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# Maximizing the utility of a single site randomized controlled psychotherapy trial

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ABSTRACT

Purpose of the research: There is increasing interest in including measures of biological mechanisms as mediators and moderators of treatment outcome in randomized controlled trials (RCT's) of psychotherapy efficacy. However, examining biological mechanisms is often expensive and budget caps of most major funding agencies have remained stable in recent years. The goal of this manuscript is to describe how a psychotherapy efficacy trial is using a model of collaborative, affiliated grants to maximize resources and the potential knowledge to be gained from a single site RCT.
Principal results and conclusions: The trial is an ongoing RCT comparing two psychotherapies for the treatment of concurrent posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) with a sample of treatment seeking veterans. Through collaboration with a team of investigators with independently-funded but affiliated grants, measures of select sleep, neurobiological, and genetic biomarkers were integrated into this single site RCT. This model has allowed us to pose research questions regarding the role of biological mechanisms, maximize the utility of recruitment, and be efficient in maximizing knowledge to be gained in a way that would not be possible solely on the funding of a single site RCT. Challenges of this model include high participant burden in regard to assessment and complicated coordinating procedures among studies. Strategies to address these challenges are described.

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## 1. Introduction

In a 2007 article, Schnurr [1] highlighted many challenges to designing and executing psychotherapy treatment studies that inform the efficacy and/or effectiveness of specific psychotherapies in the field of traumatic stress. The author offered suggestions for designing studies that maximize the validity of inferences that can be drawn from the findings. In recent years, additional challenges to conducting psychotherapy research have emerged. Many studies with traumatized populations have difficulty meeting recruitment targets and demonstrate low treatment and study completion rates [2–4]. Budget maximums for randomized controlled trials (RCTs) funded through common sources such as the National Institutes of

*Abbreviations:* RCT, randomized controlled trial; fMRI, functional magnetic resonance imagining; PTSD, posttraumatic stress disorder; AUD, alcohol use disorder; COPE, Concurrent Treatment of PTSD and Substance Use Disorders using Prolonged Exposure; SS, Seeking Safety; VASDHS, Veteran Affairs San Diego Healthcare System; SAMI, substance use disorder and mental illness; PSG, polysomnography; REM, rapid eye movement; COMT, Catechol-o-methyl-transferase; CDA, VA Career Development Award; PI, principal investigator; CAPS, Clinician Administered PTSD Scale; IRB, Institutional Review Board; PE, prolonged exposure.

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Health or the Department of Veterans Affairs have remained stable in recent years, yet there is increasing importance placed on examining biomarkers of treatment outcomes in addition to treatment efficacy [5]. The methods for examining mechanisms, such as collecting, storing, and analyzing biological samples or conducting functional magnetic resonance imagining (fMRI), are costly and may not be feasible on a RCT budget. An additional challenge is that many clinical trials researchers are not versed in biomarker research and vice versa. Finally, a smaller percent of research proposals are getting funded relative to previous years, raising questions about how to optimize the likelihood of getting well designed studies that will inform psychotherapy efficacy and effectiveness funded.

The goal of this paper is to describe how a psychotherapy efficacy trial is using a model of collaborative, affiliated grants to maximize resources and the potential knowledge to be gained from a single site RCT. The trial is an ongoing RCT comparing two psychotherapies for the treatment of concurrent posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD). The study compares the efficacy of an integrated exposure based therapy (Concurrent Treatment of PTSD and Substance Use Disorders using Prolonged Exposure; COPE [6]) to a present-focused coping skills therapy (Seeking Safety, SS [7]) with a sample of treatment seeking veterans. Through collaboration with a team of investigators with independently-funded but affiliated grants, measures of select sleep, neurobiological, and genetic biomarkers were integrated into this single site RCT of psychotherapy for PTSD/AUD. In this manuscript, we describe our methodology to maximize recruitment and retention, funding, and the potential knowledge to be gained from a single site RCT. Where applicable, we note specific challenges and strategies we have taken to address these challenges.

## 2. Design and method

### 2.1. Overview of study design and aims

The primary study presented as an example herein takes place within the Veteran Affairs San Diego Healthcare System (VASDHS) within an outpatient program that treats concurrent substance use disorder and mental illness (SAMI). The RCT is projected to enroll 148 participants over five years who are randomized to one of the two treatment conditions. The primary aim is to assess differences in PTSD symptoms and alcohol use (abstinence and drinking reduction) across the two treatment conditions at the end of therapy and at 3- and 6-months post-treatment completion. Participants who are eligible for this RCT may also opt to participate in affiliated sleep, neuroimaging, and genetic studies if they are eligible. The overarching goal of these affiliated studies is to examine specific biomarkers as mediators and/or moderators of treatment outcome. The sleep study involves polysomnography (PSG) pre- and post-treatment. This pilot study aims to recruit up to 16 participants per year. The neuroimaging study involves having an fMRI scan at pre- (projected $n = 114$) and post-treatment (projected $n = 76$). The genetic study involves providing a saliva sample (projected $n = 115$).

#### 2.1.1. Challenge — designing an RCT that evaluates both treatment efficacy and biological markers related to treatment outcome

One challenge of integrating an efficacy trial with investigations of biological mechanisms related to treatment outcome is designing studies that ask questions that are timely and relevant to both areas of study. In our case, the efficacy RCT was proposed and funded first. The overarching goal of the RCT is advancing the knowledge base that informs treatment for comorbid PTSD/AUD. Partnering investigators who specialized in the study of specific biomarkers developed their hypotheses in one of two ways, either 1) the design and research question were developed in light of the design of the primary RCT which had already been determined (i.e., What interesting question can we answer about sleep in tandem with this RCT?), or 2) partnering investigators already had a question in mind (i.e., Do humans with a certain gene show reduced response to exposure therapy?) and found that it was possible to integrate with the RCT to address the question more efficiently than running a standalone study.

Partnering investigators developed the following aims/hypotheses that could be evaluated within the design of the primary RCT. Specifically:

1. *Sleep disruption as a mediator of treatment outcomes*. Lower Sleep Efficiency, as well as increased percent rapid eye movement (REM) sleep, is expected to be associated with greater risk of relapse in both conditions. Greater night-to-night variability in Sleep Efficiency and increased REM Fragmentation will be associated with worse PTSD outcomes in the exposure condition.
2. *Neural substrates of aversive anticipation and alcohol cue reactivity as predictors and mediators of treatment outcomes*. Greater baseline brain response in limbic regions and less ventral prefrontal cortex response during anticipation of unpleasant images, and greater brain response in the pregenual anterior cingulate cortex, striatum, and amygdala during visual alcohol cue presentation is expected to predict worse treatment outcomes in both conditions. Relative to those subjects randomized to the coping skills therapy condition (Seeking Safety), exposure psychotherapy (COPE) recipients are expected to show greater increases in the functional connectivity between the bottom-up neurocircuitry of aversive anticipation (i.e., insula, amygdala) and alcohol-related cue reactivity (i.e., pgACC, striatum, amygdala) with top down regulatory regions (i.e., ventral anterior prefrontal cortex and dorsolateral prefrontal cortex.
3. *Catechol-o-methyl-transferase (COMT) as a moderator of treatment outcome*. Subjects carrying the methionine allele of the COMTval158met polymorphism are expected to show reduced response to the exposure treatment arm compared to valine carriers. Integrating with the RCT enabled the team to examine COMT genotype association with exposure vs. a non-exposure based therapy, providing a critical control in determining if COMT genotype is associated simply with poor treatment response overall or is specific to a certain kind of treatment.

The primary RCT (VA Merit Award to Sonya Norman) was funded in October, 2012. The sleep study was written into the primary RCT proposal as an exploratory aim with a commitment from the VA Center of Excellence for Stress and Mental