, and subsequent meetings will be held at about 6 months interval, either in conference calls or in person. A DMC report will be distributed to all members 2 weeks prior to meeting. The DMC may recommend early termination of the trial based on interim analyses.

1. Monitoring of safety and study progress

   Study safety will be monitored by CSPCC and CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC), and reported to the DMC at the DMC meeting. A complete description of monitoring and reporting adverse events is given in Section XI of the study protocol. In the event that serious adverse events are noted to be excessive in either group, the DMC may consider recommending the study be stopped. At the initial DMC meeting (2/25/2014) the DMC requested to see all SAEs as they are reported to the study team.

In addition to interim monitoring for safety, the DMC will also monitor patient intake (overall and within site), site adherence to the study protocol, data quality, completeness and timeliness of follow up and data submission, and baseline comparability of treatment groups. The DMC will review the accumulating data and be responsible for determining whether or not to recommend to the CSR&D Director that the trial be continued or stopped. Data summaries will be prepared for the DMC for these purposes. To aid the DMC in their deliberations, other relevant information pertaining to (e.g., secondary analyses) and outside of (e.g., other studies) CSP #591 will be made available.

2. Interim analysis for potential early stopping for efficacy or futility

The study does not plan to conduct interim analyses to allow early stopping of the study for efficacy (when there is sufficient evidence that one treatment is superior to the other treatment) or for futility (when it is futile to establish a statistical significant difference at the end of the trial). The rationales are (1) both PE and CPT are effective treatments for PTSD, so there are no ethical concerns in continuing the study even when it is unlikely to establish a statistical significant difference at the end of the trial; (2) even when there are treatment differences between PE and CPT, the differences are not likely to alter the VA policy to make all evidence-based treatment available to PTSD patients based on interim analysis results; (3) it is important from a public health, policy, and scientific perspective to collect sufficient data on the secondary outcomes to support findings in the primary outcome, in the hope that the totality of the evidence will be able to provide guidance to or change clinical practice; (4) it allows us to examine the impact of patient preference on treatment effectiveness, which is one of the key elements in personalized medicine.

The DMC agrees with what is written in the protocol (as stated above) that there should be no early stopping for efficacy or futility; however, DMC requested CSPCC to

calculate means and standard deviations of outcome data by treatment group in each DMC report and also carry out the treatment comparisons.

E. Levels of clinical and statistical significance (one-tailed or two-tailed)

The level of statistical significance is two-tailed tests at $p<0.05$, with 90% power. The Planning Committee considered an effect size of 0.25 to be a clinically meaningful difference, that translates to a $\Delta\mu\approx5$ points difference in the primary outcome.

F. Methods for handling more than two treatment groups – multiple comparison methods

Not applicable. This study has two treatment groups to compare.

G. Primary and secondary outcomes

See Table I.1 and Section II.H.3 for details.

H. Hypotheses to be tested and analyses to be performed to meet the trial objectives

1. Baseline comparability

Because of the large sample size of this study, we expect the randomization process to balance baseline characteristics and produce comparable groups of participants. Baseline comparability between treatment groups will be evaluated with respect to demographic and baseline physical and psychological characteristics. Summary statistics (e.g., means and standard errors for continuous variables, and frequencies and percentages for categorical variables) and graphical techniques (e.g., boxplots for continuous variables, and histograms for categorical variables), will be used to compare the baseline characteristics of the two treatment groups within study sites and the whole study. In addition, we will use t-tests to compare continuous variables and Chi square tests for categorical variables.

2. Primary objective

The primary objective is to compare the effectiveness of PE and CPT for reducing the severity of PTSD symptoms as measured by CAPS total score. The primary outcome is change of CAPS total score from baseline (pre-treatment) to the average in the six months post-treatment (measured at post-treatment and 3 and 6 months follow-up visits).

Primary analysis: The primary analysis will follow the intent-to-treat (ITT) principle. Participants will be counted in the treatment group to which they were randomized, regardless of the number of sessions they completed. Linear mixed effects models, with time, treatment, treatment by time interaction and site as fixed effects and participant and therapist as random effects, will be used to estimate and compare the primary outcome between PE and CPT. The point estimate and the 95% confidence interval for the mean difference will be provided.

Secondary analysis: We will provide point estimates and pointwise 95% confidence intervals for the mean differences in the CAPS total scores at the three post-treatment timepoints as well as the mean differences in changes of CAPS total score from baseline at these post-treatment timepoints. We will also compare the longitudinal profiles of CAPS total score (including the mid-treatment and post-treatment scores) between PE and CPT by testing the treatment by time interaction. When data permits, we will explore site variations in treatment effect and also explore the impact of different covariance variance structures (e.g., allowing the variance of therapist random effect to differ by treatment or allowing certain variances or covariances to vary by time). Although we anticipate minimum missing data in CAPS total score, we will perform analyses to examine the missing data patterns and the impact of missing data.

As in CSP #494, we will use the CAPS to derive additional measures of clinical outcomes: response (defined as at least 10-point improvement in severity), loss of diagnosis (response plus no longer meeting DSM symptom criteria), and remission (loss

of diagnosis plus the DSM-5 score that corresponds to a DSM-IV severity score < 20). The observed proportions and their 95% confidence intervals will be provided for each treatment group at each of the follow-up timepoints. Chi-square tests will be used to compare these outcomes between the two treatment groups.

3. Secondary objective

   The secondary objective is to compare the effectiveness of PE and CPT for reducing the severity of comorbid mental health problems and service utilization and improving functioning and quality of life.

   These secondary outcome measures, listed in Table II.1 below, will be compared between PE and CPT to support the comparative effectiveness of these two treatments in CAPS total score. Except for Brief Addiction Monitor and certain service utilization outcomes (which are categorical measures), all other secondary outcomes are continuous measures and will be analyzed in a manner similar to CAPS total score as described above. Generalized linear mixed effects models (SAS PROC GLIMMIX) will be used to compare the longitudinal profiles of the categorical measures between PE and CPT. Generalized estimating equations may also be used. We do not plan to adjust for multiple comparisons due to the supportive nature of these secondary outcomes.

Table II.1: Secondary Outcomes

Secondary Outcome	Time Points	Type of Data
Posttraumatic Diagnostic Scale	Baseline, Post, 3m, 6m	Continuous
Beck Depression Inventory-II	Baseline, Post, 3m, 6m	Continuous
Spielberger State Anger Inventory	Baseline, Post, 3m, 6m	Continuous
Brief Addiction Monitor (2 items)	Baseline, Post, 3m, 6m	Categorical
Short Inventory of Problems-Revised	Baseline, Post, 3m, 6m	Continuous
WHO-DAS-II	Baseline, Post, 3m, 6m	Continuous
WHOQOL-BREF	Baseline, Post, 3m, 6m	Continuous
Service Utilization	Baseline, Post, 6m	Categorical, Continuous
Client Satisfaction Questionnaire	Post	Continuous

Secondary Outcome	Time Points	Type of Data
PTSD Checklist	weekly during treatment	Continuous
Patient Health Questionnaire-9	weekly during treatment	Continuous

4. Tertiary objective

The tertiary objective is to examine whether discrepancy between patient preferences and treatment assignment reduces the effectiveness of each treatment. We will calculate the frequencies and percentages of participants' treatment preference in the entire study sample and also by site, sex, and trauma type. We will examine the impact of participant's treatment preference on treatment effectiveness. Participant's treatment preference, collected before randomization, will be included as a covariate in the regression models to assess if the effectiveness of the treatment on the primary and selected secondary outcomes differs between participants who received their preferred treatment and those who did not receive their preferred treatment. We will also examine if there are differences in treatment adherence and completeness of follow-up. This analysis will be performed in the combined sample and also within each treatment arm.

5. Exploratory analyses

We will explore potential heterogeneities of treatment effect in the primary outcome by performing tests of treatment by subgroup interaction and by displaying treatment effects with their 95% confidence estimates within subgroups. The purpose of these exploratory analyses is to detect apparent reversals of effect or major quantitative interactions, in order to describe the uniformity or variation of effect appropriately. One major subgroup analysis concerns the sex of the participant. By enlisting the help of PBRN, we will try to recruit sites with large pools of female PTSD patients in this study; however, despite our efforts, it is not expected that we will be able to recruit a sufficient number of females to provide more than a preliminary idea of the effect in that subgroup. Other major subgroups will be era, age, race/ethnicity, MST, TBI, comorbid depression, and comorbid substance abuse. Because of the exploratory nature of these analyses, we do not plan to adjust for multiple comparisons.

We will also compare the following variables between PE and CPT: (1) the proportions of study participants meeting the stable remission criterion [early (<12 weeks), on time (12 weeks), late (>12 weeks), did not reach remission], by Chi-square tests; (2) the number of weeks to reach the stable remission criterion, by logrank tests; and (3) the number of sessions and total number of hours delivered, by two-sample t-tests. Mixed effects models or generalized estimating equations may be used to incorporate correlations due to therapists or to explore site variation. Interpretation of these results will incorporate early withdrawal of study treatment, early withdrawal of study, and initiation of non-study treatment for PTSD. We will also examine whether and how treatment dose (such as number of sessions and total number of hours), treatment engagement (homework) and treatment fidelity (therapist adherence and competence) relate to primary and secondary outcomes within and between treatments, and whether and how time to stable remission (such as early vs. on time vs. late) relates to outcomes within and between treatments.

I. Presentation of results

Interim reports will be presented in tables and graphs.

J. Visit windows

Table II.2: Visit Windows

Visit	Range
Phase 1 Screening	No range for phase 1
Phase 2 Screening	0-30 days after phase 1
Phase 3 Screening	0-30 days after phase 2
Randomization	0-7 days after phase 3
Treatment Session 1	0-30 days after randomization
Treatment Session 2-14*	7-21 days after previous session
Mid-Treatment Assessment (Session 6)	0-14 days after session 6
Post Treatment Assessment	0-14 days after final treatment session
3-month Assessment	3 months ±2 weeks after final treatment session
6-month Assessment	6 months ±2 weeks after final treatment session

* The site SC and therapist will make sure Treatment Session 7 is scheduled after the "Mid-Treatment Assessment (session 6)" visit.

K. Rules for handling windows with more than one visit

Visit follows sequentially from previous visit. Thus, it won't be an issue for this study. If a visit is late in the follow-up phase, the late visit will be assigned to the visit with the closest target date.

L. Data inclusion/exclusion decision rules

Plan to use the data from all randomized participants in the analyses, regardless of the number of sessions they have completed. However, for sites with questionable data the study Executive Committee and Data Monitoring Committee will make recommendation to CSR&D Director whether to exclude the data from analyses or not.

M. Definition of compliance

Treatment compliance and termination will be reported and monitored. Regardless of their treatment compliance levels, the data from all participants will be used for analyses.

N. Methods for handling multiple observations

Appropriate methods for analyzing repeated measures data (e.g., mixed effects models, generalized estimating equations) as described in Sections II.H.2 and II.H.3 above.

O. Use of baseline variables

See Section II.H.1 above.

P. Rules for calculation of derived variables

See Section II.H.2 above.

Q. Use of covariate data

See Sections II.H.4 and II.H.5 above.

R. Rules for stopping the trial, and allowance for them in the analysis

See Section II.D.2 above.

S. Methods for handling missing data – use of tabulation and/or other presentation methods

It is expected that there will be some missing data. Imputation techniques, such as linear interpolation and multiple imputation methods will be examined to assess the robustness on the results. Completer analyses will also be done based on participants who remained in the study throughout the 6-month follow-up period. When large fractions of information are missing, we will perform sensitivity analyses under weaker assumptions (e.g., non-ignorable missingness). It is recognized, however, that the best approach to missing data is to make all efforts to minimize it, since imputation is difficult when the missing data are non-ignorable or not missing at random. We will attempt to collect outcome data from all participants at all timepoints regardless of whether they continue or complete the study treatment. We will also attempt to collect reasons for missing data when possible. Also, the telephone CAPS assessment can facilitate completeness by enhancing the convenience for participants, who will not have to travel for assessment sessions.

T. Methods for handling outliers

Data edits will identify outliers. Sites will receive data query reports and be asked to modify values or verify current value in database is correct.

U. Identification of fixed or random effects models

Linear mixed effects models (SAS PROC MIXED) will be used to compare the primary outcome between the two treatment groups. The mixed effects model will include time, treatment, treatment by time interaction and site as fixed effects, and participant and therapist as random effects.

V. Methods for handling withdrawals and protocol deviations

Tallies will be reported. Data Monitoring Committee and study's Executive Committee may be asked for recommendations on how to handle these (e.g., should erroneously randomized participant be allowed to continue participation after participant found to be ineligible)

W. Methods for point and interval estimation

See Section II.H above for individual study outcomes. In general, summary statistics will include mean, SD, and range for continuous variables, percentage for categorical variables, and 95% confidence intervals when appropriate.

X. Approach to handling concomitant medications

Reported as percentage of participants who were on a given medication at some time during the study

Y. Planned sample size re-estimation

There is no plan to re-estimate the sample size.

Summary of Updates to Statistical Analysis Plan

Version Number	Version Date	Details of Major Changes
1	02/21/2014	Initial plan
1.1	04/15/2014	From first DMC meeting, 02/25/2014: Section II.D: The second DMC meeting will be held one year after recruitment starts, and subsequent meetings will be held at about 6 months interval, either in conference calls or in person. Section II.D.1: The DMC requested to see all SAEs as they are reported to the study team. Section II.D.2: The DMC agrees with what is written in the protocol that there should be no early stopping for efficacy or futility; however, DMC requested CSPCC to calculate means and standard deviations of outcome data by treatment group in each DMC report and also carry out the treatment comparisons.

APPROVAL SIGNATURE AND DATE

	4/15/2014
Bruce Chow, MS Study Biostatistician	Date (mm/dd/yyyy)
	4/21/2014
Ying Lu, PhD Director, Palo Alto CSPCC	Date (mm/dd/yyyy)
	4/28/14
Paula P. Schnurr, PhD Study Co-Chair	Date (mm/dd/yyyy)
Kathleen M Chard	4/23/14
Kathleen M. Chard, PhD Study Co-Chair	Date (mm/dd/yyyy)
	4/23/14
Josef I. Ruzek, PhD Study Co-Chair	Date (mm/dd/yyyy)