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Maximizing the Utility of a Single Site Randomized Controlled Psychotherapy Trial

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Abstract

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. 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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Keywords

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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, 3, 4] Budget maximums for randomized controlled trials (RCTs) funded through common sources such as the National Institutes of 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.

Design and Method

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 $n = 115$).

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 Health to fund PSG (laboratory and technician time) for a portion of participants (funding to Sean Drummond and Sonya Norman). The sleep hypotheses were developed to fit within the design of the RCT and answer questions that would inform the role of sleep for the specific treatments that were to be evaluated in the RCT. The imaging (VA Career Development Award [CDA] to Andrea Spadoni Townsend) and genetics (VA Merit Award to Victoria Risbrough) proposals were submitted once the primary RCT was funded. Both investigators were planning proposals to address questions regarding the role of specific biomarkers of interest in exposure therapy for PTSD. Once we received notification that the primary RCT would be funded, the investigators decided it would be a more efficient use of time and resources to integrate with the RCT rather than to run independent studies.

Several adjustments had to be made to the research questions and methodology in order fit within the design of the RCT. For example, Spadoni developed hypotheses specifically in regard to coping skills therapy in addition to exposure therapy because that was one of the treatment conditions in the RCT. Spadoni's proposal specified how her study would be integrated with the primary RCT such that all qualifying participants in the RCT would be offered the ability to take part in fMRI pre- and post-psychotherapy, that measurement data would be shared where reasonable (e.g., diagnostic interviews), and that the teams would meet weekly to coordinate flow between the two studies. Risbrough detailed in her proposal that she would collect a saliva sample from participants in the funded RCT in order to test her aims regarding a genetic biomarker of exposure therapy outcome.

Challenge – developing collaborations—The principal investigators (PI's) were all faculty in the Center of Excellence for Stress and Mental Health (CESAMH) and faculty in the University of California San Diego psychiatry department. Both of these environments encourage collaboration among faculty. CESAMH has regular meetings where investigators share research ideas and brainstorm collaborations. The ideas for the collaborations described here emerged from these meetings or individual meetings among the investigators, some of whom have a history of collaboration on previous grants. For example, Dr. Spadoni invited Dr. Norman to be a mentor on her CDA and the idea to link studies emerged during a planning meeting for the CDA proposal.

The investigators agreed that the RCT would run as planned and that the PI's of the affiliated studies would be primarily responsible for their respective studies. A primary concern in early meetings was whether the collaborations would add to participant burden and make participation in the RCT less attractive. It was felt that making participation in the affiliated studies optional rather than required to participate in the RCT would allay these concerns.

In regard to authorship, each PI is responsible for publishing the results of their study aims and will be primary and/or corresponding author on the resulting publications. The RCT PI will collaborate with other PI's on publications. Other PI's may also collaborate with each other on publications that examine multiple biomarkers.

Challenge – different start dates among affiliated studies—A challenge of having the neuroimaging and genetics study proposals submitted and funded after the primary RCT was set to be funded was that both studies missed the opportunity to recruit some of the early participants from the RCT. The neuroimaging study was funded in October 2013 and began recruitment in March 2014. The study was powered to recruit a smaller sample than the primary RCT ($n = 114$) with consideration that some participants would be missed and some would qualify for the RCT but not for the neuroimaging study.

The genetics study was funded and data collection began in October 2014. Of note, Risbrough and Norman began working on Institutional Review Board (IRB) approval about 5 months prior (once notification that the genetics study would be funded was received) but, because of the complexity of linking the two proposals, did not receive IRB permission to link the studies and procedures until the start of the funding period. For the genetics study, participants who were previously consented are being re-consented so that a saliva sample may be collected.

In an effort to make the timing of linking grants work when the primary RCT was already funded while other grants were not yet funded, the PI's of the fMRI and genetics proposals stressed in their proposals that timely funding was critical because the RCT was already underway, however, we cannot say with certainty that stressing this helped secure their funding. We did not make program officers aware of our efforts to link grants in advance, although we would do so in the future.

Inclusion/Exclusion Criteria

For the primary RCT and all affiliated studies, veterans (both male and female) who are obtaining care at the VASDHS are eligible for study participation. Veterans from all eras of service and with any type of past trauma are eligible. Broadly, eligible participants are victims of psychological trauma in childhood or adulthood who meet DSM-5 criteria for current AUD and PTSD with at least 20 days of alcohol use in the last 90 days. Exclusion criteria include moderate or severe cognitive impairment, acute suicidality and unmanaged current psychosis or mania independent of substance use.

Challenge – affiliated studies may have additional inclusion/exclusion criteria —The associated studies have additional inclusion/exclusion criteria for participation that do not effect eligibility for the primary RCT. Exclusion criteria for the PSG study include

the presence of obstructive sleep apnea, periodic limb movements, or abnormal sleep/wake schedule (i.e., working night shift). Additional exclusion criteria for the fMRI study include the use of benzodiazepines and the presence of ferromagnetic metal in the body. There are no additional exclusions for the genetics study. Participants are screened for the additional inclusion and exclusions for the affiliated studies at the time they are screened for the primary RCT by the RCT study coordinator. Those who are not excluded based on screening criteria are invited to participate in the affiliated studies with an explanation that their decision to participate or not will not affect their ability to participate in the RCT.

Recruitment

High variability in treatment dropout is a concern for PTSD treatment studies [3, 4], particularly for populations with co-occurring substance use disorders [2]. A recent Cochrane review [2] highlighted that PTSD/AUD treatment research has been limited by challenges in recruiting and retaining participants in treatment and in research trials. The primary RCT is charged with recruitment for the trial. Recruitment methods include flyers and brochures posted throughout the VASDHS, as well as referrals from providers in VA mental health clinics and primary care clinics. In an effort to improve recruitment and retention, the study is housed within a clinical program and research staff and therapists are integrated into the treatment team. Specifically, the study operates within the SAMI clinic which provides specialty mental health services within the VASDHS. The research study is offered by clinic staff to all Veterans who are referred to the clinic who screen positive for PTSD and have an alcohol use disorder. The study is integrated such that the study coordinator and study therapists attend weekly SAMI team meetings. Ryan Trim, a co-investigator on the study, directs the SAMI clinic and supervises the therapists together with Principal Investigator, Sonya Norman. Therapists and study staff do not disclose treatment condition to other providers and notes are written such that treatment condition is not disclosed until the end of study participation. Participants have access to psychiatric care and case management through SAMI. Thus, the study team is part of the treatment team and participants do not need to give up the care of a treatment team to participate in the research.

Study Procedures

Challenge: coordinating procedures for multiple studies—Several challenges have emerged in coordinating the primary RCT along with the other three studies, some of which have procedures that must be completed before therapy is initiated. The following procedures are in place to facilitate flow among studies. After a brief telephone screen to evaluate basic eligibility criteria (i.e., presence of PTSD symptoms and current alcohol use), potential participants meet with the project coordinator where they complete a consent to be screened and initial screening. At this session, participants also answer questions to assess eligibility for the adjunct PSG and functional neuroimaging (fMRI) studies (e.g., participants are asked about the presence of irremovable metal in their bodies). Following screening, the project coordinator discusses participants' eligibility with the Principal Investigator (Sonya Norman), as well as other relevant PI's when questions arise about eligibility for the additional studies. Participants who do not meet study criteria or who decline participation are referred to other VA mental health services as appropriate.

Participants who meet initial screening criteria are contacted and scheduled to meet with the project coordinator to provide informed consent for participation in the RCT. The project coordinator reviews with potential participants a single consent form that has options to participate in the primary treatment study, as well as the adjunct PSG and genetic studies. Participants check a box to indicate whether they would like to participate in the PSG portion of the study. If they check yes and they meet inclusion for the PSG, they are eligible to take part in the PSG. For the genetics study, participants are asked to consent/decline to providing a saliva DNA sample, as well as to consent/decline to have their sample and data (without personal identifiers) banked for future studies. Participants have the option to consent to either, both, or neither of these options. For the neuroimaging study, participants provide consent to be screened at this session. Participants who express interest and appear eligible are scheduled to meet with a separate project coordinator for informed consent and the pre-treatment fMRI. Whether participants decide to take part or qualify for the affiliated studies does not affect eligibility for the primary treatment study.

The study coordinator reviews the consent form and other required forms with the potential participant, explains the primary RCT and each optional study, and answers questions. Finally, participants complete a consent quiz which consists of seven open ended questions asking about key features of the study (e.g., “do you remember how it will be determined which treatment you get?”). This is to ensure that participants understand what they are consenting to and are truly providing informed consent. This consenting process generally takes 60–90 minutes.

Following informed consent, participants meet with a trained research assistant to complete a battery of measures including a self-report battery, the Clinician Administered PTSD Scale (CAPS; [8]) for DSM-5 to confirm PTSD diagnosis and assessment of DSM-5 criteria for AUD (using the Structured Clinical Interview for the DSM-IV-TR [9]with additional items for DSM-5 criteria including the Penn Alcohol Craving Scale [10]to capture cravings) and the Time-line Followback Procedure [11] to confirm at least 20 days of heavy alcohol use in the past 90 days. Eligible participants meet with a study therapist (not necessarily the one that will be assigned to them) to ask any questions they may have about psychotherapy and talk through pros and cons of participating in psychotherapy. Participants who meet criteria and decide to proceed are then randomized (stratified by gender) to COPE or SS. Participants are also assigned an actigraph watch and asked to wear it and complete a sleep diary for the next seven days.

Participants who consent to the PSG and/or fMRI are scheduled for the respective pre-treatment assessment prior to beginning therapy. The RCT study coordinator works with the PSG lab technician to schedule the participant for the sleep lab and communicates with the participants about the procedure. Once the participant arrives at the sleep lab on the first evening of the assessment, the sleep technician works with the participants to complete brief measures (e.g., a breathalyzer) and complete the procedure. For fMRI, once the participant consents to be contacted, the RCT coordinator passes on the information to the fMRI study coordinator who contacts the participant, conducts further screening, and schedules the fMRI. The fMRI coordinator is also present at the fMRI scan. Participants who consent to the genetics study are asked to provide a saliva sample. A research associate

from the genetics lab is contacted and informed that a participant is ready to have the sample collected. The research associate then checks a secure shared calendar that has the time each participant will be assessed and comes during the assessment to collect the sample. Procedures are in place so that the clinical interviews are not interrupted but rather the sample is collected prior to beginning the assessment.

Once randomized, participants engage in 12 to 16 sessions of psychotherapy. The average length of time from the screening session to the first treatment session is about two weeks. Following treatment, participants are scheduled for a post-treatment assessment, then the 3- and 6-month post-treatment follow-up assessments. Participants in the PSG and/or neuroimaging studies are scheduled for their respective post-treatment assessments upon completion of psychotherapy. Two weeks before participants complete therapy, the therapist notifies the appropriate research coordinators so that post-treatment assessment, PSG, and neuroimaging can be scheduled at treatment completion.

Dr. Norman holds a weekly meeting for the RCT that other investigators attend as needed to make necessary decisions or accomplish specific tasks. The RCT, fMRI, and genetics studies each have their own coordinator; however, the RCT's coordinator conducts initial screening for all of the studies and oversees coordination in regard to navigating participants across the different studies. The RCT proposal specified that the study coordinator would oversee the sleep portion of the study as well (since this is a pilot study written into the RCT proposal). Even though the RCT coordinator conducts initial screening for the fMRI study, the fMRI study does not pay for any portion of the RCT coordinator's time. Dr. Norman is a mentor to Dr. Spadoni on her fMRI study and it was written into the proposal that Dr. Norman would share resources of her lab necessary to accomplish the award (as is common for mentors to do for training awards). The genetics study pays about 15% of the coordinator's time.

Payment for assessments for the primary RCT and for the PSG come from the budget of the primary RCT. The fMRI study pays participants separately when they complete each fMRI. Payment for the saliva sample comes from the genetics study budget but is paid by the RCT coordinator in tandem with payment for the assessment that generally happens at the same visit.

Challenge: minimizing participant burden with participation in multiple studies—The study teams make it very clear to participants that taking part in any of the affiliated studies is optional; they can take part in none, some, or all of them and still take part in the RCT. In addition, they can choose to discontinue participation in an affiliated study, but still continue in the RCT. Thus, participants can choose to take part in just the treatment study or in additional studies (if they qualify). Because the study is still in progress, we do not yet know if participation in multiple studies affected adherence or drop-out. We made participation in affiliated studies optional to minimize the likelihood that it would. One barrier we have found is that many participants are in recovery homes or other sober living environments where the rules do not allow them to spend nights in a sleep lab or leave in the weekend to take part in the fMRI. This has been a common barrier to taking part in the affiliated studies.

In an effort to reduce the burden for participants taking part in affiliated studies, data from relevant measures collected as part of the RCT are shared across studies so that participants do not have to repeat shared measures such as the CAPS and the TLFB within a matter of days.

We examined rates of enrollment in affiliated studies among the first eleven RCT participants to whom we were able to offer participation in all three affiliated studies (once all studies were funded and IRB approval was in place). Table 1 shows that the vast majority of participants (81–91%) expressed interest in all three affiliated studies (as evidenced by signing the consent or screening form) and 100% of those who qualified in each additional study completed the baseline requirements of that study. Among all 11 participants, 27% (n = 3) completed all three studies and 45% (n=5) completed two of the three studies.

Assessment

Participants who agree to participate in all studies complete a battery of self-report and interview measures, spend two nights in a sleep lab, wear an actigraph watch and keep a sleep diary for a week, have an fMRI prior to beginning therapy, and provide a DNA sample. Measures for the RCT are administered by a trained research assistant who is blind to participants' treatment condition. In addition, self-report measures of PTSD symptoms, substance use and cravings, depression, and treatment satisfaction are administered every other session throughout treatment.

Measures for the affiliated studies are described below.

Sleep measures.—Veterans who who participate in the PSG study spend two consecutive nights in the sleep lab pre- and post-treatment. The first night is used to acclimate participants to the sleep laboratory environment and to screen for obstructive sleep apnea or periodic limb movements. The second PSG night is used to characterize participants' sleep.

Neuroimaging.—Veterans who consent and are safe for fMRI participate in two fMRI sessions, one prior to therapy and one following therapy completion. During the scan subjects complete an alcohol-cue reactivity task [12] and an aversive anticipation task [13] to characterize the neural substrates of alcohol cue reactivity and anticipation of a fear-conditioned stimulus.

Genetic measures.—Participants who consent to the genetic portion of the study provide a saliva sample for DNA testing. We will extract DNA and identify genotypes for the COMTval158met polymorphism as well as for genetic markers of ancestry. DNA will also be banked for future testing of samples if repository consent was provided.

Treatment

Participants are randomized to one of two psychotherapies which were selected based on the aims of the primary study, to compare the two most prominent integrated (i.e., addressing both PTSD and AUD) models of psychotherapy for co-occurring PTSD and AUD. COPE [6] is an integrated PTSD and SUD treatment that augments prolonged exposure therapy (PE), a frontline evidence based treatment for PTSD [14], with cognitive behavioral therapy

techniques used to treat AUD/SUDs and prevent relapse. SS [7] is a present-focused integrated therapy that centers around the idea that establishing safety is often one of the most important clinical needs of patients struggling with both PTSD and substance use. Exposure is not included in this therapy.

Both psychotherapies take place in 90 minute, individual sessions once or twice weekly (based on participants' preferences). Both interventions include 16 sessions with the option of ending after 12 sessions if participants have met their treatment goals. Participants are strongly encouraged to attend sessions at least once per week but are given up to six months to complete therapy if needed. Therapist training, ongoing supervision, and fidelity monitoring occur within the scope and funding of the primary study.

Participants are asked not to take part in other PTSD treatment but can take part in other substance use interventions such as Alcoholics Anonymous. Medications are prescribed by psychiatrists in the SAMI clinic in an open-label format. Standard VA pharmacology protocol for treatment of PTSD is used with dosage determined by the psychiatrist and altered as appropriate to meet the patient's needs. The VA uses treatment guidelines that require standardized patterns of prescription for individuals with PTSD and suggests SSRIs as the preferred treatment. Based on these guidelines, we believe that this pattern of prescribing will be comparable across treatment groups. To ensure that we are adequately accounting for medication, we collect self-report information and receive permission from participants to track their medications in their medical record. We considered restricting recruitment to participants who were not on medication or requiring participants to be medication stable prior to study entry. However, withholding medication would be inappropriate for this high-risk population.

Statistical Methods

Power.—Power was initially determined based on the parent RCT. The RCT's target sample size (N= 148) was determined to ensure adequate statistical power to detect between group differences in PTSD symptoms and percentage days abstinent from alcohol (PDA) at end of treatment and follow-ups. Sample size was based on the outcome of alcohol PDA at follow-up, as between group effect sizes for PDA were expected to be smaller than for PTSD symptoms. The estimated between group effect size for PDA at 12-months after treatment for veterans without PTSD was calculated to be $d = .58$. This effect size requires 48 participants per group to be detected with 80% power and a two-tailed test with alpha at .05. We increased the total sample size to N = 148 in anticipation of 35% study drop-out by the third post-treatment assessment.

The PSG study is exploratory and thus a power analysis was not conducted. The fMRI and genetics studies conducted independent power analyses based on their hypotheses and will be able to test their aims with the number of participants anticipated in the primary RCT.

For the fMRI study, we aim to recruit approximately 57 participants in each therapy condition. Attrition is estimated at 35%, thus a follow-up sample size of n=38 is projected for each group. Published data from Mills and colleagues [15] indicates an effect size of.96 for integrated exposure based therapy versus the community setting therapy on CAPS

scores obtained at the 9 month follow-up visit. The projected measurable brain effect size of treatment is less than half that of the measurable behavioral effect size (0.48). In a multiple regression where all three PTSD symptom clusters were entered separately, an alpha of 0.05 and power of 0.9 was achieved with the inclusion of 34 AUD/PTSD participants. Published data from Coffey and colleagues [16] examining treatment effects of exposure based therapy against imagery based relaxation, indicated an effect size of .85 on self-reported craving ratings. The projected measurable brain effect size of treatment in this case would be .425, and an alpha of 0.05 and power of 0.9 with 3 predictors can be achieved with the inclusion of 38 AUD/PTSD participants. These power calculations were performed by using routines provided online. [17,18]

For the genetics study, it is projected that out of the 75 subjects in each treatment arm, at least 25% will be homozygous for Met/Met (based on CEU-HapMap Population [19]) given the expected ethnicity profiles in the San Diego Veteran Population (>70% Caucasian ancestry). It is also likely, given the higher prevalence of Met/Met carriers in PTSD positive groups, that there will be more than 25%. [20,21,22] Thus, we projected an N of 19–20 Met/Met and 56 total Val carriers (Val/Met or Val/Val). Using Gpower, we calculated that a total N of 75 will give us 0.9 power to detect a small-moderate effect size (f = 0.4) using a 2 way repeated measures ANOVA (gene with 2 levels and time with 4 levels). It is important to distinguish that although we may not be well powered to detect small effect sizes, this study is powered adequately to detect an effect size with clinical utility (i.e. an effect size supporting further research of the clinical applicability of Val158Met to predict treatment response).

Discussion and Conclusions

This manuscript describes a core efficacy study combined with associated sub studies using a model of independently funded grants affiliated with a parent 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. The primary RCT compares an integrated trauma processing psychotherapy to an integrated present-focused coping skills psychotherapy for the treatment of concurrent PTSD and AUD in a Veteran sample. Although trauma-focused and present-focused treatments have been the most studied and best disseminated modalities for treating PTSD/AUD, this study is the first RCT directly comparing the two approaches. The study will provide information about both relative efficacy and about which patient may do best in which condition.

Examining several biological mechanisms in tandem with the RCT will further help inform how to best treat PTSD/AUD. Sleep is disrupted in both AUD [23] and PTSD. [24,25,26] Moreover, sleep disturbances, particularly insomnia, have been shown to exacerbate symptoms in PTSD [26], predict relapse in AUD [23,27], and play a potentially mechanistic role in PTSD treatment response. [28] This is the first study to examine whether sleep can predict treatment response and/or relapse in a PTSD/AUD sample. Depending on the exact pattern of findings, implications may highlight the importance of sleep treatment prior to, or in conjunction with, treating PTSD/AUD. FMRI will allow us to study patterns of

brain activation during symptom provocation which may help to define the mechanisms of treatment modality, pathophysiology of PTSD/AUD comorbidity [29,30], provide treatment targets [31,32], and predict response to empirical interventions [33,34]. This study is the largest neuroimaging study of comorbid PTSD/AUD and the first translational study to examine whether patterns of brain activation can predict differences in treatment response in individuals with PTSD/AUD.

One of the most promising clinical applications of genetics is in personalized medicine, using patient genotypes to develop a targeted treatment approach. This approach is now commonly used in cancer treatment as well as other diseases. This field is in its infancy in mental health. The COMT gene is associated with PTSD risk [35,36,37] and is associated with reduced response to exposure therapy in panic disorder patients [38,39]. This is the first study to examine COMTval158met polymorphism in the response to PTSD treatment. The ability to compare genotype effects across an exposure and non-exposure based therapy will allow clear interpretation of COMT genotype effects on response to exposure therapy specifically. Data from the first 11 RCT participants to whom we were able to offer all three affiliated studies suggest that the vast majority of participants were interested in participating in multiple studies and followed through on this interest when they qualified for the affiliated studies.

Several strengths and challenges of our collaborative approach have emerged. Among notable strengths is the potential maximization of the knowledge to be gained from a single site RCT. Recruitment and retention can be a challenge for any psychotherapy RCT where participation involves numerous treatment and assessment visits over many months. Difficulty in recruiting and retaining individuals with PTSD/AUD in particular has limited our knowledge of how to treat this comorbidity.[2] Collaborative, affiliated grants allow for the maximization of knowledge to be gained from participants who are recruited into the RCT. In this regard, it is also an efficient model in that one treatment study will help shed light onto the potential role of several biomarkers of treatment outcomes. The model of collaborative, affiliated grants also maximizes resources for a single site RCT. For example, the genetics study pays for a portion of the RCT coordinator’s time since she consents and coordinates saliva collection. The savings on coordinator time has allowed the primary RCT to pay for more therapist time, which benefits the primary and affiliated studies. Assessments are also efficient. Participants complete one set of interviews at all time-points and the data is shared among studies. The affiliated studies may have small batteries of additional measures but there is no redundancy. The model also allows for multiple publications from investigators with different areas of expertise (e.g., neurobiological, genetic, etc). Many studies bring together teams of collaborators with complementary areas of expertise. This model allows for multiple principal investigators with their own funding. Also, the data resulting from this study will be more comprehensive than that of many RCT’s and can potentially be used to answer questions about the interaction of multiple biomarkers in regard to treatment outcome.

There are also challenges to this model of collaborative, affiliated grants. For participants, the consenting procedures are long (often over an hour), and participant fatigue is a concern. In addition to the usual consenting process, it is critical to ensure participants understand

that the affiliated studies are optional. The burden on participants who choose to take part in multiple studies is high. For investigators, linking multiple human subjects protocols has proven to be time consuming for multiple principal investigators and coordinators. For example, it took five months to get IRB approval to link the primary RCT and the genetics study. Multiple research teams must coordinate with each other through emails, meetings, and use of shared calendars. There is a lag in funding between the primary RCT and the affiliated grants which affects the number of participants than can be recruited into the affiliated grants and, of course, there is no guarantee that the affiliated grants will be funded. It is possible that linking a well-designed study to an already funded RCT may help the affiliated proposal secure funding, but whether that is true is not known at this time and may vary by funding source. The timing requirements of affiliated biomarker sampling will also affect feasibility of affiliated grants, genetics testing is the most flexible, allowing for re-consenting for already enrolled subjects. Procuring funding for other types of biomarkers that require sampling at specific stages in the treatment process likely can only occur in parallel with the parent RCT to be feasible to maximize recruitment. Although all efforts are being made to conduct the studies with best practices for running RCT's [1], if there were to be a bias in the data it would affect multiple studies.

One notable feature of this study has been to integrate the research into a treatment program for SUD and other co-occurring mental health conditions. The goal of doing so is to help recruit and retain of a very challenging population [2] into the RCT and affiliated studies. Thus, the study is grounded in a treatment program where the patients are encouraged by their psychiatrist and case manager to attend their psychotherapy sessions. The patients do not have to forfeit the benefits of receiving care within a treatment team in order to take part in the research. Providers also do not need to "send their patients away to research" but rather perceive the research team to be part of the treatment program. We are evaluating whether integrating the research into a treatment program helps with successful recruitment and retention relative to other PTSD/AUD treatment studies.

The goal of the primary RCT as well as the affiliated studies is to advance our understanding of how best to treat individuals with concurrent PTSD and AUD. Understanding not just which treatments work for mental health problems, but also the mechanisms underlying the problems and their treatments and if we can determine new ways to predict treatment response at enrollment is part of the national research agenda.[5] This manuscript presents one model for how to conduct research in line with this agenda. The model we present is not without its limitations. However, it is hoped that presenting this model will facilitate further discussion of: (1) how to maximize the potential utility of treatment studies for difficult to recruit and retain populations, and (2) ways to conduct research that meets the goals of understanding the mechanisms that underlie effective treatments.

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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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Table 1

Rates of participation in affiliated studies among the first 11 RCT participants to whom we were able to offer all three affiliated studies

	PSG	fMRI	Genetics
# expressed interest on consent or screening form	9	10	10
% interested	81%	91%	91%
# qualifying	3[a]	9[b]	10
# completed baseline assessment or saliva sample	3	9	10
% interested who completed baseline assessment or gave saliva sample	27%	81%	90%
% qualifying who completed baseline assessment or gave saliva sample	100%	100%	100%

Note. PSG = Polysomnography. fMRI = functional magnetic resonance imagining.

[a]Six excluded because of shift work, untreated sleep apnea, or residing in restricted environment that did not allow attending polysomnography assessments

[b]One excluded because residing in restricted environment that did not allow attending fMRI assessment