Data Analysis Plan for IIR 14-288-3, An RCT of a Primary Care-Based PTSD Intervention:

Clinician-Supported PTSD Coach

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**Design and Methods Overview**

This study is a two-site, two-arm, parallel RCT. Veterans with PTSD (*N* = 260) will be recruited from VA PC clinics at Syracuse and Palo Alto. Participants will be randomized in equal proportions to receive 1) PC-MHI treatment as usual (PC-MHI TAU) or 2) CS PTSD Coach. Assessments will occur at baseline, 8 (post-treatment), 16, and 24 weeks post-baseline. Primary outcomes will be changes in PTSD severity and engagement in 2 sessions of specialty MH treatment. Thirty CS PTSD Coach participants will also complete a brief qualitative interview at post-treatment to evaluate their satisfaction with care. The study will use cutting-edge methodologies, including an innovative intervention package and objective app usage data to overcome limitations of self-report data.

**Data Collection Methodology.** The table below presents the measures that will be employed at each assessment time point. Baseline assessments will be conducted in person. Research staff will obtain informed consent and HIPAA authorization. Next self-report measures will be administered to assess inclusion criteria. Within one week of baseline (and prior to session 1 of CS PTSD Coach) participants will complete the CAPS-5 by phone with an independent assessor blind to condition. A post-treatment assessment (8 weeks) and two follow-up assessments (16 weeks and 24 weeks) will be conducted following baseline (Table 3). Follow-up assessments will be in person or by phone (based on participant preference) by local study staff, with the exception of the post-treatment CAPS-5, which will be conducted by phone by the independent assessor blind to condition. Several aspects of our assessment procedures, including options to assess by phone and brief assessment batteries, were designed to reduce participant burden and minimize drop-out.

**Table of Measures**

| Measure | Construct | 0 wk | 8 wk | 16 wk | 24 wk |
|---|---|---|---|---|---|
| Blessed Orientation Memory Concentration | Cognitive Impairment | X | | | |
| Demographics & Military Background | Demo & Military Service | X | | | |
| Columbia-SSRS | Suicidal Ideation | X | X | X | X |
| Alcohol Use Identification Test (AUDIT) | Alcohol Use | X | X | X | X |
| Drug Abuse Screening Test (DAST) | Drug Abuse | X | X | X | X |
| Clinician Administered PTSD Scale-5 (CAPS-5) | PTSD (interview) | X | X | | |
| VA Administrative Data | Treatment Engagement | X | | | X |
| Client Satisfaction Questionnaire (CSQ) | Treatment Satisfaction | | X | | |
| Patient Feedback Interviews | Patient Feedback | | X | | |
| Coping Self-Efficacy Scale | Coping Self-Efficacy | X | X | X | X |
| Patient Health Questionnaire-9 (PHQ-9) | Depression | X | X | X | X |
| WHO QOL-BREF | Quality of Life | X | X | X | X |
| PTSD Checklist-Specific-5 (PCL-5) | PTSD (self-report) | X | X | X | X |

**Method of Randomization**

Both sites will have separate randomization schemes to allow simultaneous randomization at each site. Participants will be randomized in equal proportions to conditions. Randomization schemes will be created in a password protected excel files and local study coordinators will be able to access these files to determine the randomization outcome for each participant.

**Data Analysis and Statistical Considerations**

**Power Analysis:** We propose randomizing 130 participants per condition (N = 260). Given this sample size, power was evaluated under a range of assumptions including a 15% loss to follow-up or 110 participants per condition (although under the ITT principle all 130 participants will be included in the analysis). Attrition in our pilot (Possemato, Kuhn, Johnson et al., in press) at 8 weeks was 10%, similar to the 15% rate of a VA multi-site RCT with VA primary care patients. Attrition will be minimized by allowing intervention and follow-up sessions to be by phone and offering flexible scheduling of assessments (e.g., evening/ weekend times). The proposed sample size provides 80% power to detect a meaningful between group effect corresponding to a CAPS-5 difference of 7-15 points (or a Cohen's *d* of 0.4 or greater). These calculations conservatively assume a CAPS-5 SD ranging from 16-20 and a two-sided Wald test conducted with an alpha of .05. The effect size needed to detect a meaningful difference (i.e., *d* = .4) is smaller than what we found in our pilot work (i.e., *d* = .55). Equally important, this sample size provides adequate power to detect a statistical difference between conditions on percentages achieving clinically significant outcomes (i.e., can detect a 20% minimal difference, which is smaller than what our pilot data demonstrated, i.e., a 50% difference).

**Data Analysis:** The main goal of Aim 1 is to determine the effect of CS PTSD Coach on PTSD symptoms. More specifically, we will measure the impact of CS PTSD Coach on change in CAPS-5 score at 8 weeks. Mixed effects linear regression will be used to determine whether the effect of CS PTSD Coach on change in CAPS-5 score at 8 weeks is different from that of the comparison condition (i.e., PC-MHI TAU). As all participants will have a baseline score, they all will be included in the model, adhering to the ITT principle. The mixed effects model will include a subject-specific random effect to account for the correlation of CAPS-5 score within a person over time. Finally, because randomization is stratified by site, site will be included as a fixed effect in our model.

The objective of Aim 2 is to correlate treatment arm with engagement in specialty MH care. We will evaluate the effect of the CS PTSD Coach condition on rate of attendance to at least 2 specialty MH visits post randomization (week 1 to week 24). To evaluate whether rates of attendance differ by condition, we will fit a mixed effects logistic regression model with a subject-specific random effect, an indicator for condition, and indicators for each time point. We are particularly interested in the effect of condition at 24 weeks. The parameter of interest, therefore, is the interaction term that corresponds to rate of treatment attendance at 24 weeks.

Several approaches will be used to evaluate our Exploratory Aims. To explore potential mediators (i.e., amount of app use, improvement in coping self-efficacy), we will fit 2 models for each potential mediator. One will include condition only and the second will include condition and the potential mediator. Change in the coefficient corresponding to condition after inclusion of the mediator may indicate a mechanism of action. To examine possible moderators (e.g., baseline PTSD severity), interaction terms between possible moderators and condition will be assessed. Significant interaction terms will suggest that the effect of intervention varies by

levels of the moderator. Lastly, to evaluate symptom trajectories over time, we will consider a mixed effects model of PCL scores at all time points with indicators for each follow-up visit (at 8, 16, and 24 weeks), randomization group, and an interaction between the indicators for time and condition as represented by the 3 product terms. A test evaluating all 3 product terms will address whether CS PTSD Coach affects the overall trajectory of PCL score. We will also explore if trajectories are moderated by continued PTSD Coach use and receipt of MH treatment. A similar approach proposed to test Aim 1 will be used to determine if CS PTSD Coach has broader effects, beyond PTSD symptom improvement, on depression and quality of life.

Qualitative Analyses: For Aim 3, a team-based approach will be used to analyze the patients' interview data following a qualitative descriptive study approach. The team will engage in a two-stage process for analysis: top-level coding and sub-coding. The team will first review several interview transcripts to identify a provisional list of broad initial top-level codes that reflect key concepts from the interview schedule (e.g., intervention utility/usefulness, strengths, weaknesses). A codebook will be developed that will contain code names, definitions, rules for code assignment, and text exemplars. Following agreement on the initial top-level code definitions, team members will independently begin applying top-level codes to the transcribed interviews. To ensure accuracy and consistency of coding, the full team will meet weekly to discuss findings, resolve inconsistencies, and reach consensus throughout the coding process. We anticipate that top-level codes will be very broad and will develop sub-codes for a more descriptive analysis using an inductive approach to identify emergent concepts. For example, sub-codes for the top-level category "intervention utility" may be "distress management" or "social connectedness". To finalize the analysis, team members will all code to reach consensus on the interpretation of the patterns within and across codes to suggest themes. ATLAS.ti software will be used to manage data and facilitate analysis across multiple coders. Interviewing a random sample of 30 participants in the CS PTSD Coach arm of the trial will provide ample text data to identify themes regarding patient satisfaction and suggestions for future modification to CS PTSD Coach90. Although there will be insufficient provider interviews (n = 4) for a detailed qualitative analysis, the analytic team will collectively review transcripts to search for consistencies in key strengths and weaknesses of the intervention.

**Missing Data:** Based on previous studies with similar samples and study procedures conducted by the PIs, we estimate a 15% attrition rate at post-treatment. We will fully describe all missing data at each time point. In addition we will characterize any patterns of missing data where possible (e.g., we will describe whether those missing a PCL score at any time point are older on average). Our primary analytic approach relies on a flexible assumption that the data are "missing at random" (MAR) or that missingness may be systematically related to observed features only

**Analytic Sets**: In sensitivity analyses, we will assess the robustness of our findings to the MAR assumption by incorporating multiple imputation-based tools into our regression models that assume data are not missing at random as well as alternative models under the missing at random assumption.

**Data Safety Plan**

The PIs will jointly oversee all data and safety monitoring functions to ensure the safety of participants and the validity and integrity of the data obtained in the study. The PIs and project coordinators will meet weekly to track study progress and review these monitoring procedures. The PIs, along with this investigative team, will

regularly oversee all aspects of the study, including participant recruitment, informed consent, data collection, data management and data analysis procedures, as well as regularly assess the risk/benefit ratio associated with participation in the study. On an annual basis the PIs and study staff will provide a report to the Data Safety Monitoring Board (DSMB) that includes data on enrollment, baseline and follow-up clinical data, protocol compliance, data quality, adverse events, and protocol deviations. The DSMB will meet, discuss the report, and give a written report to the PIs, which will be shared with the IRBs. The PIs will also call a special meeting of the DSMB if any patient safety issues arise beyond what is expected in the protocol.

The PIs will train all project staff to recognize and report any adverse events immediately to the site PI. Adverse events involving human subjects include physical injuries, worsened physical or mental health, suicidal ideation, panic attacks, and depression. Other adverse events may also include the inadvertent disclosure by research staff of confidential research information to other persons. The PIs will provide an annual summary report of all adverse events to the IRB as part of the annual review and to the Federal Agency as part of the annual Progress Report. Serious Adverse Events (SAE) may include: deaths, hospitalization, and all life threatening or disabling/incapacitating events among research subjects. SAEs must be reported to the PI immediately and the PI will report them to the relevant IRB within 3 days. If necessary, the event will first be reported to the Federal Agency by telephone followed by a written report within three days.

If the PIs determine that there is sufficient evidence of an adverse event to necessitate suspension of data collection, further IRB review, modification of the protocol or other changes, the PIs will immediately discuss the recommendation with the Chairpersons of the IRBs and reach a determination whether to suspend data collection or to stop the study from proceeding and also consult with the DSMB. Resumption shall be based on the concurrence of the PIs, DSMB, and the Chairpersons of the IRBs. The Federal Agency will receive a written report within three days of any such suspension and/or resumption of data collection.

**Interim Analyses**

On an annual basis the PIs will compile data on enrollment, baseline and follow-up clinical data, protocol compliance, data quality, adverse events, and protocol deviations. These analyses will be conducted as follows. First, for purposes of the annual review summary to the DSMB, simple analyses will be conducted to determine the presence of issues related to recruitment, randomization, biases in attrition, or other operational problems that might affect the integrity of the study.