Study Name: Integrated CBT-I and PE on Sleep and PTSD Outcomes (Impact Study)
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PI: Peter Colvonen

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Power analyses: Sample size was determined to ensure adequate statistical power to detect between group differences in PTSD and sleep at end of treatment and 3-month follow-up. For both outcomes the effect size was estimated as **d** defined as [**d** = | $m_1 - m_2$| / σ] where m_1 and m_2 are change from intake in the outcome scores of the two conditions and σ is the common within-group standard deviation of the change score.[109] The effect size for the between group difference in PTSD CAPS scores from intake to end of treatment was estimated from several studies that have evaluated the effect of PE[110, 111] on PTSD. Four studies of PE have demonstrated large within group effect sizes ranging from 1.3[111] to 4.1[112] with an average ES of 2.5. However, given that both conditions will receive PE, and it is already known that CBTI shows large effects on insomnia (e.g., Ulmer[80] ES = 2.15), we powered on the effect of CBTI on PTSD symptoms.

Three studies reported effect sizes of CBTI on PTSD symptoms with an average ES of 1.8.[79-81] We conservatively used a large effect size (0.8) requiring 34 participants per group to be detected with 90% power and a two-tailed test with alpha at .05. We increased the total sample size to be randomized to N = 90 in anticipation of 25% study drop-out by the 3 month assessment. Overall, we believe this sample size balances three needs: (1) sufficient power to compare the study groups; (2) the reality of recruiting a sample with dual insomnia and PTSD; and (3) project cost considerations.

Missing Data. All laboratory-based measures will be reviewed for completeness immediately following collection and prior to the participant's dismissal. Despite our intensive protocol to limit participant attrition, we do expect missing data over the course of this study (i.e., 25%) and have adjusted our recruiting sample accordingly. The primary outcomes will be tested using an intent-to-treat framework. If the extent of missing data is small and the data appear to be consistent with a missing-at-random model (MAR), then the maximum-likelihood analysis using all randomized cases and the observed data is an appropriate method for handling the missing data. In the MAR model the missingness can be a function of the observed covariates and observed outcomes. The MAR assumption is effective in treatment situations.[113] The critical element when conducting MAR-based analyses is to include variables related to the missingness in the statistical model.[113] Potential variables we will measure that may be related to study drop out are group assignment, social *interactions*, employment status, and income. As a check on the sensitivity of our conclusions to the assumption that the missing data are MAR we will conduct pattern-mixture modeling, which is appropriate with data that is likely MAR.[87] The distinction between ignorable (MAR) and non-ignorable missingness (missing not at random; MNAR) is generally not empirically testable and we acknowledge the possibility that data may be missing not at random. Therefore, we propose to perform MNAR sensitivity analyses using pattern mixture models. With 2 follow-up assessment points there are 4 potential missing data patterns that can emerge. Some patterns will likely have small numbers of cases precluding parameter estimation for these patterns separately. In this case we will apply the Hedeker and Gibbons[87] approach that combines missing data patterns to estimates model parameters that are conditional on the missingness using a binary variable in the model to denote missing data at one or more time points.

Data Analysis. Preliminary analyses will consist of examining the descriptive statistics of the study sample. Outliers will be assessed and variables whose distributions depart significantly from normality will be transformed. Internal consistency of scales will be examined to determine reliability. *All analyses will be run with the full, validated PTSD scales (e.g., CAPS and PCL5) and with sleep items removed from the PTSD scales.*

Primary Aim 1 (Treatment outcomes): Investigate the efficacy of CBTI-PE on PTSD, sleep, and quality of life among Veterans with co-occurring PTSD and insomnia.

Hypothesis Aim 1: Veterans who receive CBTI-PE, compared to Hygiene-PE, will demonstrate lower PTSD symptoms, better sleep efficiency, and better quality of life at follow-up.

Independent variables: Treatment group (CBTI-PE versus Hygiene-PE) and Time (Baseline 0 weeks, Post-treatment 14 weeks, Follow-up 28 weeks).

Dependent variables (three separate models): CAPS-5 scores, Sleep Diary Sleep Efficiency, WHOQOL-BREF.

Covariates: *gender, age, medications, pain, depression.*

Analyses Aim 1: Analyses of this data will be conducted using three separate Random Regression Models, a generalized linear model described by Gibbons et al.[86], Hedeker et al.[114], and Laird et al.[115] The random effects method has several advantages over more traditional analytic approaches such as a change score, end-point, or repeated measures ANOVA. This method allows the inclusion of subjects with missing data or those who were terminated early in the study, without relying on data imputation procedures. This method provides an

estimate of the individual variability around the population trend, the variability of the individual intercepts (baseline values) and slopes (changes across time), and the correlation between them. The model will include a random intercept, a random effect for assessment time, and fixed effects for comparison groups and group-by-time interaction. A fully saturated treatment by time model will be utilized for inference. Co-variance structure will be chosen based on Akaike's Information Criterion (AIC) and *compared to each other using a chi-square test*. Random group level treatment effects will also be evaluated for importance based on the model AIC. This allows for any group level effects to be incorporated into the model. Data will be analyzed from all randomized subjects using all available data collected at baseline, post-treatment, and at follow-up. The models *will* be expanded to determine an adjusted intervention difference by including additional covariates such as *gender, age, medications, pain, and depression.* A chi-square test will compare attrition rates between groups.

Secondary Aim 2: Examine the effects of sleep efficiency on PTSD outcomes at post-treatment.

Hypothesis Aim 2: *All Veteran's CAPS-5 scores will decrease from pre- to post-treatment.* However, Veterans who demonstrate larger increases in sleep efficiency will exhibit lower PTSD symptoms at the end of treatment compared to Veteran's with lower sleep efficiency.

Independent variables: Sleep Efficiency (sleep diary) at week 6, *Pre-treatment CAPS-5 scores*

Dependent variables: CAPS-5 scores at post-treatment.

Covariates: *age, gender, medications, pain, depression.*

Analyses Aim 2: A multivariate regression equation will be used to statistically test this hypothesis. Regression *analyses* will be *used to* examining *the relationship between* SE *at week 6* on follow-up CAPS-5 scores *controlling for pre*-treatment *CAPS-5 scores*. *A significant finding for SE will indicate that Veterans who are sleeping more efficiently at week 6 of treatment has an additive influence on the effectiveness of PE.*

Secondary Aim 3 (Moderator): *Determine the extent to which SE and changes in PTSD symptoms relate to global quality of life outcomes.*

Hypothesis 3: *There will be an interaction effect of SE at post-treatment and changes in PTSD symptoms from pre- to post- treatment predicting quality of life outcomes.*

Independent variables: Sleep Efficiency (sleep diary) *at post-treatment*, *change in CAPS-5 scores from Pre- to Post-treatment, interaction of SE and change in CAPS-5 scores.*

Dependent variables: *WHOQOL-BREF at follow-up.*

Covariates: *age, gender, medications, pain, depression.*

Analyses Aim 3: *A multivariate regression equation will be used to statistically test this hypothesis. Four Regression analyses will be run examining the effects of SE and changes CAPS-5 scores from pre- to post-treatment on quality of life outcomes. The first two regressions will examine SE and changes CAPS-5 scores independently to predict qualify of life outcomes. We expect that both SE and changes in CAPS-5 scores will generalize to quality of life as indicated by significant p values. The third regression will analyze both SE and CAPS-5 scores in the same regression model to examine the influence of sleep and PTSD symptoms together on quality of life. The final regression analysis will examine SE, changes in PTSD symptoms, and the interaction of SE and changes in PTSD symptoms on quality of life outcomes. We expect that Veterans with efficient sleep and larger decreases in PTSD symptoms will have higher quality of life at follow-up.*