Study Title: An Integrative Technology Approach to Home-based Conjoint Therapy for PTSD

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Study Protocol

Research Design and Methods

Study Design Overview: The primary aim of this 4-year RCT is to evaluate the superiority of CBCT delivered via two modalities (i.e., office-based [CBCT-OB] and home-based via CVT [CBCT-HB]) compared to a clinic-based PTSD Family Education (PFE) control condition on clinical efficacy (PTSD symptoms, relationship quality, functional impairment) and process outcomes (Figure 1). Participating couple (N = 137 dyads) at a US Department of Veterans' Affairs (VA)-based clinical site were randomly assigned to one of three treatment arms (CBCT-OB, CBCT-HB, or PFE-OB) and assessed at five time points: pre-treatment, mid-treatment, post-treatment, 3-months post-treatment, and 6-months post-treatment.

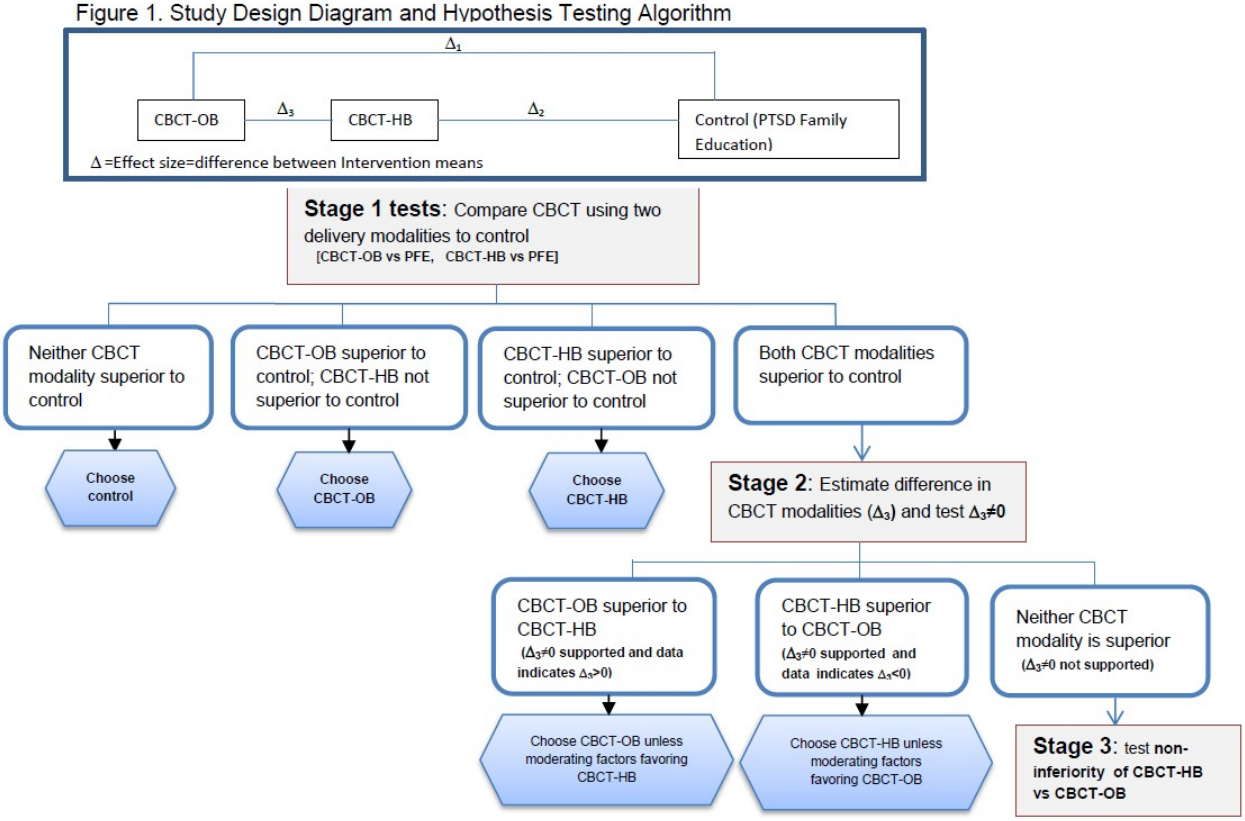
The primary analyses are pairwise comparisons of each CBCT modality with the control condition: CBCT-OB vs. PFE control and CBCT-HB vs. PFE control (Stage 1 analyses in Figure 1). These comparisons are considered primary in the sense that establishing superiority of each modality to control is a necessary condition before consideration of each modality's relationship to each other. Progression to Stage 2 testing (comparison of the two CBCT modalities) will occur only if Stage 1 analyses show that both modalities are superior to control; progression to Stage 3 (a non-inferiority trial, not part of the current proposal) occurs only if no statistically significant differences are found for Stage 2.

The primary hypothesis predicts that CBCT delivered via either (CBCT-OB and CBCT-HB) modality will result in significantly greater reductions of **PTSD symptoms,**

couples' relationship distress, and functional impairment than the PFE control. A non-inferiority trial comparing CBCT-OB to CBCT-HB was ruled out because there is insufficient research at this time to establish CBCT's superiority over a control/placebo condition, which is a necessary step for establishing an acceptable non-inferiority margin (i.e., delta). Results of this study will guide future CBCT non-inferiority studies (Stage 3 analysis in Figure 1) by formally testing the superiority of CBCT to a control, and by providing an estimate of the observed difference between CBCT delivery modalities (Δ3). A tertiary hypothesis predicts that therapy process outcomes such as enrollment and drop-out, therapeutic alliance, and treatment satisfaction will be significantly higher in CBCT-HB compared to the two office-based conditions.

Design strategy and algorithm for pairwise treatment comparisons (see Figure 1): The primary pairwise comparisons for the 3-arm study are comparing each CBCT delivery modality with the control condition: CBCT-OB vs. PFE control and CBCT-HB vs. PFE control (Stage 1). These comparisons are considered primary in the sense that establishing superiority of each modality to control is necessary before evaluation of each modality's relationship to each other. Specifically, progression to Stage 2 testing (comparison of the two delivery modalities) will occur only if it is found in primary analyses that both modalities are superior to control; progression to Stage 3 (a fully powered non-inferiority trial, not part of the current proposal) occurs only if no statistically significant differences are found for Stage 2.

Figure 1. Study Design Diagram and Hypothesis Testing Algorithm



Participants: To be included in the study, participants must: (1) be a Veteran (age 18 or older) with a current DSM-5 diagnosis of PTSD (as assessed by the CAPS-5) no less than 3 months after the index trauma occurred (to allow for potential natural recovery) and (2) be on a stable psychoactive medication regimen for at least 2 months (if eligible) or (3) be an intimate partner (age 18 or older) who is willing to participate in the intervention. Both members of the couple must be willing to (4) be randomized into any of the three treatment conditions, (5) have assessment and treatment sessions audio recorded; and (6) agree not to receive other individual or conjoint psychotherapy for PTSD during the treatment portion of the study. Finally, consistent with home-based clinical trials and actual clinical practice (7) participants enrolled into the study will need

to have access to internet via DSL or a cable provider in case they are randomized into the home-based condition. If they do not, they will be provided a VA tablet installed with Wi-Fi through the VA clinical TMH program. The frequency of occurrence of no internet service will be tracked.

Exclusion criteria are: (1) current substance dependence in either member of the couple not in remission for at least 3 months, as assessed by the Alcohol Use Disorders Identification Test (AUDIT) and Drug Abuse Screening Test (DAST); (2) any current uncontrolled psychotic disorder in either member of the couple; (3) imminent suicidality or homicidality in either member of the couple; (4) any severe cognitive impairment in either member of the couple; (5) any perpetration of severe physical or sexual relationship aggression in the past year (as assessed by the CTS-2-S, EHITS, and a 5-item IPV assessment). Participants who report experiencing severe physical or sexual relationship aggression will be excluded from the study. The partner reporting interpersonal violence will be referred to local resources for victims of domestic violence and given a brochure containing information regarding these resources. Participants who do not meet study criteria will be offered referrals to alternate services, as well as assistance in contacting the referral sites as needed; or (6) Partner cannot have a probable PTSD diagnosis as indicated by a score of greater than 33 on the PCL-5.

Our procedure related to collateral charts matched that of the Family Mental Health Program. During the assessment, we obtained all of the information necessary in the event that we need to create a collateral chart. We would only open a chart if it is needed to avoid risk to the partner's confidentiality. We did not typically see the partner alone, except as part of the assessment, because the VA roll out of treatment includes

an assessment session for the partner and because our assessments are conducted in non-count clinics, there is no billing code associated with the encounter. If the partner were being seen for something that required documentation (domestic violence, SI, or other safety concern) then we would create a collateral chart using the information provided to us during the assessment.

Recruitment, Attrition, and Retention Procedures: A convenience sample of 137 Veterans eligible to receive services from the VA San Diego Healthcare System (VASDHS) who met DSM-5 diagnostic criteria for PTSD, and their intimate partners, were recruited. Most of the recruitment and treatment occurred through the VA Family Mental Health Program (FMHP) in San Diego, CA. We screened 174 couples in order to enroll 137 for the ITT sample. Our recruitment strategy was threefold: (1) capitalized on existing relationships with area clinics both within the VA/DoD and the community (e.g., Vet Centers, University counseling centers) to receive clinician referrals; (2) utilized the VA electronic medical records database to identify Veterans, Reserve, and Guard with relevant mental health diagnoses (e.g., PTSD, Military Sexual Assault) and invited them to participate in the study via mailed letter; and (3) employed a comprehensive outreach strategy to raise public awareness of the study and invited participants to self-refer. Outreach methods were informed by experience conducting previous clinical trials and included (but are not limited to) posting materials (e.g., pull-tab flyers) in strategic community locations; attending tabling events at the VA, DoD, and in the community; participating in local media (e.g., write a piece for local papers and newsletters); publishing announcements in local newspapers and online at Veteran-focused blogs,

social networking sites, newsletters, etc.; distributing notices on relevant list serves; and listing the study in online directories of ongoing clinical trials. Recruitment activities were managed by the study staff, who developed and disseminated recruitment materials, met with VA providers to identify potential participants, and conducted phone screenings with referred Veterans.

Based on the findings from pilot CBCT research and the lack of a waitlist condition, we projected a 20-30% attrition rate, resulting in approximately 110 couples completing treatment. To enhance retention, we asked couples to provide contact information for collateral informants who can reach them if we are unable to do so via their primary contact information. Participants received a stipend of up to $375 in order to offset costs associated with study participation (e.g., transportation, reduced childcare costs). For completed baseline, post-treatment, 3 months post-treatment, and 6 months posttreatment assessment appointments, the participants in the study received the following compensation: a) Baseline assessment: $50 for the Veteran and $25 for the partner; b) Posttreatment follow-up assessment: $50 for the Veteran and $50 for the partner; c) 3 month post-treatment follow-up assessment: $50 for the Veteran and $50 for the partner; and d) 6 month post-treatment assessment: $50 for the Veteran and $50 for the partner. Participants received the stipend through direct deposit to their bank accounts. Study personnel routinely reminded couples of therapy and assessment appointments via telephone and/or letters and met weekly to review and problem-solve retention strategies.

Description of the CBCT Intervention: CBCT is a manualized couple-based intervention for PTSD designed to simultaneously reduce PTSD and enhance relationship functioning. The therapy consists of eight 75-minute sessions organized into two phases that build upon each other and includes both in-and out-of-session exercises to increase skill acquisition. **Phase 1** (Sessions 1–2) focuses on the rationale for the therapy and establishing safety within the relationship (e.g., recognizing early warning signs of anger, use of conflict management strategies). **Phase 2** (Sessions 3-7) focuses on increasing relational satisfaction and undermining PTSD-related distress. The ways avoidance can generalize beyond specific trauma memories and the role of avoidance in maintaining both PTSD and relationship problems are addressed. Couples develop a list of people, places, situations, and feelings that they have avoided as a result of PTSD and begin in vivo exposure exercises to approach these situations in a graduated manner. Special attention is paid to the selection of in vivo approach activities that will address behavioral and experiential avoidance, and concurrently double as shared rewarding activities for the couple. Enhanced dyadic communication is used as an antidote to PTSD-related emotional numbing and avoidance, as well as a means of increasing emotional intimacy. **Final Session** (Session 8) culminates with a discussion of the potential for consolidating newly acquired skills and a review of gains made and challenges expected in the future.

Description of PTSD Family Education (PFE) Control: PTSD Family Education (PFE) consists of eight 60-minute couples' sessions adapted from the Support and Family Education (SAFE) program and the Behavioral Family Therapy (BFT) program.

Both programs involve educating family members about trauma and other comorbid conditions using didactics, discussion, and written materials. Dr. Becker-Cretu (study consultant) and colleagues translated the educational aspects of the SAFE and BFE programs into PFE, a manual-based PTSD education intervention for couples. PFE session content does not include skills training, and clinicians providing PFE are specifically trained to avoid skills training and other therapeutic interventions beyond psychoeducation. Example discussion topics include “Causes of PTSD,” “Symptoms of PTSD,” and “The Role of the Family.” A structured training protocol and a rating form have been developed to assess PFE fidelity and competence. PFE was recently used as a comparison condition in a RR&D-funded RCT evaluating the Structured Approach Therapy (SAT) for PTSD intervention. Results showed that while Veterans in both the experimental (SAT) and control (PFE) groups demonstrated significant reductions in PTSD post-treatment and at 3-month follow-up, SAT was more efficacious (as evidenced by its greater rates of improvement). Thus, including PFE as a comparison condition allowed the investigators to demonstrate that the PTSD reductions associated with SAT were a function of its therapeutic aspects, and not due to non-specific effects of attending a couples’ intervention.

Assessment Administration: Assessments for both members of the couple were conducted at (1) baseline, (2) mid-point of treatment, (3) within a month of post-treatment, (4) 3 months post-treatment, and (5) 6 months post-treatment. The couple were asked to come in for assessment appointments at baseline, post-treatment, 3 months post-treatment, and 6 months post-treatment. After baseline, if a couple was

unable to attend an assessment appointment in person, the assessment(s) were offered over the phone. The mid-treatment assessment (between sessions 4 and 5) consisted of self-report questionnaires that the participants completed prior to their mid-treatment therapy session. Both members of the couple completed a baseline assessment interview designed to gather background information and to screen for psychiatric disorders. The PTSD-positive Veteran completed an additional baseline interview to assess PTSD symptoms and DSM-5 diagnosis via the CAPS-5. Participants were advised that each assessment meeting was approximately 2-3 hours in length. Informed consent for each participant was performed by study staff. All diagnostic assessment procedures were performed by the Independent Evaluator (IE) who is trained to administer the CAPS-5 to fidelity via practice interviews until a minimum interrater reliability rating of 90% is achieved. CAPS-5 fidelity was monitored in an ongoing fashion to prevent drift (see Assessment and Treatment Fidelity Monitoring).
Study staff (e.g., IE, research assistants) administered self-report questionnaires to the partner and discussed with the IE about inclusion/exclusion criteria. Study staff alerted the therapist if either member of the couple showed a marked worsening of symptoms (e.g., suicidal ideation) or a score of a 2 or higher on item 9 of the BDI-II at any assessment occasion. To minimize the risk of bias, the IE stayed blinded to participants' study condition throughout the study.

Randomization Procedures: Eligible couples were randomly assigned 1:1:1 to receive CBCT-HB, CBCT-OB, or PFE using a permuted block randomization scheme using an excel file, which required confirmation of eligibility criteria before treatment assignment

is revealed. The randomization schedule was developed and monitored by Dr. Golshan, the study biostatistician, and randomization was communicated to the Veteran by a study approved RA. Study therapists provided care in all conditions. When multiple therapists were available to provide care for the eligible couple, randomization was carried out separately for each therapist, using blocks of decreasing sizes to maintain an approximate balance in the sample sizes for the three arms. However, if a client was recruited from the Oceanside area, placement with an Oceanside therapist was given priority. Only Dr. Golshan, Dr. Mackintosh (study statistician), clients and therapists were aware of condition assignment. Once a couple was randomized, they were entered into the study and were included in the ITT analysis. We took the following steps to minimize contamination between the three arms of the study: (1) couples were instructed not to share intervention materials with family members, friends, or other clinic patients; (2) treating VA providers were informed of their patients' participation in the study, but not their condition; and (3) couples were asked not to disclose their treatment assignment to any other counselors or treating physicians.

Treatment Delivery Modality: CBCT-OB and PFE were delivered in the traditional office-based (OB) format - that is, the PTSD-positive participant, his/her partner, and the therapist met in-person in the therapist's office. OB visits took place at two facilities: (1) the Veterans Medical Research Foundation/HSR&D (VMRF/HSR&D) building in La Jolla, CA and (2) 28 miles from La Jolla at the VA clinic in Oceanside, CA. CBCT-HB Couples randomized to the CBCT-HB condition must have had access to DSL or cable internet service or were provided with a VA tablet installed with Wi-Fi through the VA

clinical TMH program. CBCT-HB was delivered to couples via their personal computer, if it can be located in a private, quiet setting within the home. Couples without a video-capable home computer, or one that can be located in a private area of the home, were provided with an Android-compatible or iOS tablet. Project or VA IT staff was available for home-based equipment set-up, if necessary. To assure patient confidentiality and HIPAA compliance, we used VA-approved CVT software (i.e., VA Video Connect). The most recent Home-Based Telemental Health Standard Operating Procedures Manual was used in order to best implement CBCT via CVT-HB. Descriptive data on the type and amount of assistance required for successful home-based delivery was tracked.

Treatment Providers: Treatment was provided by clinicians ("Intervention Specialist" [IS]) who have a Master's degree or higher and a minimum of 2 years of clinical experience. IS's were trained to administer both CBCT and the PFE protocols. They were assigned to treat couples randomized to each condition in equal numbers and attended weekly consultation meetings with Drs. Blount and Macdonald (CBCT experts) and Dr. Becker-Cretu (PFE expert). CBCT training consisted of a 2-day workshop led by Dr. Fredman and PFE training consisted of a 2-day workshop led by Dr. Becker-Cretu. Both were followed by a certification process that included completing a minimum of two training cases, which were monitored for competency and fidelity to study protocols. All sessions were audiotaped to monitor continued fidelity to protocol and were available for ongoing weekly consultation.

Treatment Adherence & Competence: The fidelity to the treatment were closely monitored to ensure that the therapy is being delivered true to the protocol. Aside from weekly supervision to assure ongoing treatment fidelity, treatment adherence, and competence were determined by independent raters who were not otherwise involved in the project. The raters have served on prior studies as adherence and competence raters. In order to ensure that the treatment was administered in accordance with the manual, all sessions in the study were recorded for supervision purposes and for possible selection for fidelity rating. The raters determined adherence to and competence in delivering the therapy. Approximately 10% of the recordings were randomly selected for viewing and determination of inter-rater reliabilities (kappas).

Assessment and Treatment Fidelity Monitoring: All diagnostic clinical interviews (i.e., CAPS-5) were conducted by Independent Evaluators (IEs). IEs participated in four stages of training to include: relevant readings, didactic instruction with an expert in the field, mock interviews with co-workers, and co-rating exercises with previously taped assessments. After the completion of training, all IEs engaged in weekly calibration exercises to ensure that they continued to meet high quality standards. Any drift in scoring (i.e., failure to match decisions about PTSD diagnosis or a discrepancy of greater than 5 points in the total score with the trainers) were brought to the attention of the IE so that the problem can be corrected in future assessments. Recordings for a random selection of 10% of CAPS-5 interviews were reviewed for fidelity. Fidelity monitors assessed adherence to overall assessment procedures and re-scored the measure. Interrater reliability was calculated. A doctoral-level clinician with extensive

experience providing CBCT to Veteran populations evaluated CBCT fidelity by reviewing a random sample of 10% of sessions and completing a CBCT fidelity measure. Similarly, a doctoral-level clinician with experience providing PFE to Veterans reviewed a random sample of 10% of PFE sessions using the PFE Fidelity and Competence measure.

Data Management: All personnel have met the required human subjects and confidentiality training, which includes information about maintaining data integrity and security. Data from clinician administered interviews and self-report measures were coded with research numbers and protected in accordance with the confidentiality procedures approved by the site's local IRB. Additionally, Dr. Morland obtained the NIAAA Certificate of Confidentiality to further protect participants' privacy. Electronic data were stored on secure VA servers and accessed on VA-encrypted computers. No unencrypted identifiable data were placed, stored, or transferred on portable media, including laptops. Physical records were kept in locked cabinets in a locked office (room 418) in Building 13 at the Veterans Medical Research Foundation. Data were retained in accordance with VA record control schedule RCS 10-1.

Data Sharing Plan: The investigators have extensive experience with data sharing through previous federally funded studies; however, this study has not built a data archive.