Human Protocol (Version 1.8)

General Information

*Please enter the full title of your protocol::		
Pilot Test of Intranasal Oxytocin as an Enhancer of Brief Couples Therapy for PTSD		
***Please provide a short name (nickname) to reference this protocol::**		
CBCT + OT * This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.		

Add departments

and Specify Research Location:

Is Primary?	Site Name
◉	**VASDHS** - VASDHS

Identify protocol staff members

***Please add a Principal Investigator for the study:**

Morland, Leslie A., PsyD

3.1 Add all other VA research staff personnel (if name is not in the list, please contact Research Staffing to confirm appointment status)

A) Additional Investigators

B) Research Support Staff

Borigini, Mark, (ORO)
Auditor
Chargin, Bette
Research Associate
Galvan, Rachel, (ORO)
Auditor
Grubbs, Lauren Maiko
Clinical Research Associate
Hoang, Amy
Clinical Research Associate
Holcomb, Julie M.
Research Associate

Kerenyi, Cynthia, (ORO)
Auditor
Khalifian, Chandra E., PhD
Post-Doc
Knopp, Kayla C., PhD
Post-Doc
Lin, Alex
Clinical Research Associate
Maglione, Jeanne E., MD, PhD
Participating Clinician
Moxey, Monique, (ORO)
Auditor
Rashkovsky, Katerine T.
Research Associate
Schnitzer, Janina S., BA
Research Associate
Sohn, Min Ji
Data Manager
Wachsman, Tamara
Research Associate
Webster, Katelyn D., MA
Study Coordinator

***Please select the Research Contact(s)**

Morland, Leslie A., PsyD
Webster, Katelyn D., MA

The Research Contact(s) will receive all important system notifications along with the Principal Investigator. (Research Contacts are typically Study Coordinators or the Principal Investigator themselves).

VASDHS IRB
Human Subjects Protocol
v20190121

Section 1 - Preliminaries

Principal Investigator:

Leslie A. Morland, PsyD

Protocol Title:

Pilot Test of Intranasal Oxytocin as an Enhancer of Brief Couples Therapy for PTSD

IRB Protocol Number:

H210143

Protocol Nickname:

CBCT + OT

Form Template Version:

v20150115

Date Prepared:

09/01/2022

Please be advised that this protocol application form has changed as a result of the 2018 Common Rule. There are new questions and sections, and you may be required to provide additional information to previous sections.

1a) Is this study considered human research?

- (●) Yes
- ( ) No
- ( ) I don't know

1b) Please select:

- (●) This is an application for a NEW human subject research protocol
- ( ) This is a revision of an existing protocol

Section 2 - Research Subjects

2a) What is the total planned number of VA-consented subjects?

Include the total number of subjects who will prospectively agree to participate in the study (e.g., documented consent, oral consent, or other).

40

2b) What is the total number of VA subjects who WILL NOT be consented?

Include the total number of subjects that will be included without consent (e.g., chart review). *Note: Data about people are still considered "human subjects" by the IRB, so even if you do not intend to contact the patients whose charts you will review, you still should enter the number of charts as your "planned subjects."*

0

Section 2.1 Consented Subject Groups

2.1) For each of the subject categories listed below, indicate whether or not these subject groups will participate in the study:

2.1a) Children under the age of 18
Note: If neonates or children will be involved in this study, certification by the Medical Center Director will be required. Only minimal risk research may be performed with children. Only non-invasive monitoring and/or prospective observational and retrospective record review studies that are minimal risk can be conducted in VA involving neonates.

( ) Yes (●) No

2.1b) Pregnant women

( ) Yes (●) No

2.1c) Individuals with cognitive/decisional impairment

( ) Yes (●) No

2.1d) Non-English-speaking individuals

( ) Yes (●) No

2.1e) Prisoners of War (explicitly targeting this group)

( ) Yes (●) No

2.1f) Non-Veterans (Note: Justification for inclusion of non-Veterans will be required)

(•) Yes ( ) No

2.1g) Incarcerated individuals (Note: VA CRADO approval will be required)

( ) Yes (•) No

2.1h) VA employees - including VA paid, IPA, or WOC (Note: Union review and authorization may be required)

( ) Yes (•) No

2.1i) Students of the institution (e.g., resident trainees) or of the investigator

( ) Yes (•) No

2.1j) Patients with cancer (or high cancer risk) [explicitly targeting this group]

( ) Yes (•) No

Section 3 - Study Features (these items default to "No" for convenience)

3) This section consists of several Yes/No questions addressing protocol characteristics. Click on *Save and Continue*.

Section 3.1 Protocol Basics

Select all that apply

3.1a) The research **intends to change** the participant.

(•) Yes ( ) No

3.1b) **Interactions** with living participants to collect data or specimens with no intent to change them.

( ) Yes (•) No

3.1c) This is a study that **never** has any **subject contact and does not collect subject identifiers**

( ) Yes (•) No

3.1d) This is a **chart review** study involving retrospective or prospective medical records.

( ) Yes (•) No

3.1e) This is a **multi-site** study occurring in-part or in-full at other locations.

( ) Yes (•) No

3.1f) There is an **international** component to this research. *International research includes sending or receiving human derived data or specimens (identifiable, limited data set, coded, or deidentified) to or from an international source. International research does not include studies in which VA is only one of multiple participating sites where the overall study-wide PI is not a VA investigator.*

( ) Yes (•) No

3.1g) This study includes **off-station activity** (not including VA-leased space or CBOC clinics) conducted under VASDHS IRB approval. *Note: this does not include research conducted by a collaborator at their home institution under their institutional approval.*

(•) Yes ( ) No

3.1h) VA subjects will **participate** in part or in full **at other locations** (not including VA-leased space or clinics) under VASDHS IRB approval. *Note: if this study involves remote participation of subjects, please*

indicate "no" and describe their remote participation in section 9 of the application. This question is intended to understand whether participants must physically go to a non-VA location to participate in this VA research study.

(●) Yes ( ) No

Section 3.2 Specimen Use and Data Repository

Indicate whether or not each of the following applies to this protocol

3.2a) Involves specimens that are left over from pathological or diagnostic testing (**non-research specimens**)

( ) Yes (●) No

3.2b) Involves **specimens collected for research** purposes **only**

( ) Yes (●) No

3.2c) This study includes **specimen banking** (specimens are retained for use outside of the purposes of this protocol)

( ) Yes (●) No

3.2d) The study involves **DNA** genotyping or other **genetic analysis**

( ) Yes (●) No

3.2e) Biological **specimens/material** will be sent outside of the VA.

( ) Yes (●) No

3.2f) A **data repository** is maintained (data are retained after completion of the protocol for other uses, IMPORTANT: see **?** before checking "yes")

( ) Yes (●) No

3.2g) **Data will be shared outside** of the VA (identifiable, coded, limited data set, or deidentified)

( ) Yes (●) No

Section 3.3 Treatment and Clinical Trials

Indicate whether or not each of the following applies to this protocol

3.3a) Includes a **treatment** component (a research treatment)

(●) Yes ( ) No

3.3b) Study is a **clinical trial.** *Note: A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.*

(●) Yes ( ) No

3.3c) Has a data safety monitoring board (**DSMB)** or data safety monitoring committee.

( ) Yes (●) No

3.3d) Has a **data safety monitoring plan** (but not a DSMB) (this is not the data security plan, it is a safety plan).

(●) Yes ( ) No

Section 3.4 Drugs and Devices

Indicate whether or not each of the following applies to this protocol

3.4a) **Drugs** that require **FDA** action such as an Investigational New Drug (IND) approval or exemption or 510 (k) approval.

(•) Yes ( ) No

3.4b) Other drugs, supplement, etc. that **do not require FDA** action for inclusion in the study.

( ) Yes (•) No

3.4c) Medical **devices requiring FDA** IDE approval or waiver

( ) Yes (•) No

3.4d) **Other** medical **devices**

( ) Yes (•) No

Section 3.5 Risk and Hazards

Indicate whether or not each of the following applies to this protocol

3.5a) Study places subjects at **greater than minimal risk** (do not include risks that are due to standard care)

(•) Yes ( ) No

3.5b) Human subjects are exposed to **radioisotopes** (do not include standard care).

( ) Yes (•) No

3.5c) Subjects have other **radiation exposure** (e.g., x-rays) (do not include standard clinical use).

( ) Yes (•) No

3.5d) Target population has psychiatric diagnosis or behavioral complaint.

(•) Yes ( ) No

Section 3.6 Clinical Facilities and Standard Care

Indicate whether or not each of the following applies to this protocol

3.6a) Study **uses VA clinical services** (e.g., adds required tests run in the VA lab for study purposes; research procedures concurrent with clinical care)

( ) Yes (•) No

3.6b) Includes procedures or drugs that will be considered **part of standard care.**

( ) Yes (•) No

3.6c) Involves **lab tests done for research** purposes.

( ) Yes (•) No

Section 3.7 Subject Expenses and Compensation

Indicate whether or not each of the following applies to this protocol

3.7a) There may be expense or added **costs to the subject** or the subject's insurance.

( ) Yes (•) No

3.7b) This is a **qualifying cancer treatment trial** and subjects may be billed for study drugs or procedures.

○ Yes ◉ No

3.7c) This is a cancer treatment trial but **subjects will not be billed** for study drugs or procedures.

○ Yes ◉ No

3.7d) Subjects will be **compensated** (either in cash or other means such as a gift certificate).

◉ Yes ○ No

Section 3.8 Subject Activities

Indicate whether or not each of the following applies to this protocol

3.8a) Involves **surveys or questionnaires** completed by subjects

◉ Yes ○ No

3.8b) Includes the use of **recruitment materials** such as flyers, advertisements, or letters

◉ Yes ○ No

3.8c) Involves facial **photographs** or audio or video **recordings** of **patients**

◉ Yes ○ No

Section 3.9 Sponsors and Collaboration

Indicate whether or not each of the following applies to this protocol

3.9a) This research is a funded research project **(commercial (industry) sponsor, NIH, VA, other).**

◉ Yes ○ No

3.9b) Other **commercial (industry) non-financial support** is provided (e.g., drugs or supplies).

○ Yes ◉ No

3.9d) The protocol has **Department of Defense** involvement (e.g., subjects or funding).

○ Yes ◉ No

3.9c) The PI or other study staff member has a financial interest or other **real or potential conflict** related to this study.

○ Yes ◉ No

3.9e) This study involves **collaborative** research activities (research conducted at other institutions under the authorities or approvals of the other institution/s). *Note: this may include other VA and/or non-VA institutions, but does not include off-site VA research.*

○ Yes ◉ No

Section 4 - Estimated Duration

4) What is the estimated duration of the entire study? (From IRB approval to IRB closure)

12 months

Section 5 - Lay Language Summary

5) Provide a summary or synopsis of the proposed study using non-technical language (not more than 1 paragraph)

In 2019 VA mandated that all Veterans seeking mental health care have access to flexible family mental health services in VA (VHA directive 1163.04). This study aims to respond to this mandate by further improving an evidence-based PTSD treatment designed to decrease PTSD symptoms and improve relationship satisfaction for Veterans and their romantic partners. Brief Cognitive-Behavioral Conjoint Therapy (B-CBCT), an 8-session dyadic psychotherapy for PTSD, has been found to significantly reduce PTSD symptoms, but the effects of B-CBCT on relationship satisfaction are less reliable and robust. Pharmacological augmentation of psychotherapy utilizing intranasal oxytocin, a neurohormone that influences mechanisms of trauma recovery and social behavior, may help improve relationship satisfaction outcomes. If successful, the proposed study will advance knowledge of strategies for improving Veterans' quality of life by improving their intimate relationships along with PTSD symptoms.

Section 6 - Specific Aims

6) Provide a statement of specific aims and hypotheses that serve as the basis for this protocol. Emphasize those aspects that justify the use of human subjects.

The goal of this proposal is to examine the initial clinical feasibility of B-CBCT augmented with intranasal oxytocin (B-CBCT + OT) for improving relationship satisfaction in an open trial among twenty dyads composed of Veterans with PTSD and their intimate partners. We also plan to explore secondary outcomes such as PTSD symptoms, other aspects of social functioning, and quality of life.

In addition to establishing feasibility of methods (i.e., recruitment and retention of dyads and acceptability to participants), specific hypotheses for this project are as follows:

• Primary Hypothesis: There will be improvements in each partner's self-reported relationship satisfaction measured by the Couples Satisfaction Index following completion of B-CBCT + OT.
• Secondary Hypotheses: Following the completion of B-CBCT + OT, Veterans will report improvements in PTSD symptoms measured by the PTSD Checklist for DSM-5, psychosocial functioning measured with the Brief Inventory of Psychosocial Functioning, and quality of life measured with the World Health Organization Quality of Life – BREF.

Section 7 - Background and Significance

7) Provide a succinct discussion of relevant background information to justify performing the proposed study.

Interpersonal relationships are critical to Veterans' recovery from trauma and PTSD.

Military Veterans often experience challenges when reintegrating into their communities after their military service, due in part to mental health problems such as posttraumatic stress disorder (PTSD). PTSD, a psychiatric disorder that develops in response to exposure to traumatic events, such as military combat and sexual assault, disproportionately affects Veterans, leads to poorer physical health, and impairs psychosocial functioning and quality of life.[12,28,29] Mitigating the negative effects of PTSD on Veterans' health, functioning, and well-being is therefore a major goal of the Veterans Health Administration (VHA).

The premise that interpersonal relationships play a key role in resilience, risk, and recovery from trauma[11] is supported by research showing a robust association between PTSD and social support.[34] Longitudinal research shows that this association changes over time; during early trauma recovery, positive social support is associated with reduced likelihood of developing PTSD; at later stages of trauma recovery, PTSD symptoms degrade social support.[35] The quality of social environments before trauma exposure are important, too; for example, family problems before or after a deployment increase risk of PTSD.[36] Treatment approaches that bolster Veterans' internal strengths and enhance the capacity of their social environments to provide support are most likely to have powerful effects on well-being.[33] Post-deployment programs for recently separated Veterans often emphasize the role of relationships in promoting reintegration.[37] Many Veterans in the VA, however, have chronic PTSD, often accompanied by problems of impairment in social functioning and poorer quality of life.

VA is invested in improving Veterans' intimate relationships to support their trauma recovery.

Many Servicemembers and Veterans with PTSD experience impairment and distress within intimate relationships at greater levels than among civilian couples.[15] Consistent with this, Veterans seeking treatment for PTSD often identify relationships as targets of intervention[17] and express the desire to involve close others in treatment.[18] The VA has been responsive to these needs, as shown by the continuum of services available to Veterans and their families through the VA Family Services program. The Veterans' Mental Health and Other Care Improvements Act of 2008 (Public Law #110-387, Title III §301 - Assistance for Families of Veterans) stated that marriage and family counseling were to be available to Veterans to facilitate their treatment and rehabilitation. In 2009 VA began an initiative to select evidence-based family therapies and train mental health providers in these treatments. More recently, Directive 1163.04 indicated that Veterans with a mental health diagnosis should be asked about their interest in having family involved in their care and be offered marital and family counseling. The VA Family Services program supports several treatment approaches to meet the diverse mental health needs of Veterans and their loved ones. One such option for Veterans who want to simultaneously improve their PTSD symptoms and their relationship functioning is Cognitive-Behavioral Conjoint Therapy (CBCT) for PTSD.[19] The VA has been disseminating CBCT since 2013.

Effects of CBCT on Veterans' relationship satisfaction may be less robust than its effects on PTSD.

CBCT is a PTSD-specific cognitive-behavioral psychotherapy attended by the couple that uses close relationships as the vehicle for recovery.[19] Across fifteen 1.25-hour sessions, this manualized therapy addresses the patient's PTSD, the partner's well-being, and relationship functioning simultaneously via its focus on psychoeducation about PTSD within relationship contexts, social skills, behavioral approach exercises, and cognitive interventions. CBCT effectively treats PTSD, exhibiting large within-group effect sizes on clinician-rated PTSD symptoms.[20]

Across studies, however, CBCT has had less robust, more variable effects on relationship satisfaction than on PTSD. This is likely because the factors governing relationship satisfaction—in general and within couples in which a partner has PTSD—are complex and rely on a number of independent, interpersonal factors. The largest published study of CBCT (N = 40 dyads), in which CBCT was compared to a waitlist control group, found a moderate within-group effect (g = 0.64) and between-group effect (g = 0.47) of CBCT on Veterans' relationship satisfaction.[20] This sample, however, was composed of only about 25% Veterans. Given that Veteran couples are known to have lower relationship satisfaction than non-Veteran couples[15], it is important to further examine CBCT among Veteran couples that are more representative of couples seen in general VA practice to increase generalizability of findings. However, preliminary data from couples treated as part of VA's dissemination of CBCT suggest that effects on relationship satisfaction are noticeably smaller than in previous studies (personal communication, S. Glynn). This may be due, in part, to poor engagement in the intervention. Couples experience many logistical obstacles to engaging in care (e.g., the need to coordinate schedules, lack of childcare). Veterans with PTSD can encounter additional obstacles related to beliefs about mental health and mental health treatment. Given these obstacles to treatment engagement, the field must develop ways of ensuring that when a couple expresses interest in treatment, so they can have their needs met as effectively and efficiently as possible.

To this end, Dr. Leslie Morland (PI) recently completed a study of an 8-session version of CBCT (B-CBCT) delivered either in-office or via telehealth to home compared to a family education control condition, designed to improve access to and retention in care. She and her team similarly found robust reductions in PTSD symptoms in B-CBCT (B-CBCT within-group *d's* = 1.05-1.12, between-group *d's* = 0.59-0.76) but only a small effect on both partners' relationship satisfaction that was on par with the family education condition (B-CBCT within-group d = 0.38; b etween-group *d's* = 0.04-0.12).

Medication augmentation is a promising strategy for enhancing outcomes of behavioral interventions.

Medications that potentiate the mechanisms of action in psychotherapy could enhance their effects.[9] The neuropeptide oxytocin in particular appears to be a promising medication because it mediates processes central to PTSD and relationship functioning. Oxytocin is a 9-amino-acid nonapeptide hormone produced by the paraventricular and supraoptic nuclei of the hypothalamus that regulates human emotions, social cognition, and social behaviors.[57] Endogenous oxytocin assists in milk production for breastfeeding, induces contractions during childbirth, is released during orgasm, may reduce urine volume, and may induce sodium release from the kidneys. Intravenous oxytocin is used in medical practice to induce labor in pregnant women and to

increase muscle tone in the uterus in the case of postpartum bleeding. Oxytocin is released to several brain areas, including the amygdala, hypothalamus, hippocampus, insula, and striatum,[58] and effects are mediated by oxytocin receptors found in these regions.[59]

Intranasal administration of oxytocin is an elegant approach for understanding the causal effects of oxytocin on human behavior. Intranasal oxytocin is safe and easy to administer,[60] with a short half-life that makes it highly suitable for adding to behavioral interventions. Intranasal oxytocin is best known for its widespread effects on affiliative processes and behaviors. For example, intranasal oxytocin increases trust[22], empathy[23], generosity[61], positive communication[24], and emotional disclosure.[62] Oxytocin also improves social cognition, including emotion recognition[22] and empathic accuracy.[63] The combination of intranasal oxytocin with provision of social support suppresses cortisol release and subjective responses to social stress.[64]

Intranasal oxytocin can be conceptualized as a "psychotherapy process catalyst"[9], in that oxytocin could enhance patients' openness to intervention, attention to others' communication, and willingness and ability to develop therapeutic alliance.[67] A recent systematic review of 14 studies of the effects of intranasal oxytocin on PTSD symptoms concluded that there is tentative evidence for the clinical utility of intranasal oxytocin for PTSD,[68] although more studies with chronic administration are needed.[69] To date, only one pilot study has examined the effects of oxytocin-enhanced psychotherapy for PTSD.[70] Findings indicated that participants randomized to Prolonged Exposure (PE) for PTSD augmented with oxytocin demonstrated lower PTSD and depression symptoms and had higher working alliance scores compared to participants randomized to PE with placebo. A large, two-site phase II RCT of oxytocin-enhanced PE is currently being conducted in the VA by a Collaborator on this project (PI: Dr. Julianne Flanagan; NLM: NCT04228289).

Intranasal oxytocin is ideally suited to enhance the effects of CBCT on relationship satisfaction.

Administering intranasal oxytocin in a safe, therapeutic context in which interpersonal skill-building takes place is hypothesized to lead to prosocial effects and facilitated recovery. CBCT is therefore the ideal treatment platform for oxytocin augmentation. CBCT and oxytocin are both inherently interpersonal and could operate in a coordinated, synergistic manner to improve relationship satisfaction. For example, increasing Veterans' trust in their partners and providers may promote emotional engagement in CBCT. Increasing Veterans' empathy for the partner's experience of how PTSD affects their relationship could elicit motivation to remain engaged in the treatment. Facilitating positive communication could enhance all aspects of the therapy, including both partners' sharing of thoughts and feelings and their ability to join together in cognitive restructuring of trauma-related beliefs that interfere with recovery. Findings that intranasal oxytocin increases neural activation to socially rewarding stimuli[73] and facilitates social approach behavior[26] suggest that it could help Veterans and their partners embrace social situations, which is central to CBCT behavioral interventions. Lastly, generalization of improvements in trust, empathy, positive communication, and approach behavior could help Veterans participate more fully with their families (e.g., improved parenting skills) and many other domains of society (e.g., engagement in education and employment). To date, however, oxytocin has not been tested as an adjuvant to CBCT nor any relationship-focused therapy for trauma-exposed Veterans.

Intranasal oxytocin pharmacodynamics and dosing considerations.

Based on compelling pre-clinical data implicating the oxytocin system in affiliative behavior, the study of intranasal oxytocin in humans expanded very rapidly. However, these developments were followed by calls for caution after acknowledgment of lack of replicability of findings, methodological limitations such as low statistical power, and poor understanding of the pharmacodynamics of intranasal delivery of synthetic oxytocin.[6,74] Intranasal oxytocin is thought to exert effects by bypassing the blood-brain barrier and reaching the brain directly (i.e., nose-to-brain transport), but definitive data have been lacking.[75] More recently, pre-clinical, primate, and human research have converged to indicate that intranasal oxytocin does, in fact, reach the brain to a degree that leads to clinically relevant changes in behavior, ostensibly through olfactory and trigeminal nerve fibers.[67,75,76] Another issue that has affected the translation of oxytocin research to treatment has been the lack of dose-ranging studies in humans. Notably, most intranasal oxytocin studies have administered only one dose of intranasal oxytocin, typically 24 or 40 international units. The pharmacodynamics of repeated oxytocin administration are not well-established[69], but given the short half-life of intranasal oxytocin (i.e., 20 or more minutes in cerebrospinal fluid[77] and 2 minutes in blood[78]), repeated dosing (e.g., daily, weekly) is not hypothesized to operate differently than single doses.

Significance and relevance to Veterans and VA patient care mission.

The proposed study to augment CBCT with intranasal oxytocin and to examine its effects on intimate relationship adjustment, social functioning more generally, and quality of life directly addresses the mission of the VA, as outlined in the VA FY 2018–2024 Strategic Plan. Specifically, the proposed study seeks to advance knowledge of how to help Veterans have good quality of life—which the VA identifies as including satisfying relationships—in three ways: First, findings from the proposed study will inform whether B-CBCT social functioning outcomes can be improved with adjunctive medication. By potentiating the effects of B-CBCT with oxytocin, we could increase the clinical response rate of patients and their loved ones receiving B-CBCT. Second, if oxytocin enhances the mechanisms described in this proposal as predicted, it could further strengthen rationale for providers administering eight-session B-CBCT rather than 15-session CBCT. Effectively truncating CBCT would mean that more patients could be seen by the same number of VA providers, potentially improving Veterans' access to treatment. Greater effectiveness and efficiency of treatment could lead to lower costs to VA. Third, by targeting mechanisms that are salient not only to intimate relationships but all interpersonal relationships (such as trust) oxytocin could help the effects of CBCT extend to other, non-intimate relationships, thereby improving overall quality of life and potentially having downstream effects on other issues facing the VA (such as suicide) which is known to be related to interpersonal difficulties. Lastly, improving Veterans' social environments could help them maintain their gains and respond effectively to future stressors—potentially lowering the likelihood of future need for episodes of care.

Section 9 - Design and Methods

9) Describe the research design and the procedures to be used to accomplish the specific aims of the project. Provide a precise description of the planned data collection (include what systems or databases will be used/accessed to gather data), analysis and interpretation. For chart review studies, include the timeframe of collection. Address sample size, inclusion of women and minorities. Define in clear terms exactly what will be done to the human subjects.

STUDY DESIGN OVERVIEW:

This pilot study will enroll up to 20 couples (40 individuals) in B-CBCT + OT over this 12-month project. Participants will be recruited from the San Diego VA Healthcare System. Couples will participate in 8 sessions of B-CBCT augmented with 40 IU of intranasal oxytocin administered 30 min before each session. At baseline and post-treatment, dyads will be asked to complete brief assessments of the outcomes described above. After treatment, they will also provide feedback about factors associated with feasibility of methods and treatment engagement. Quantitative and qualitative data will be used to assess the feasibility and acceptability of the intervention and will be utilized in preparing a proposal for an RCT. We will compare within-group effect sizes on PTSD and relationship satisfaction to effects observed within the historical controls from Dr. Morland's RCT of B-CBCT.

RESEARCH SITE:

This pilot study will be conducted at the VA San Diego Healthcare System.

PARTICIPANTS:

Participants will be 20 Veteran couples (i.e., 20 Veterans and their 20 partners; 40 individuals total) who are interested in receiving couples therapy for PTSD and relationship problems. Couples of all genders, ages, and ethnicities will be included. Participants must enroll and participate together as a couple; if one partner is not interested in participating, the couple will not be enrolled, and referrals for alternative individual services will be offered.

Inclusion criteria for the study will require one member of the couple be a Veteran enrolled in the San Diego VA Healthcare System with a Posttraumatic Stress Disorder Checklist-5 score of > 33, indicating a likely PTSD diagnosis. Veterans must agree not to receive other individual or conjoint psychotherapy for PTSD during participation in the study. If already on psychoactive medication prior to study referral, Veteran participant must remain on a stable psychoactive medication regimen for at least 45 days.

Exclusion criteria will be acute suicidality; psychosis; active substance use disorder; severe ongoing medical problems, including heart disease and neuroendocrinological disorders (e.g., diabetes); uncontrolled hypotension (systolic blood pressure <100 mm Hg) or hypertension (>160/100 mm Hg); pregnancy, delivery in the past 6 months, or current breastfeeding; or severe intimate aggression reported by either partner (established with validated measures). A list of alternative resources will be provided to ineligible participants.

DESCRIPTION OF THE BRIEF CBCT INTERVENTION:

CBCT is a manualized couple-based intervention for PTSD designed to simultaneously reduce PTSD and enhance relationship functioning. The brief version of the therapy (B-CBCT) 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. The 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. B-CBCT will be delivered via video teleconferencing.

TREATMENT DELIVERY MODALITY:

Couples must have access to DSL or cable internet service. B-CBCT will be delivered to couples via their personal computer if it is in a private, quiet setting within their home. Project or VA IT staff will be available for home-based equipment set-up if necessary. To assure patient confidentiality and HIPAA compliance, we will use VA-approved CVT software (AK Summit software with FIPS level encryption). The most recent Home-Based Telemental Health Standard Operating Procedures Manual will be used to best implement B-CBCT. Please see Humans Subject document for further participant safeguards in place.

DESCRIPTION OF INTRANASAL OXYTOCIN:

A 40 IU dose of oxytocin will be self-administered by the Veteran with PTSD only (not the partner) intranasally 30 minutes prior to the start of each weekly B-CBCT session. A 40 IU dose has demonstrated extensive safety and efficacy, is within the normal dosing range, and is one of the most common concentrations utilized in human research[60,73]. The medication administration protocol is based on previous research by Dr. Flanagan (Collaborator), a leading oxytocin researcher in the area of PTSD, and others.[10,70,94] While intranasal oxytocin has most frequently been used in studies utilizing single doses, several recent published studies of repeated dosing have provided evidence of safety in clinical populations[64,43,44], including a study of once-weekly dosing for eight weeks among Veterans with PTSD conducted by Drs. Flanagan and Sippel (Collaborators).[45]

The study prescriber (Dr. Jeanne Maglione) will verify study eligibility and provide prescriptions for oxytocin to the VA Research Pharmacy. Oxytocin will be compounded, refrigerated, and shipped directly to the participant's home with administration and refrigerated storage instructions by Harbor Compounding Pharmacy in Costa Mesa, CA with operational support from the VA Pharmacy, which will be responsible for sending prescriptions and documenting the medication in Veterans' medical charts. Research staff will instruct participants on the correct method of administration to achieve the 40 IU dose and will observe participants' self-administration via Veterans Video Connect (VVC). Participants will blow their nose, exhale through their nose, then spray into one nostril while inhaling, alternating nostrils until the 40 IU dose is achieved. Side effects and adverse events will be evaluated weekly.

TREATMENT PROVIDERS:

Treatment will be provided by clinicians ("Intervention Specialist" [IS]) who have a Master's degree or higher and a minimum of 2 years of clinical experience. B-CBCT providers, Katelyn Webster, Kayla Knopp, and Chandra Khalifian, are trained on B-CBCT and have administered the therapy on a four-year clinical trial to fidelity.

The research pharmacist at VA San Diego (Steven Funk, PharmD) is facilitating the procurement of intranasal oxytocin from Harbor Compounding Pharmacy in Costa Mesa, CA. Dr. Jeanne Maglione, a VA psychiatrist, will oversee the prescription of oxytocin.

ASSESSMENT ADMINISTRATION:

The assessment protocol will include well-validated measurement in the spheres of safety, desirability, and symptoms/functioning for each participant (i.e., Veteran and partner) at baseline, post-intervention (i.e., after all eight sessions have been completed), and three months post-intervention. Depending on participant preference, assessment may be completed over the phone or documents can be returned via encrypted email (using VA Azure RMS). Pre-treatment and post-treatment assessments will occur approximately 20 to 28 weeks apart. The study will also include qualitative interviews with couples to improve study delivery and methods.

DATA COLLECTION:

Responses to measures at all assessment time points are collected with each partner individually with the other partner leaving the room to avoid coercion or fear of reprisal if one partner were to disclose disqualifying information such as domestic violence. Participants will complete the following measures prior to study enrollment to determine if inclusion/exclusion criteria are met:

- *PTSD Checklist for DSM-5* (PCL-5; Weathers et al., 2013) – 20-item self-report measure for the past month that assesses symptoms of PTSD based on the DSM-5; scores at or above 33 indicate probable PTSD. Couples will be included if the veteran partner scores at or above 33 on this measure.
- *Columbia-Suicide Severity Rating Scale* (C-SSRS; Posner et al., 2011) – 8-item self-report measure of suicidal ideation, plan, and intent. Individuals who endorse acute suicidality will be excluded from the study.
- *IPV Assessment-Extended* (IPV-5) – assesses behaviors that individuals engage in during conflict with their partner as well as past and current fear and intimidation in the relationship. Couples with individuals who endorse any severe physical assault behaviors in the past year will be excluded from the study.
- *Alcohol Use Disorders Identification Test* (AUDIT; Bohn et al., 1995) – measures problematic substance use. Individuals endorsing symptoms of an active substance use disorder will be excluded.

Additional measures administered at baseline assessment only include:

- *Traumatic Life Events Checklist* (TLEC; Blake et al., 1995) – a 17-item self-report scale that assesses for a lifetime history of exposure to traumatic events (veteran only)
- *Demographic information* and *past experiences receiving mental health treatment* (both partners)
- *Coronavirus Stressor Survey* – assesses stress related to COVID19 (both partners)

The primary (relationship satisfaction) and secondary (PTSD symptoms, quality of life) outcomes will be assessed with both partners at baseline, post-intervention, and three months post-intervention using the following quantitative measures:

- *Couples Satisfaction Inventory-32* (CSI-32; Funk & Rogge, 2007) – a well-validated measure of relationship satisfaction
- *Changes in Sexual Functioning Questionnaire Male Clinical* (CSFQ-M; Keller et al., 2006) – the male version of a 14-item measure that provides a brief measure of sexual functioning with good construct validity and internal reliability
- *Changes in Sexual Functioning Questionnaire Female Clinical* (CSFQ-M; Keller et al., 2006) – the female version of a 14-item measure that provides a brief measure of sexual functioning with good construct validity and internal reliability

- *Intimate Safety Questionnaire* (ISQ, Cordova & Blair, 2014) – a 28-item measure of the degree to which partners feel safe being vulnerable with each other across several different domains of the relationship
- *PCL-5* – described above for PTSD+ partner. Will also include version for non-PTSD+ participants (PCL-C) that asks about the extent to which they perceive their partners have experienced PTSD symptoms in the past week
- *Brief Inventory of Psychosocial Functioning* (B-IPF; Kleiman, Bovin, & Black, 2020) – a 7-item self-report measure of past month psychosocial functioning with good psychometric properties. The measure will be amended to assess functioning in the past two weeks and administered biweekly with the CSI-4 throughout treatment.
- *World Health Organization Quality of Life – BREF* (WHOQOL-BREF; The WHOQOL Group, 1998) – assess quality of life. It consists of 26 items that measure physical and psychological health, social relationships, and environment.

Measures for other broader outcomes to be assessed at baseline, post-intervention, and three months post-intervention include:

- *Dyadic Adjustment Scale-7 (DAS-7*; Hunsley, Best, Lefebvre, & Vito, 2001*)* – the self-report DAS-7 is based on the original 32-item measure. It assesses domains of relationship functioning and has demonstrated strong psychometric properties
- *Patient Health Questionnaire-9* (PHQ-9; Kroenke, Spitzer, & Williams, 2001) – measures depressive symptomatology
- *Brunnsviken Brief Quality of Life Scale* (BBQ; Lindner et al., 2016) – measures subjective quality of life
- *Significant Others Responses to Trauma (SORTS) Inventory* (Fredman et al., 2014) – measures partner responses to PTSD symptoms and will be completed by non-PTSD+ partners only
- *Experiences in Close Relationships-Revised* (ECR-R; Franley, Waller, & Brennan, 2000) – measures adult attachment style

Measures administered at post-assessment only include:

- *Client Satisfaction Questionnaire* (Attkisson, 1982) – measures client satisfaction with the intervention they received
- *Qualitative Feedback Questionnaire* – captures verbal feedback from participants regarding their experience of the study

Prior to each B-CBCT session, each participant will complete brief self-report assessment measures for the primary and secondary outcomes. The outcomes measures are listed below. The Veteran participant will complete a questionnaire assessing any side effects of the intranasal Oxytocin. If the Veteran participant is able to become pregnant, she will also take a pregnancy test.

- *PCL-5* and PCL-C (Weathers et al., 2013) – past-week version for PTSD+ participant and partner respectively
- *Couples Satisfaction Inventory-4 (CSI-4; Funk & Rogge, 2007)* – a well-validated and brief (i.e., 4 items) measure of relationship satisfaction completed by both partners

No PII will be stored with participants' data; data will be identified by coded study identifier only. Electronic deidentified data will be stored on restricted VA research servers accessible only on VA-networked, password protected computers. Records linking coded study identifiers to participants' identifiable information will be kept separately from any data, and electronic records will be password-protected. Any hard-copy data (e.g., transcribed questionnaires) will be stored in locked file cabinets in locked offices in Dr. Morland's office space in the San Diego VMRF/HSR&D Building (Building 13), with any identifiable hard-copy data being stored separately from coded research data.

If able to become pregnant (i.e., assigned female at birth, fertile, following menarche and until becoming post-menopausal unless permanently sterile), the Veteran participant will be required to take a pregnancy test (provided by study staff) at baseline assessment and weekly during treatment before self-administration of oxytocin. A participant is considered not able to become pregnant if they are premenarchal, surgically sterile (documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, and/or tubal ligation), postmenopausal, or assigned male

at birth. These pregnancy tests will be purchased by the study and mailed to Veteran participants who are able to become pregnant only. Veteran participants who are able to become pregnant will be required to verbally confirm a negative result prior to continuing with each oxytocin administration.

Section 9.2 IND Drugs

9.2) For each drug requiring an IND, provide the drug name, dose, and route of administration

Name: Oxytocin
Trade Name: Pitocin
Description: Peripherally, oxytocin causes the contraction of uterine smooth muscle and of the myoepithelial cells within the mammary gland. In the central nervous system, oxytocin is a modulator of social behaviors, facial recognition, fear, anxiety, and trust. Oxytocin is metabolized by hepatic oxytocinases and disposed by biliary and renal excretions.
Molecular Formula: C43H66N12O12S2
Chemical Structure: Cysteine - tyrosine - isoleucine - glutamine - asparagine - cysteine - proline - leucine - glycine (CYIQNCPLG)
Pharmacologic Class: Neuropeptide
Formulation: Each 1.5 mL vial contains 60 units/mL (.1056 mg/mL).
Route of Administration: Intranasal
Storage and Stability: Refrigerator (2°-8°C)

Clinical studies of the effects of intranasal oxytocin administration have been conducted successfully worldwide for more than 10 years. In the US, intranasal administration of oxytocin is used in clinical studies, similar to the proposed one, in two possible routes: 1. Under an IND from the FDA. 2. Under an IND exemption (described here; Kubzansky et al 2009).

We are seeking an exemption from IND filing requirements for a clinical investigation of a drug product that is lawfully marketed in the United States under exemption category 1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. Lastly, the investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

To our knowledge, oxytocin was never found to have been withdrawn from investigation or marketing in any country due to any safety or efficacy related reasons. The application of the substance is considered safe for administration to human subjects under the conditions of the study since intranasal oxytocin at this dosage is known from decades of use to be safe and well tolerated, as evidenced by their routine usage in protected patient populations, such as nursing mothers (The nasal form of Oxytocin – Syntocinon, manufactured by Novartis Pharma – is listed in the FDA website as being used routinely from the 1962 until 1995). The only contraindications are known hypersensitivity reactions to oxytocin. The dosage proposed in this study conforms to clinical doses and have been used previously in normal and clinical volunteers for research studies by others and ourselves, including Collaborator Dr. Julianne Flanagan in a VA-funded study. Any side effects for this application form are rare, and no serious side effects have been recorded for intranasal application of up to 60 IU OT (Epperson et al. 1996). Nausea and vomiting, and transient cardiac arrhythmias have been described rarely. In addition, anaphylactic reactions are described in the data sheet, although the medical literature only contains case reports related to intravenous application of OT.

Furthermore, a previous IND exemption (#75429) states, "Intranasal oxytocin has previously been approved for marketing in the United States from March 20, 1962 until its withdrawal from the market on August 7, 1997." The Federal Register notice issued on that date [Federal Register, Vol. 62, No. 152, Docket No. 97N-0326, pp. 42575 – 42577] clearly states that this withdrawal was at the request of the manufacturer, because the drug was no longer being marketed. No safety reasons were cited in connection with the withdrawal. The intranasal form of oxytocin remains on the market outside of the United States.

Finally, this investigation is conducted in compliance with the requirements for review by an IRB and with the requirements for informed consent. This investigation is also conducted in compliance with the requirement that the investigation is not intended to promote or commercial the drug product.

Since this protocol involves weekly doses of a hormone that has been shown to have minimal side effects, a short half-life in adults, and a good safety profile in adults even with chronic administration (Horta et al., 2020), an IND exemption appears to be justified.

9.2b) Enter the IND Number:

9.2c) Identify who/what entity holds the IND and the status of the IND

9.2d) Identify the storage and security of the drug. For example, at the VASDHS, state "The investigational drug will be stored in the Research Pharmacy in accordance with 119-SOPP-10/151-SOPP-38." Also, identify whether the drug is a controlled substance.

Oxytocin will be compounded, refrigerated and shipped directly to the participant's home with administration and refrigerated storage instructions by Harbor Compounding Pharmacy in Costa Mesa, CA with operational support from the to the VA Pharmacy, which will be responsible for sending prescriptions and documenting the medication in Veterans' medical charts.

Section 9.8 Questionnaires & Surveys

9.8) Provide the name and a reference for questionnaires/surveys that are standard or identify them here and attach a copy of the questionnaire/survey. ***Questionnaires or surveys that are not clinical standard references must be uploaded. Reference the help link for additional information related to surveys administered to VA personnel and approved platforms for web-based surveys.***

•Traumatic events at baseline: Traumatic Life Events Checklist
•PTSD: Posttraumatic Stress Disorder Check List-5 (weekly and monthly versions as well as a collateral version for non-PTSD partners)
•Partner's response to PTSD: Significant Others Responses to Trauma (SORTS) Inventory
•Couples' satisfaction: Couples Satisfaction Inventory-32 and -4 item
•Sexual functioning for male partners: Changes in Sexual Functioning Questionnaire Male Clinical
•Sexual functioning for female partners: Changes in Sexual Functioning Questionnaire Female Clinical
•Safety and vulnerability in relationship: Intimate Safety Questionnaire
•Relationship functioning: Dyadic Adjustment Scale-7
•Relationship Conflict at baseline: IPV 5-item screen
•Attachment: Experiences in Close Relationships
•Functioning: Brief Inventory of Psychosocial Functioning
•Quality of life: World Health Organization Quality of Life – BREF
•Depression: Patient Health Questionnaire-9
•Suicidal ideation, plan, intent: Columbia-Suicide Severity Rating Scale
•Pregnancy test
•Substance abuse at baseline: Alcohol Use Disorders Identification Test
•Life satisfaction: Brunnsviken Brief Quality of Life Scale
•Participants' satisfaction with treatment at post-treatment: Client Satisfaction Questionnaire
•Demographic information and past experiences receiving mental health treatment at baseline
•Questionnaire assessing side effect of intranasal Oxytocin
•Qualitative Feedback Questionnaire
•COVID impact at baseline: Coronavirus Stressor Survey

Section 9.9 Data Safety Monitoring Board or Plan

9.9) Provide a Data Safety Monitoring Plan (DSMP) or the details of a Data Safety Monitoring Board; if a written plan is available, attach a copy of the plan to the submission form.

Consistent with current the CBCT RTC IRB protocol (# H150181), no data safety monitoring board (DSMB) is in place; however we will collect data on all adverse events including all unscheduled office visits, urgent care visits, emergency room visits, hospitalizations, and deaths. All adverse event data will be reported to the Human Subject Sub-committee on an ongoing basis. In addition, we will provide interim analyses data on adverse events as part of yearly project reports to the IRB and Human Subject Subcommittee.

Section 9.11 Pictures and Audio/Video Recordings of Patients

9.11) Describe the purpose of photographs (facial), or audio, or video recordings of patients. Describe whether the recordings will contain, or potentially contain, identifiers. ***Note: use of photographs or recordings must be covered in the informed consent process and documented consent documents (e.g., consent form, information sheets, telephone screen scripts).***

Consistent with the current CBCT RTC and Connecting Women to Care (CWC) RTC IRB protocols (# H150181 and # H170109), the study will collect audio recordings of patient therapist meetings and assessments. This study will not collect photographs or video recordings. The audio recordings will be used to ensure treatment fidelity and make modifications to the protocol based on patient feedback. The recordings will not be used in presentations or for other purposes. These recordings are considered PHI under HIPAA and VA definition of PHI. All audio recordings will be maintained and stored in accordance with VA guidelines. Only study personnel will have access to the audio recordings. Audio-recordings will be deleted when permitted pursuant to the VA Record Retention Schedule. Though uncommon, should a participant not agree to be audio recorded, this is not exclusion from participation. Appointments with this participant would not be audio recorded, however, all other study protocol steps will be completed as usual.

Specifically, these audio recordings will be recorded via USB microphones; these audio files will be stored on the study folder on the VA server. The microphones do not store or retain any part of the recordings, rather they are directly uploaded. These devices were reviewed by Carol Johnson, ISSO, for the CWC Study (protocol # H170109) who concurred that these devices do not need IT security approval at that time. The procedures for this study will match those of the CWC study.

Section 9.12 Off Station Activities

9.12) Describe each off-station activity including where it occurs, subject involvement, and any additional required protections. ***Note: if the off-station activity is being conducted under the approval authority of another institution, this is not VA offsite research and should be described as collaborative research effort. Please contact the HRPP office if you have any questions***

Study staff will work with the participants remotely via VA Video Connect, Webex, or the phone while the participants are in their homes for the informed consent visit, assessments, and therapy appointments. Therapists will work with participants to identify appropriate spaces within each participant's home that is conducive to completing study appointments (e.g., private and quiet spaces with appropriate seating). Each session conducted in the home over a video teleconferencing modality will be audiotaped using a digital recorder set up by the study therapist. Electronic medical records of each Veteran participant will be available to the therapists by accessing the VA's computer network before and after sessions. A progress note for each visit will be entered into the Veteran patient's electronic medical record.

Section 10 - Human Subjects

10) Describe the characteristics of the proposed subject population. Include age, gender, ethnicity, and health status as appropriate. ***Note: Data about people are still considered "human subjects" by the IRB, so even if you do not intend to contact the patients whose charts you will review, you still describe the characteristics related to the subjects whose charts you will review.***

- **Provide inclusion and exclusion criteria as appropriate. Provide a statement how non pregnancy is confirmed if pregnancy is an exclusion criteria.**
- **For multisite studies, provide the total number of subjects from all sites and include description of the local site's role as a coordinating center if applicable.**
- **Indicate the number of VA participants to be studied.**
- **Indicate the estimated number of consented subjects that will fail the screening process, if any.**

A total of 40 participants will be enrolled: 20 Veterans plus their partners (who may or may not also be Veterans). Therefore, between 20 and 40 VA participants will be studied.

Inclusion criteria for the study will be a veteran enrolled in the San Diego VA Healthcare System with a Posttraumatic Stress Disorder Checklist-5 score of > 33, indicating a likely PTSD diagnosis. Veterans must agree not to receive other individual or conjoint psychotherapy for

PTSD during participation in the study. If already on psychoactive medication prior to study referral, Veteran participant must also be on a stable psychoactive medication regimen for at least 45 days.

Exclusion criteria will be acute suicidality; psychosis; active substance use disorder; severe ongoing medical problems, including heart disease and neuroendocrinological disorders (e.g., diabetes); uncontrolled hypotension (systolic blood pressure <100 mm Hg) or hypertension (>160/100 mm Hg); pregnancy, delivery in the past 6 months, or current breastfeeding; or severe intimate aggression reported by either partner (established with validated measures). Because the effects of oxytocin on pregnancy outcome are well known, pregnant and lactating females will be excluded from the trial. We will instruct participants who are able to become pregnant to use appropriate forms of contraception, and we will instruct them to perform urine pregnancy tests at baseline and weekly during treatment before self-administration of oxytocin if a Veteran participant is considered able to become pregnant.

Consistent with our CBCT trial (IRB protocol # H150181), participants who are not eligible for this pilot study will be given information about and, if desired, referrals to appropriate other services. Specifically, individuals whose partners are not interested in participating will be informed about options for individual therapy in the VA (for Veterans) or community (for partners). Couples who report experiencing or perpetrating severe physical or sexual relationship aggression will be excluded from the study and referred for individual treatment; the partner reporting experiencing interpersonal violence will be referred to local resources for victims of domestic violence and given a brochure containing information regarding these resources (see Domestic Violence Resources Brochure).

Section 10.1 Non-Veteran Subjects

10.1a) Recruitment of non-Veterans cannot be for the sake of convenience for this study. Provide the objective and justification for the inclusion of non-Veteran subjects. Identify how the research results will be generalizable to the Veteran population. ***NEW: ORD now requires completion of a Request to Enroll Non-Veterans form (available in the help section of OnRAMP) for any VA studies requesting to enroll non-Veterans. This form will be reviewed by the local RDC before the application may be considered by the IRB. Complete the form and upload with this submission.***

This is a study on adult Veterans and their partners. Therefore, approximately 50% of the participants may or may not be a Veteran themselves.

10.1b) Non-Veterans must be given a copy of the VA Notice of Privacy Practices (NOPP) and sign the acknowledgement form when their health information is used/collected for research purposes. In addition, the Privacy Officer must be notified of the non-Veteran enrollment and be provided with a copy of the signed NOPP, when applicable. If CPRS notes are entered, and the acknowledgement must also be scanned into CPRS. ***The NOPP, Acknowledgement form, and instructions to provide the completed form to the PO are available under the ? at the top right corner of this page.***

(•) Agree ( ) Disagree

Section 11 - Recruitment

11) Describe, step-by-step, the plans for recruitment of subjects (or selection of subjects as in record review). This description must include how, when, and where potential subjects are approached as well as procedures for identifying potential participants (through medical records, physician referral, third-party sources, etc.). Include how selection is equitable. Indicate if vulnerability to coercion may be present and if so plans to ensure voluntary participation.

Recruitment will primarily occur using existing procedures already in place from the ongoing CBCT trial (IRB protocol H150181).

First, we will recruit participants who have (1) agree to be contacted for other research opportunities and (2) meet eligibility requirements for this pilot study. We will contact those participants via approved means to offer them an opportunity to participate in this pilot study.

Second, we will recruit directly through referrals from the San Diego VA Family Mental Health Program (FMHP). FMHP clinical providers will discuss the study with eligible Veterans who are waiting for couples services. If the Veteran indicates interest in learning more about the study, clinical providers will obtain verbal permission from the Veteran to alert Katelyn Webster (study coordinator) and/or Dr. Morland via a CPRS note. Clinical providers will document that that Veteran indicated interest in the study and agreed to be contacted by phone in a CPRS note.

Finally, we will recruit participants via referrals from VA providers in other clinics and services, including general (e.g., BHIP) or specialty mental health (e.g., PCT) and Primary Care / PCMHI. We will work with providers to facilitate direct referrals via the methods described above.

We will provide a brief informational sheet for providers (not to be shared with participants) which will list study facts and inclusion/exclusion criteria. We will also send providers a basic study flyer to give to their patients who may be interested in participating.

Section 11.1 Recruitment Materials

11.1) Identify all recruitment materials (flyers, advertisements, letters, etc.) that will be used; include the web address for any web-based advertisements. The text of all communications with prospective participants must be reviewed and approved by the IRB before it can be used. You will be reminded to attach copies of recruitment materials to the initial submission packet. ***Note: Posting of flyers with pull tabs is not permitted within VASDHS (including the VMRF building). However, you may request to advertise on the e-boards (located at the elevators and throughout the facility) or on the VASDHS Research Opportunities web-page.***

Recruitment materials (a provider information sheet and participant flyer with basic study facts) will be used for the study. A phone screen will be used to screen participants referred to the study through the VA Family Mental Health Program, other VA clinics (e.g., PTSD clinic), or self-referral.

We will provide a brief information sheet to VA providers (not to be shared with participants) which will list study facts and inclusion/exclusion criteria. We will also send providers a basic study flyer that they can give to interested patients who want more study information. This flyer will include an overview of the research study purpose, details, procedures, and compensation, as well as contact information for study staff. The provider information sheet and study flyer are attached to this application.

Section 12 - Informed Consent

12) Indicate whether or not each category of consent is involved in this study:

12a) Will the study team obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without (or prior to) obtaining informed consent of the prospective subject or the prospective subject's LAR?

(•) Yes ( ) No

Check one or both of the below boxes if they apply to this study:

Information will be obtained through oral or written communication with the prospective subject or the subject's Legally Authorized Representative (LAR) and this is not a FDA regulated study.

( ) Yes (•) No

Identifiable information or biospecimens will be obtained by accessing records or stored identifiable biospecimens and this is not an FDA regulated study.

( ) Yes (•) No

Since both boxes were checked "no", a request for an informed consent waiver is needed.

12b) **Signed** informed consent

(•) Yes ( ) No

12c) Waiver of documented consent (e.g., **oral** consent) for all or part of the study.

○ Yes ◉ No

12d) Request for a **waiver** of consent for all or some study activities.

◉ Yes ○ No

12e) Alteration of **other required elements** of consent.

○ Yes ◉ No

12f) **Child** assent to participate (Director approval will be required)

○ Yes ◉ No

12g) Will any language **other than English** be used by those obtaining consent and understood by the prospective participant or the legally authorized representative?

○ Yes ◉ No

12h) **Decisional Capacity Assessment** to determine if participants have the capacity to consent for themselves.

○ Yes ◉ No

12i) **Surrogate** consent (legally authorized representative)

○ Yes ◉ No

Section 12.1 Informed Consent Process

12.1a) Will consent be obtained before any study procedures are performed (including screening procedures except screening procedures with Consent and/or HIPAA waiver when required)?

◉ Yes ○ No

12.1b) Will the information being communicated to the participant or legally authorized representative during the consent process include exculpatory language through which the participant or legally authorized representative is made to waive or appear to waive any of the participant's legal rights or release or appear to release the Researcher, Sponsor, the VA or its agents from liability for negligence.

○ Yes ◉ No

12.1c) A master list of all VA subjects consented (written or not) under this protocol will be maintained.

◉ Agree ○ Disagree

12.1d) Identify the circumstances under which consent will be obtained including where the process will take place; any waiting period between describing the research and obtaining consent including sufficient time for the prospective participant to consider participation, and any steps taken to minimize the possibility of coercion or undue influence.

Consent will be obtained from both partners during a Webex or VVC telehealth appointment. Prior to the appointment, the DocuSign document including approved informed consent, HIPAA document, and CA Experimental Subjects Bill of Rights will be sent to the couple. The information in the informed consent document will be discussed with the couple during the telehealth visit. Specifically, both members of the couple will be informed that their participation is voluntary, that all information will be kept confidential [except when information pertaining to threat of harm to self (i.e., suicidal intent) or others (i.e., homicidal intent, child abuse, elder abuse) is disclosed by one or both members of the couple], and that they can terminate participation at any time without negative consequences. They will also be informed that they will complete eight 75-minute therapy appointments and assessment measures three times (baseline, post-

program, and three months post-program). It will be explained that the purpose of this study is to find out whether Brief Cognitive Behavioral Conjoint Therapy augmented with intranasal oxytocin results in improvements in PTSD symptoms and relationship satisfaction. It will also be explained that both members of the couple must participate to be eligible for the study.

If either member of the couple cannot demonstrate sufficient comprehension of the consent information by briefly explaining the purpose and risks and benefits of the study, the couple will not be included in the study and the assessment clinician will refer them for alternative treatment.

If interested in participating, couples will sign the DocuSign consent which will be stored in a secure electronic research folder (i.e., PI folder on the R drive). During the consent process, we will also verbally obtain and transcribe all the information necessary in the event that we need to create a collateral medical record for the non-veteran partner. However, we will only open a chart if it is needed in order to avoid risk to the partner's confidentiality. We do not typically see the partner alone, except as part of the initial consent and assessment. 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. This procedure matches that of the Family Mental Health Program.

Section 12.4 Waiver of Informed Consent

12.4a) Is it practicable to conduct the research without the waiver or alteration of consent?

○ Yes ◉ No

12.4b) Does the research examine public benefit or service programs and is subject to state or local government approval?

○ Yes ◉ No

12.4c) Will the research involve greater than minimal risk?

○ Yes ◉ No

12.4d) Will waiving or altering informed consent adversely affect the subjects' rights and welfare?

○ Yes ◉ No

12.4e) Is it appropriate to provide pertinent information to subjects later BUT this information will NOT be provided?

○ Yes ◉ No

12.4f) Identify to what aspects of the study you are requesting a waiver of consent (i.e., full study or specific aspects). Describe the waiver or alteration needed and why it can be granted (include why the research is not practical without the waiver or alteration and how the waiver enables conducting the study).

Waiver of informed consent or alteration of consent elements may be allowed if the IRB documents these findings and approves waiver or alteration.

The study is not able to be conducted without the waiver since it is necessary that all veteran patients be screened over the phone to determine the couple's initial eligibility for the study. It is important that we schedule assessment appointments for only those couples that are deemed initially eligible at the phone screen, as it would add unnecessary burden to couples for whom ineligibility could easily be determined by veteran phone screen if they were required to attend a full baseline assessment screening.

12.4g) Explain why the research could not practicably conducted without using identifiable information.

The use of PHI access and use enables us to conduct research as it allows us to communicate with participants (both veterans and veterans' partners). Also, it is required that we document all veteran contact and appointments. In rare instances, we may also need to document contact /appointments with veteran's partners (e.g., partner discloses SI or IPV concerns). We must collect PHI in order to properly document study progress and appointments.

Section 12.9 HIPAA Authorization

For each category below, indicate whether or not this study involves the indicated process:

12.9a) **Signed** HIPAA Authorization. ***New Template is available in the ? Help section***

(•) Yes ( ) No

12.9b) HIPAA waiver to cover the entire study

( ) Yes (•) No

12.9c) HIPAA waiver for recruitment, screening, and/or for a portion of the study.

(•) Yes ( ) No

12.9d) HIPAA Authorization or waiver is **not required** for some or all of the study subjects (e.g. no health data).

( ) Yes (•) No

Section 12.10 HIPAA Waivers and Alterations

12.10a) Describe the purpose/nature of the HIPAA waiver or alteration and list specifically, what identifiers and health information are being requested under the waiver/alteration and identify whether the waiver is for access, use, and/or collection of this information.

All referrals for potential participants will come directly from clinical providers after Veterans have indicated interest in the study. For Veterans who indicate interest, Ms. Webster will be tagged on the CPRS note. Ms. Webster will contact the couple only after they indicate to their clinical provider a desire to be contacted (which will be documented on the Veteran's CPRS note), to further describe the study, screen for eligibility, and schedule the couple for a pre-treatment assessment session.

Because we will screen Veteran patients for eligibility over the phone, we are requesting a partial HIPAA/consent waiver for screening. This will help us eliminate unnecessary burden for those couples who may not qualify for the study by not scheduling a full assessment visit, and instead facilitating efficient referrals to other appropriate care. At this screen, we will collect the following data for the veteran partner: gender, name (first and last), address, phone contact numbers, and social security numbers. With the waiver we will utilize the following for looking at prospective participants when added as signers to patient CPRS notes: First and Last name, last four of the social security number, address, and phone number.

Pre-eligibility screening questions will include: age; Veteran status; scheduling conflicts and technology availability; whether or not the individual has been told by a medical provider that he or she has a psychotic disorder or a neurocognitive disorder; suicide attempts in the past year; pregnancy or recent birth; exclusionary medical condition; and intimate partner violence in the relationship. See Phone Screen attachment. These screening procedures match currently approved CBCT trial (protocol # H150181) as well as OurRelationship.com Pilot (protocol # H190163).

A HIPPA waiver is also necessary to allow for the disclosure of prospective subjects' names and email addresses to DocuSign for the purposes of emailing them the consent and HIPPA forms

prior to the informed consent appointment. HIPAA authorization will be documented using Docusign which will be stored in a secure electronic research folder (i.e., PI folder on the R drive).

12.10b) The proposed access, use, and/or disclosure of PHI involves no more than a minimal risk to the privacy of individuals.

◉ Agree ○ Disagree

12.10c) The plan to protect the identifiers from improper use and disclosure is adequate.

◉ Agree ○ Disagree

Describe the plan

We will never use patient names to identify patients. Instead, we plan to identify all patients (veterans and partners) with subject identification numbers. This data will be stored in an encrypted Access Database. Only approved study staff will have access to this database.

12.10d) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

◉ Agree ○ Disagree

12.10d2) Describe the plan:

Data will only be destroyed according to RCS-10 under Records Control Manager guidance.

12.10e) By signing this protocol for submission, the PI is providing written assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by the Privacy Rule. 38 U.S.C. 7332 Information: If the waiver of HIPAA authorization is for the use of 38 USC 7332 information (applicable to drug abuse, alcohol abuse, HIV infection, and sickle cell anemia records), by signing this protocol for submission the PI is providing written assurance that the purpose of the data is to conduct scientific research and that no personnel involved may identify, directly or indirectly, any individual patient or subject in any report of such research or otherwise disclose patient or subject identities in any manner. (Ref: 38 U.S.C. 7332(b)(2)(B))

◉ Agree ○ Disagree

12.10f) The research could not practicably be conducted without the waiver or alteration.

◉ Agree ○ Disagree

12.10f2) Describe how the waiver/alteration enables the research to be conducted

The study is not able to be conducted without the waiver since it is necessary that all veteran patients be screened over the phone. It is important that we schedule assessment appointments for only those couples that are deemed eligible at the phone screen, as it would add unnecessary burden to couples for whom ineligibility could easily be determined by veteran phone screen if they were required to attend a full baseline assessment screening.

12.10g) The research could not practicably be conducted without access to and use of the PHI.

◉ Agree ○ Disagree

12.10g2) Describe why it would be impracticable to conduct this research without the PHI described 12.10a. (v3 /8/18)

The use of PHI access and use enables us to conduct research as it allows us to communicate

with participants (both veterans and veterans' partners). Also, it is required that we document all veteran contact and appointments. In rare instances, we may also need to document contact /appointments with veteran's partners (e.g., partner discloses SI or IPV concerns). We must collect PHI in order to properly document study progress and appointments.

Section 13 - Alternatives to Participation

13) Describe the alternatives to participation in this research study (see ? for guidance)

The alternative to participation is to not participate or to access standard care via the VA Family Mental Health Program or other individual outpatient clinics (BHIP, PTSD clinic, Mood Clinic). Alternative psychosocial treatments may include treatment for PTSD or non-trauma-focused counseling provided in either an office-based setting or virtually via the VA's Telemental Health program. Pharmacological treatments for disturbances in mood, arousal, and sleep often associated with PTSD symptomatology may also be available through the VA. Additionally, participants can access a number of other free VA-supported mobile apps and web programs for various mental health concerns, as well as non-VA self-help programs and books. The risks of these alternate treatments are similar to that of B-CBCT with adjunctive intranasal oxytocin, but participants may prefer individual over couple-based treatment, not to take intranasal oxytocin, and/or in-person over web-based treatment.

Section 14 - Potential Risks

14) Describe any potential or known risks or discomforts and assess their likelihood and seriousness (see ? for guidance)

Potential psychological risks of the treatment include exacerbation of PTSD-related anxiety during the approach assignments, relationship distress during the couple intervention, and/or sadness, tension, or other negative emotions when talking about relationship problems. It is possible that, if experienced, some participants will withdraw from the project in response to such discomfort. Risks associated with study assessments include the possibility that participants may become distressed while answering questions pertaining to their emotional functioning and /or their relationship, or they may find some detailed questions intrusive. However, our prior research experience, including substantial research with distressed couples, suggests that data collection using the aforementioned measures can be conducted without undue psychological distress or exacerbation of symptoms among participants. This experience includes substantial research with distressed couples and those with combat-related or victimization-related PTSD.

Potential physical risks are related to participant use of Oxytocin. Oxytocin is a neuropeptide hormone commonly administered intravenously to women during labor and delivery. Risks associated with oxytocin administration have been observed with intravenous, but not intranasal administration, related to its Food and Drug Administration (FDA)-approved purpose to induce labor and facilitate lactation. Risks include seizures, mental disturbances, nausea, vomiting, irregular heartbeat, high blood pressure, and unexpected bleeding or contraction of the uterus and have been observed in a small number of women. Previous studies show that risks of intranasal oxytocin administration are minimal and manageable through the proposed human participants protection methods described below (see 4B. Adequacy of Protection from Risk). Collaborator Dr. Flanagan has administered intranasal oxytocin at the planned dose of 40 international units (IU) to over 900 research participants to date, including Veterans with PTSD and distressed couples with alcohol use disorder and intimate partner violence, without a single severe adverse event reported. Oxytocin is contraindicated for pregnant and lactating women, who will be excluded from the trial. Participants may also experience physical or psychological discomfort during the medication self-administration.

Social risks of this study center around potential threats to confidentiality. We do not anticipate risk of physical, legal, or financial harm as a result of participating in the study. Measures to minimize the identified psychological and social risks are described in Protections Against Risks. Overall, we feel that we have stringently addressed potential risks to participants and that the benefits of the treatment outweigh the risks. Rare but serious risks are with the handling of medical and research records, as there is always the possibility of a breach of confidentiality.

Alternative psychosocial treatments generally include individual treatment for PTSD as well as non-trauma-focused couples counseling provided in an office-based setting similar to the standard services condition offered in our study as well as pharmacological treatments for disturbances in mood, arousal, and sleep often associated with PTSD symptomatology. The risks

of these alternate treatments are similar to that of B-CBCT with adjunctive intranasal oxytocin, but participants may prefer individual over couple-based treatment, not to take intranasal oxytocin, and/or in-person over web-based treatment. Participants will be informed of these alternative treatment options and provided with information on how they may be obtained.

Section 15 - Risk Management

15) Describe the procedures for protecting against or minimizing any potential risks/discomforts, and the adequacy of resources for conducting the study and resources participants may need as a consequence of the research. When applicable, include detail of the following safety measures: (a) The type of safety information to be collected, including AEs; (b) Frequency of safety data collection; (c) Frequency or periodicity of review of cumulative safety data; (d) Statistical tests for analyzing the safety data to determine if harm is occurring; and (e) Conditions that trigger an immediate suspension of the research. See ? for further requirements.

As described above, anticipated risks to this study include an increase in negative emotions, such as sadness, distress, or anxiety, in response to discussing relationship problems and/or engaging approach exercises. Measures to address psychological risks include psychoeducation about PTSD symptoms as well as frequency and form of relationship distress. Risk will also be addressed through the provision of information concerning the rationale behind the intervention strategies used and their potential benefits and side effects (such as an increase in negative emotions), instruction in appropriate couple and individual coping and problem-solving skills, and additional direct therapeutic interventions, as needed, by an experienced couple therapist. To minimize the risk of upset during assessments, participants will complete assessments in private, and all participants will be informed at the outset that they may talk to the PI if they have questions or concerns about assessment items, as well as decline to answer any questions or terminate their participation at any point.

If participants do experience notable distress, they will be provided with contact information for licensed psychologists on study staff, including the PI, and follow-up referrals as appropriate. In addition, they will be given access to a 24-hour crisis psychiatry telephone service. However, our prior research suggests that data collection using the aforementioned procedures can be conducted without undue psychological distress or exacerbation of symptoms among participants. This experience includes substantial research with distressed couples and with technology-mediated interventions. In the event of an Adverse Event (AE), Serious Adverse Event (SAE), or Unanticipated Problem Involving Risks to Subjects or Others (UPR), all notification procedures outlined in the Data Safety and Monitoring Plan section will be followed.

Steps to protect against risk associated with intranasal oxytocin administration will be taken. During informed consent, participants will be informed about the potential side effects of intranasal oxytocin. Participants will not be enrolled unless the study psychiatrist, Dr. Maglione, concurs that no oxytocin-related exclusion criteria are met and the Veteran participant is eligible. Participants will self-administer intranasal oxytocin while being monitored on video by research staff who have ready access to clinicians who can consult on the need for emergency care, if necessary. They will be closely monitored by the research team after each drug administration. Women who are pregnant and lactating women will be excluded from the trial. We will instruct participants who are able to become pregnant to use appropriate forms of contraception, and we will instruct them to perform urine pregnancy tests at baseline and weekly during treatment before self-administration of oxytocin if a Veteran participant is considered able to become pregnant.

Numerous steps will be taken to protect against social risks related to confidentiality. Data will be identified via subject ID number only. The master list linking ID numbers to participants' names will be stored locally on secure, restricted-access San Diego VA research servers in a password-protected database only accessible on password protected computers. Only IRB-approved research staff that has completed training in the handling of confidential data, and re-trained at least once annually, will have access to participant data and files. Lastly, no individual or couple will ever be identified by name, audio recording, or other identifiers in professional presentations or manuscripts related to this study. Given the success of these measures in our previous research experience, we believe these procedures are extremely likely to be effective at minimizing the emotional and social risks to study participation.

Section 17 - Potential Benefits

17) Discuss benefits that may be gained by the subject as well as potential benefits to society in general (see ?

for guidance)

Free access to B-CBCT is a benefit of participating. Specifically, participants may gain information that helps them to better understand and manage the affected partner's symptoms of PTSD, as well as improve communication skills and relationship satisfaction for both members of the couple. Second, findings from the proposed study will inform whether B-CBCT social functioning outcomes can be improved with adjunctive medication. By potentiating the effects of B-CBCT with intranasal oxytocin, we could increase the clinical response rate of patients and their loved ones receiving B-CBCT. Third, if oxytocin enhances the mechanisms described in this proposal as predicted, it could further strengthen rationale for providers administering eight-session B-CBCT rather than 15-session CBCT. Effectively truncating CBCT would mean that more patients could be seen by the same number of VA providers, potentially improving Veterans' access to treatment. Greater effectiveness and efficiency of treatment could lead to lower costs to the VA. Fourth, by targeting mechanisms that are salient not only to intimate relationships but all interpersonal relationships, such as trust, oxytocin could help the effects of B-CBCT extend to other, non-intimate relationships, thereby improving overall quality of life and potentially having downstream effects on other issues facing the VA (such as suicide, substance use, and co-occurring disorders) which are known to be related to interpersonal difficulties. Lastly, improving Veterans' social environments could help them maintain their gains and respond effectively to future stressors—potentially lowering the likelihood of future need for episodes of care.

Section 18 - Risk/Benefit Analysis

18) Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

Risk from participating in B-CBCT augmented with intranasal oxytocin is relatively minor in comparison with the potential benefits to relationship quality and PTSD symptoms to be gained by Veterans and their partners in this study, and is not anticipated to be any greater than risks they may encounter during standard clinical care. This investigation may help subjects manage the symptoms and functional impairment associated with PTSD and will provide valuable knowledge about the treatment of PTSD in Veterans. Furthermore, it may also help couples manage and improve relationship problems and associated functional impairment and will provide valuable knowledge about the treatment of relationship distress in Veterans with PTSD. Thus, the risk benefit ratio warrants this study being conducted.

This conclusion is supported further by the protection procedures in place to address any discomfort caused by the assessment or treatment to Veterans and partners. There is minimal risk associated with gathering information about emotional symptoms and taking part in a brief treatment for such symptoms based on an evidence-supported, manualized intervention. There are no aspects of this study that place participants at additional physical, psychological, social, legal or other risk outside of routine medical and mental health care. Risks associated with oxytocin consumption are mitigated by excluding pregnant women, conducting weekly pregnancy tests for Veteran participants who are able to become pregnant, and weekly questionnaire completion regarding any side effects of the oxytocin. Finally, we are mitigating the current risk of COVID-19 exposure by allowing participants to remain in their homes by using entirely virtual (telehealth, web, and phone) procedures for study enrollment and consent, intervention, and assessment. This study uses the existing VA telehealth infrastructure, including secure VVC telehealth appointments and Webex.

Overall, the evaluation of a brief conjoint couple therapy for PTSD delivered via telehealth with adjunctive intranasal oxytocin appears to justify the identified risks involved in the treatment and assessment procedures in this study. This conclusion is supported further by the protection procedures in place to address any discomfort caused by the assessment or intervention to either the PTSD- affected individual or his/her intimate partner.

Section 20 - Compensation for Participation

20) Provide all details and justifications of the compensation plan. See ? for detailed requirements.

Participants will receive up to $380 per couple for completing all assessment visits according to the following compensation plan: Baseline: $50 for the Veteran and $50 for the partner; Post-treatment: $65 for the Veteran and $65 for the partner; and 3 month follow-up: $75 for the Veteran and $75 for the partner.

Payments will be made by direct deposit into the bank account of the couple's choosing using electronic funds transfer. If the participant currently has a debt to the Federal Government, the debt may be subtracted from the funds transfer payment for study participation.

Under 24 USC 30, payment to Federal Employees and Active Duty military personnel for participation in research while on duty is limited to blood donation and may not exceed $50. If the individual is a Federal Employee, it is understood that they may not receive any other payment or non-monetary compensation for participation on this research study unless they are off duty or on leave during the time they are participating in the research study.

Section 21 - Responsibilities and Qualifications

Here are the identified study staff members

Leslie A. Morland, PsyD

Alex Lin, Amy Hoang, Lauren Maiko Grubbs, Katelyn D. Webster, MA, Jeanne E. Maglione, MD, PhD, Min Ji Sohn, Bette Chargin, Janina S. Schnitzer, BA, Julie M. Holcomb, Katerine T. Rashkovsky, Tamara Wachsman, Chandra E. Khalifian, PhD, Kayla C. Knopp, PhD, Cynthia Kerenyi, (ORO), Mark Borigini, (ORO), Monique Moxey, (ORO), Rachel Galvan, (ORO)

21) For each staff member listed above, describe their role and qualifications. Also indicate which of the study staff are authorized to obtain consent, when applicable to the study.

•Leslie A. Morland, PsyD, Principal Investigator: As project principal investigator (PI) based at the VA San Diego Healthcare System (VASDHS), Dr. Morland will supervise Ms. Webster in all aspects of this pilot research.

•Katelyn Webster, MA, Licensed Marriage and Family Therapist: Ms. Webster will conduct participant screening, obtain informed consent, deliver the CBCT intervention, and collect verbal feedback from participants.

•Jeanne Maglione, MD, PhD: Dr. Maglione will be the licensed prescriber of the oxytocin. She will assist with verifying eligibility for enrollment and monitoring of adverse events.

•Min Ji Sohn: Ms. Sohn serves at the primary data manager and analyst, database builder and manager. She will assist in statistical analyses, methodological data collection concerns, and troubleshooting.

•Katerine Rashkovsky: Ms. Rashkovsky will aid with database management, obtaining informed consent, and other research administrative tasks.

•Tamara Wachsman: Ms. Wachsman will aid with database management, obtaining informed consent, and other research administrative tasks.

•Chandra Khalifian, PhD, research psychologist: Ms. Khalifian will deliver the CBCT intervention and aid with database management and analysis of data.

•Kayla Knopp, PhD, post-doctoral research fellow: Ms. Knopp will deliver the CBCT intervention and aid with database management and analysis of data.

•Volunteer Research assistants helping with day-to-day project tasks: Janina Schnitzer, Bette Chargin

Section 22 - Bibliography

22) List relevant articles that the IRB can use to provide necessary background for the protocol. Do not include an extensive NIH-grant-style bibliography. (Up to 5 recommended, but use more if needed to support the protocol or citations above.)

1. Monson, C. M., Fredman, S. J., Adair, K. C., Stevens, S. P., Resick, P. A., Schnurr, P. P., ... Macdonald, A. (2011). Cognitive-behavioral conjoint therapy for PTSD: Pilot results from a community sample. Journal of Traumatic Stress, 24(1), 97-101. doi:10.1002/jts.20604

2. Monson, C., & Taft, C. (2005). PTSD and intimate relationships. PTSD Research Quarterly, 16 (4), 1-7. Retrieved from https://search.proquest.com/docview/42415581?accountid=28179
3. Morland, L. A., Macdonald, A., Grubbs, K. M., Mackintosh, M., Monson, C. M., Glassman, L. H., ... Glynn, S. (2019). Design of a randomized superiority trial of a brief couple treatment for PTSD. Contemporary Clinical Trials Communications, 15, 100369. doi:10.1016/j.conctc.2019.100369
4. Shnaider, P., Pukay-Martin, N., Fredman, S., Macdonald, A., & Monson, C. (2014). Effects of Cognitive-Behavioral Conjoint Therapy for PTSD on Partners' Psychological Functioning. Journal of Traumatic Stress, 27(2), 129-136. doi:10.1002/jts.21893
5. Koch S, van Zuiden M, Nawijn L et al. Intranasal oxytocin as strategy for medication-enhanced psychotherapy of PTSD: Salience processing and fear inhibition processes. Psychoneuroendocrinology. 2014;40:242–56.
6. Flanagan JC, Mitchell JM, Baker NL, et al. Enhancing prolonged exposure therapy for PTSD among veterans with oxytocin: Design of a multisite randomized controlled trial. Contemp Clin Trials. 2020;95:106074.
7. Ditzen B, Schaer M, Gabriel B, et al. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biol Psychiatry. 2009;65:728–31.

Section 23 - Sponsors and Collaborators

23) Clarify any industry financial or other support (e.g., NIH funds the study or Company X provides the assay kits). Identify non-VA Research collaborators and their role in this protocol, including whether or not they have access to subjects or identified data.

Sponsor: NCPTSD. This project is funded by NCPTSD using non-peer reviewed special project funds.

Non-VASDHS Research Collaborators:
Lauren Sippel, PhD: Dr. Sippel is an Assistant Professor in the Department of Psychiatry at the Geisel School of Medicine at Dartmouth, an Associate Director of the Northeast Program Evaluation Center at the VA Connecticut Healthcare System, and a practicing Psychologist at the White River Junction VA Medical Center. Her program of research focuses on delineating cognitive, affective, and neurobiological mechanisms of trauma recovery and interpersonal problems experienced by trauma-exposed individuals and developing novel treatments that target these shared mechanisms in an effort to improve social functioning. Dr. Sippel will consult on study design, conduct, and interpretation of data. Dr. Sippel will have access to de-identified data.

Julianne Flanagan, PhD: Dr. Flanagan is an Associate Professor in the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina and a Staff Psychologist in the PTSD Clinical Team at the Ralph H. Johnson VAMC. Her program of research focuses on the behavioral and neurobiological mechanisms linking alcohol use with intimate partner aggression (IPA) and developing novel behavioral and pharmacological treatments for alcohol use disorders (AUD) in populations at high risk for IPA. Dr. Flanagan has extensive experience leading and collaborating on multidisciplinary projects in the area of Veterans' health, PTSD, and complex comorbidities, with unique expertise in the conduct of trials of oxytocin-enhanced psychotherapies. She is currently the PI of two such trials, one a study of a couples intervention for alcohol use disorder augmented with oxytocin (funded by NIAAA) and the other a study of Prolonged Exposure for PTSD augmented with oxytocin among Veterans with PTSD (funded by VA CSRD). Dr. Flanagan will consult on study design, conduct, and interpretation of data. Dr. Flanagan will have access to de-identified data.

Candice Monson, Ph.D., CBCT Consultant: Dr. Monson will provide consultation on the application of CBCT to Veteran couples. She is the lead developer of CBCT for PTSD and an expert in the couple-based PTSD treatment, as well as assessment of couple/family functioning. She is currently the PI on a NIH-funded RCT of CBCT for PTSD and has over 50 published articles related to PTSD. Dr. Monson will have access to de-identified data.

In the submission form, upload a copy of the grant, subaward, CRADA, etc. as appliable to the study.

Section 27 - Privacy, Confidentiality, and Information Security

27a) Provide a brief description of how participant privacy and confidentiality will be protected in this study. Describe the circumstance under which it may be possible for a research team member to identify subjects and any related protections or assurances to prohibit or avoid identification. Describe how the number of people with access to identifiers for research purposes is limited in order to protect a participant's privacy.

All study procedures will be approved and monitored by the VA San Diego's IRB, which includes an annual audit of projects files, including informed consent audits. Monitoring of safety and data quality will be the responsibility of all personnel on the project, with primary responsibility and supervision by the PI. The PI will ensure that all research team members are properly trained in the reporting of AEs, SAEs, UPRs and protocol deviations, and follow the policies and procedures of the IRB. Any adverse effects noted by any project personnel in response to, or in potential response to, any project intervention, assessment protocol, or study involvement will be immediately reported to the PI. The procedures for notification include verbal notification of all levels of AEs and UPRs directly to the PI and documentation of the discussion and/or provision of a written notification or report to the PI through a case report form, sponsor communication, AE /UPR reporting form, progress note, email or other method deemed acceptable by the PI. Any serious unanticipated adverse events or problems that may be related to the research will then be reported to the IRB within 5 business days. All other reports will be submitted at the time of the annual continuing review. Following each adverse event and in addition to the IRB determination, an investigation of the circumstances precipitating the event, all probable factors, the current status of the event, and the outcome of the event will be conducted by the project PI. A written summary of findings will be submitted to the IRB.

Any form of physical data containing PII (e.g., transcribed questionnaires) will be coded with research numbers that are matched to participant identifiers on a master list. This master list will be retained in a password-protected database on secure VA research servers accessible only on VA-networked password-protected computers.
Electronic research data will include audio recordings of B-CBCT sessions as well as responses on self-report assessment surveys. Research data will be collected by hard copy or by phone and will be entered into an electronic data set stored on VA secure local research servers accessible only by authorized users on password-protected computers.

In terms of participant safety monitoring, each participant will be given the telephone number of the PI and study clinician during the consenting process. Participants will be encouraged to call the PI or notify study staff if they experience significant distress from participating in the study. Any study staff will contact the PI about any participant who appears or reports significant distress related to study participation. All such participants will then be contacted personally by the PI and, in cases where the distress is extreme, the PI will decide upon and provide needed services or referrals. The study's exclusion and inclusion criteria provide additional clinical safeguards by identifying appropriate participants for this treatment and excluding high risk patients (i.e., suicidal/homicidal ideation, domestic violence, active SUD, pregnancy /breastfeeding, and hypertension).

This study will include a Data Safety and Monitoring Plan (DSMP) that will be developed in accordance with the National Institutes of Health (NIH) Office of Human Research Protection (OHRP) to assure the appropriate clinical safety monitoring of study subjects participating in this study. Recruitment and safety data are monitored according to the schedule established by the monitoring board, generally every 4-6 months for intervention studies. Quality control and assurance of data entered into the database is discussed above as part of Protections Against Risk. Missing data will be considered as part of the plan for statistical analysis. This study will not include a Data Safety Monitoring Board.

27.b) Entry of a CPRS Research Informed Consent Note is required when subjects will be admitted as inpatients or treated as an outpatients for research *and* the study involves research medical care or may affect medical care.

- ***If a Research consent Note is required, then a Research Progress Note should also be entered for each procedure or intervention.***
- ***Scanning the Consent and HIPAA Authorization into CPRS is not required. Linking the Consent to the Research Informed Consent Note may be permitted and can be useful for trials involving the Research Pharmacy or when research will be performed in conjunction with clinical procedures.***
- ***For Non-Veterans, if Research Informed Consent Notes are entered, then the NOPP Acknowledgment must be scanned into the record. Otherwise a copy of the signed NOPP must be retained with the Investigator's research records and a copy sent to the Privacy Officer; see the ? Help for more information.***

27.b1) Is entry of CPRS notes required based on the above criteria?

- ○ CPRS notes are needed for ALL subjects
- ◉ CPRS notes are needed for SOME subjects
- ○ CPRS notes are NOT needed for any subjects

Identify for which group or groups CPRS records will be entered and to which groups this requirement does not apply.

CPRS records will be entered for VA-enrolled Veteran subjects. Information to open a collateral medical record will be collected but will not be opened unless clinical need arises (e.g., disclosure of suicidality). If no clinical need arises, CPRS notes will not be entered for non-veteran subjects.

27c) Select the VA Sensitive Information (VASI) use category

- ○ This study does not collect or use any VASI
- ○ This study uses but does not save, collect, copy, or record VASI
- ◉ This study does collect or record VASI

Section 27.1 VA Sensitive Information (VASI)

27.1a) For each type of VASI, indicate all that apply:

Indicate which of the following will be collected/recorded:

- ☑ Protected Health Information (PHI)
- ☑ Names
- ☐ Device identifiers and serial numbers
- ☑ E-mail addresses
- ☐ Medical record numbers
- ☐ URLs (Universal Resource Locator)
- ☑ All elements of dates (except year) or any age over 89
- ☐ Health plan beneficiary numbers
- ☐ IP Addresses (Internet Protocol)
- ☑ Telephone numbers
- ☑ Account numbers
- ☐ Biometric Identifiers including finger and voice print
- ☐ Fax numbers
- ☐ Certificate or license numbers
- ☐ Full face photographic images and comparable images
- ☑ All geographic subdivisions smaller than a state
- ☐ Vehicle ID and serial numbers including license plate numbers
- ☑ Social security numbers or scrambled SSNs (describe below)
- ☑ Other unique identifying number, characteristic, or code (describe below)

27.1a1) Describe why SSN are needed for this study

Subject payment and use of clinical record.

27.1a2) Identify the specific other identifier/s that will be used or recorded

Date of birth for non-veteran partners. We must collect this in order to complete the form for opening a collateral medical record for non-veterans, in case doing so is needed to document a safety concern or other non-veteran partner information.

27.1b) Consent Forms and/or HIPAA Authorization

(•) Yes ( ) No

27.1c) Images with personal identifiers are used for this study (x-rays, MRI images with patient names, record numbers, dates, etc.)?

( ) Yes (•) No

27.1d) Photos with faces or audio video recordings are used for this study.

(•) Yes ( ) No

27.1d1) Identify the device or devices that will be used to take/make the photographs or recordings.

Audacity

27.1d2) Identify where images will be stored (e.g., in the medical record, with study hardcopy records, with study electronic VASI records

The study will collect audio recordings of patient-therapist meetings and assessments. These recordings are considered PHI under HIPAA and VA definition of PHI. These audio recordings will be collected using Audacity. The audio recordings will be saved directly to a secure VA share drive and labelled with anonymous study subject IDs. Only study personnel will have access to the audio recordings. A VA-approved USB microphone that is not capable of storing any data on it will be used to enhance the sound quality. Audio-recordings will be deleted when permitted pursuant to the VA Record Retention Schedule.

27.1e) Biological specimens with identifiers are used for this study.

( ) Yes (•) No

Section 27.2 Data Collection, Tools, and Resources

27.2a) Will any specially obtained software be used?

( ) Yes (•) No

27.2b) Will any mobile devices (laptop, tablet, portable hard-drive, etc.) be used in support of this study?

( ) Yes (•) No

27.2c) Does the study require use of an electronic data capture system?

○ Yes ◉ No

27.2d) Will any other web-based applications be used (e.g., for recruitment, completing online questionnaires, or processing data)?

○ Yes ◉ No

27.2e) Will coded data that excludes personal identifiers be used? Coded data excludes *all* HIPAA identifiers (per VHA Handbook 1605.1 Appendix B), including dates

◉ Yes ○ No

27.2e1) Identify where the code key is stored and in what format (electronic, paper).

Electronically in an Access database on a secure VA research server accessible only on VA-networked password-protected computers.

Section 27.3 Data Sharing and Transportation

27.3a) Does this study involve collecting, sharing or transporting any type of data outside of the local VA?

◉ Yes ○ No

27.3b) This study collects VASI outside of VA (i.e., at a non-VA location).

◉ Yes ○ No

27.3b1) Describe what is collected outside the VA and how it is secured in transit back to the VA. *Note: An approved Authorization to Transport will be required.*

Clinical contact is provided to Veteran's homes via VA Video Connect, VA's secure clinical video telehealth system, and Webex.

27.3c) VASI is transported outside of VA for any purpose other than sharing.

○ Yes ◉ No

27.3d) PHI may be disclosed to monitoring/auditing agencies by HIPAA Authorization. *Note: The Research Office must be notified when monitors come to audit*

◉ Yes ○ No

27.3e) Data may be shared with collaborators or others in the conduct of this protocol.

◉ Yes ○ No

27.3e1) Describe the data to be shared or disclosed, the entities to which the data are to be disclosed, how the data are to be transmitted, and how the transmitted data will be stored, retained, destroyed, and/or further disclosed and to whom. This includes data from individual subjects as well as other data developed during the research such as the analytic data and the aggregate data. For PHI and VASI, indicate the authority/ies permitting the sharing or disclosure of data (HIPAA Authorization, Limited Data Set, Data Use Agreement, VA Form 10-5345-Request for and Authorization to Release Health Information., etc.).

In general, it is unlikely that de-identified study data will be sent to collaborators. On the rare occasion that de-identified data is shared with collaborators, an Excel database would be stripped of identifiers other than the subject ID. The data sets will not contain any of the 18 HIPAA personal identifiers, and collaborators will not have access to linkage information. This Excel database would include baseline and outcome self-report measures data and would be shared for the purpose of descriptive and/or differential analysis. The files would be sent via encrypted email and would be password protected. The passwords would then be sent in a separate email to ensure security.

Section 27.4 Research Record Storage and Retention

For each type of record, indicate whether it is collected for this study

27.4a) Hardcopy records/data (includes paper, pictures, film, etc.)

◉ Yes ○ No

27.4a1) Identify precisely where hardcopy data will be stored to include physical site, building, and room number, etc. For each location identify whether VASI or non-sensitive information is stored at that location. For VASI, identify how the data is secured.

Physical VASI records will be kept in locked cabinets in a locked office (room 418) in Building 13 at the Veterans Medical Research Foundation. Data will be retained in accordance with VA record control schedule RCS 10-1.

27.4a2) Are all of the above locations at VA?

◉ Yes ○ No

27.4b) Electronic study records (includes computer files, removable disk files, digital files, etc.).

◉ Yes ○ No

27.4b1) Identify precisely where ***non-sensitive*** electronic records/data will be stored to include the full map drive, network location/server name, etc., and a brief description of what data/information is stored at each location.

S Drive; PI folder: Morland

Assessment measures, recruitment materials, consent documents, etc.

27.4b2) Identify precisely where ***VASI*** electronic records/data will be stored to include the full map drive, network location/server name, etc., and a brief description of what data/information is stored at each location.

If no VASI is collected or recorded for this study, simply indicate that the "Study does not collect or record VASI".

S Drive; PI folder: Morland

Names, phone numbers, last 4, and addresses are stored in an encrypted file at the location listed above.

27.4b3) Are any of the locations described in 27.4b outside of the VA Secure Network? *Note: this includes storage on a computer local hard drive.*

○ Yes ◉ No

27.4c) Record Retention - VHA requires compliance with Records Control Schedule (RCS-10) for retention of electronic and hard copy records. Following study closure, these temporary records must be retained for six years and then destroyed. Longer retention may be permitted if requred by other Federal regulations or requirements. Will RCS-10 requirements be followed (i.e., 6-year retention)?

◉ I will adhere to VHA Records Control Schedule-10 requirements
○ I request an exception to RCS-10 requirements

Section 27.5 Additional Privacy or Information Security Details

Provide any other privacy or information security details here.

NA

Section 27.6 Attestations

In the event of real or suspected breach of security, the Information Security Officer, Privacy Officer, VA Police (if appropriate), and the individual's supervisor will be notified within one hour of learning of the event.

◉ Agree ○ Disagree

Study staff will be up to date on any required VHA Privacy Policy and Information Security training or they will not be allowed access to VA Sensitive Information.

◉ Agree ○ Disagree

Access to research sensitive information, if any, will be removed when study personnel are no longer part of the research team.

◉ Agree ○ Disagree

At least one copy of all study records (whether sensitive or non-sensitive) will be retained under VA control and only destroyed in compliance with the approved Records Control Schedule

◉ Agree ○ Disagree

The VA retains ownership of the research data. Should the investigator leave the VA, custody of the research records will be assigned to another investigator and the Research Service notified in writing, or custody of the research records will be transferred to the Research Service.

◉ Agree ○ Disagree

Section 28 - Protocol Association to New or Existing Project

28) Is this a new R&D Project? Before you go on to complete the *Initial Review Submission Form* (which is used for attachments), please address the association of this Protocol to an R&D Committee Project. This Protocol may represent a new R&D Project, or it may be an additional Protocol under an existing R&D Project (such as when a single grant supports multiple Protocols). Will this Protocol be submitted to the R&D Committee as a new Project?

◉ Yes ○ No

The Protocol Application is now complete for a Protocol that will also be a new R&D Committee Project.

Next you will go on to the Initial Review Submission Form which is used to package up the Protocol Application and any needed attachments and submit them to the IRB.

Click on *Save and Continue*