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Complete List of Authors:	Mathersul, Danielle; Veterans Affairs Palo Alto Health Care System, War Related Illness and Injury Study Center; Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences Tang, Julia; Veterans Affairs Palo Alto Health Care System, War Related Illness and Injury Study Center Schulz-Heik, R. ; Veterans Affairs Palo Alto Health Care System, War Related Illness and Injury Study Center Avery, Timothy; Veterans Affairs Palo Alto Health Care System, War Related Illness and Injury Study Center; Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences Seppälä, Emma; Stanford University School of Medicine, Center for Compassion and Altruism Research and Education; Yale University, Yale Center for Emotional Intelligence Bayley, Peter; Veterans Affairs Palo Alto Health Care System, War Related Illness and Injury Study Center; Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences
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Study protocol for a non-inferiority randomized controlled trial of SKY breathing meditation versus cognitive processing therapy for PTSD among veterans

Danielle C. Mathersul, PhD[1,2]*, Julia S. Tang, MS[1], R. Jay Schulz-Heik, PhD[1], Timothy J. Avery, PsyD[1,2], Emma M. Seppälä, PhD[3,4], & Peter J. Bayley, PhD[1,2]*

[1]War Related Illness and Injury Study Center, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304, United States of America

[2]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, United States of America

[3]Center for Compassion and Altruism Research and Education, Stanford University School of Medicine, Stanford, CA 94305, United States of America

[4]Yale Center for Emotional Intelligence, Yale University, New Haven, CT 06520, United States of America

*Corresponding authors. Email: dcmathersul@stanford.edu; Peter.Bayley@va.gov. Address: WRIISC VA Palo Alto Health Care System, 3801 Miranda Ave, Mail Code 151Y, Palo Alto, CA 94304, United States of America.

Author's email addresses: julia.tang@va.gov; robert.schulz-heik@va.gov; timothyavery@stanford.edu; emmasep@gmail.com.

Abstract

Introduction: Posttraumatic stress disorder (PTSD) is a debilitating, highly prevalent condition. Current clinical practice guidelines recommend trauma-focused psychotherapy (e.g., cognitive processing therapy; CPT) as the first-line treatment for PTSD. However, while these treatments show clinically meaningful symptom improvement, the majority of those who begin treatment retain a diagnosis of PTSD post-treatment. Perhaps for this reason, many individuals with PTSD have sought more holistic, mind-body, complementary and integrative health (CIH) interventions. However, there remains a paucity of high-quality, active controlled efficacy studies of CIH interventions for PTSD, which precludes their formal recommendation.

Methods and analyses: We present the protocol for an ongoing non-inferiority parallel group randomized controlled trial (RCT) comparing the efficacy of a breathing meditation intervention (Sudarshan Kriya Yoga [SKY]) to a recommended evidence-based psychotherapy (CPT) for PTSD among veterans. Assessors are blinded to treatment group. The primary outcome measure is the Posttraumatic Stress Disorder Checklist-Civilian Version and a combination of clinical, self-report, experimental, and physiological outcome measures assess treatment-related changes across each of the four PTSD symptom clusters (re-experiencing, avoidance, negative cognitions or mood, and hyperarousal/reactivity). Once the RCT is completed, analyses will use both an intent-to-treat (using the "last observation carried forward" for missing data) and a per-protocol or "treatment completers" procedure, which is the most rigorous approach to non-inferiority designs.

Ethics and dissemination: To our knowledge, this is this first non-inferiority RCT of SKY versus CPT for PTSD among veterans. The protocol is approved by Stanford University Institutional Review Board. All participants provide written informed consent prior to

participation. Results from this RCT will inform future studies including larger multi-site efficacy RCTs of SKY for PTSD and other mental health conditions, as well as exploration of cost-effectiveness and evaluation of implementation issues. Results will also inform evidence-based formal recommendations regarding CIH interventions for PTSD.

Trial registration: NCT02366403.

Keywords: posttraumatic stress disorder; Sudarshan Kriya; meditation; pranayama; cognitive processing therapy; non-inferiority; randomized controlled trial

Strengths and limitations of this study:

- There remains a paucity of high-quality, active controlled efficacy studies of complementary and integrative health interventions for posttraumatic stress disorder
- In response, here we present the protocol for an ongoing non-inferiority parallel group randomized controlled trial comparing the efficacy of Sudarshan Kriya Yoga breathing meditation to cognitive processing therapy for PTSD among veterans
- The primary outcome measure is the Posttraumatic Stress Disorder Checklist-Civilian Version (PCL-C)
- Additional outcome measures (including experimental and physiological) assess treatment-related changes across each of the four PTSD symptom clusters
- This RCT is restricted to veterans; future RCTs will explore efficacy of SKY in non-veteran populations

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating condition that develops in some individuals after exposure to a traumatic event. It is associated with four clusters of symptoms: i) re-experiencing (e.g. recurring intrusive memories, flashbacks, disturbing dreams); ii) avoidance of stimuli associated with the trauma; iii) persistent negative alterations in cognitions and mood (e.g. impaired memory, exaggerated shame/guilt/blame, depression, anhedonia), and iv) altered arousal/reactivity (e.g. irritability, aggression, hypervigilance, exaggerated startle, impaired attention/concentration, sleep disturbance) (APA, 2013). PTSD is associated with poor quality of life and increased risk of suicide (Bryan et al., 2015; Panagioti, Gooding, & Tarrier, 2012; Tarrier & Gregg, 2004), which may contribute to the alarming rise of suicidal behavior amongst returning veterans (AFHSC, 2014; Kemp & Bossarte, 2012). The lifetime prevalence of PTSD in the general US population is estimated to be about 6.5% (Kessler, Berglund, et al., 2005; Pietrzak, Goldstein, Southwick, & Grant, 2011; Reynolds, Pietrzak, Mackenzie, Chou, & Sareen, 2016). Prevalence is reported to be up to 24.5% within veteran populations (Fulton et al., 2015; Gates et al., 2012; Spottswood, Davydow, & Huang, 2017). Veterans with mental health disorders also have higher rates of comorbidity and greater severity of symptom presentation than non-veterans with mental health disorders (Kramarow & Pastor, 2012; Trivedi et al., 2015). A recent systematic review revealed that the median prevalence of PTSD in primary care (across civilian and veteran populations) is equivalent to that of depression (Spottswood et al., 2017), though it is not typically the primary referral or complaint (Grubaugh et al., 2005), highlighting the need for rigorous education, screening, assessment, and appropriate treatment by providers.

Cognitive behavioral therapy (CBT), an evidence-based psychotherapy, is considered the "gold standard" (strongest evidence base) mental health intervention (Butler, Chapman, Forman, & Beck, 2006). Current clinical practice guidelines for PTSD across national and international organizations such as World Health Organization (WHO), International Society for Traumatic Stress Studies (ISTSS), Veterans Affairs/Department of Defense (VA/DoD), American Psychiatric Association (APA), National Institute for Clinical Excellence (NICE), and Australian Centre for Posttraumatic Mental Health (ACPMH) all recommend trauma-focused therapy as the first-line treatment for PTSD (ACPMH, 2013; Benedek, Friedman, Zatzick, & Ursano, 2009; ISTSS, 2008; NICE, 2005; VA/DoD, 2017; WHO, 2013). Trauma-focused therapy for PTSD includes variations of CBT such as cognitive processing therapy (CPT), prolonged exposure therapy (PE), and imaginal exposure (IE), as well as eye-movement desensitization and reprocessing (EMDR). These evidence-based psychotherapies for PTSD show large effects compared to wait-list controls (average effect size = 1.11; Bradley, Greene, Russ, Dutra, & Westen, 2005) and supportive therapy (average effect size = 1.01; Lee et al., 2016). They also have significantly higher effect sizes than medications such as selective serotonin reuptake inhibitors (SSRIs; e.g., sertraline), serotonin norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine), atypical antidepressants (e.g., nefazodone), alpha-1 blockers (e.g., prazosin), antipsychotics (e.g., olanzapine, risperidone), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) (average effect size = 0.43, n.s.; Lee et al., 2016).

Despite the relative effectiveness of trauma-focused CBT as a treatment for PTSD, these evidence-based treatments remain inadequate. First, although the majority of individuals receiving psychotherapy attain clinically meaningful symptom improvement, up to two-thirds of cases retain a PTSD diagnosis post-treatment (Schottenbauer, Glass, Arnkoff, Tendick, & Gray,

2008; Steenkamp, Litz, Hoge, & Marmar, 2015). Second, treatment non-retention is a significant problem in military-related PTSD treatment; several large studies in both the VA and DoD found that only a small proportion of individuals receive a minimally adequate number of mental health encounters after PTSD diagnosis (Hoge et al., 2014). Reasons for not seeking treatment and dropout are complex and include stigma, confidentiality concerns, time demands, perceived treatment inefficacy, and discomfort with the therapist.

Perhaps as a result of the numerous problems surrounding currently available treatments, there is a trend for individuals with PTSD to seek more holistic, mind-body, complementary and integrative health interventions (Wynn, 2015). These CIH interventions (previously referred to as complementary and alternative medicine [CAM]) may be viewed as less stigmatizing than formal mental health interventions such as CBT (Ehde, Dillworth, & Turner, 2014). Recent data show that 34% of individuals within the general US population (Clarke, Black, Stussman, Barnes, & Nahin, 2015) and 39% of individuals with PTSD (Libby, Pilver, & Desai, 2013) reported using at least one CIH intervention in the previous year. Outside of the PTSD field, a growing body of evidence underscores the efficacy of meditation/mindfulness-based CIH therapies for reducing suicidality (Barnhofer et al., 2015) and insomnia (Britton, Haynes, Fridel, & Bootzin, 2010; Wang et al., 2016) and improving symptoms of anxiety and depression (Cramer, Lauche, Langhorst, & Dobos, 2013; Gu, Strauss, Bond, & Cavanagh, 2015; Hofmann, Andreoli, Carpenter, & Curtiss, 2016; Hofmann, Sawyer, Witt, & Oh, 2010; Sloan et al., 2017; Strauss, Cavanagh, Oliver, & Pettman, 2014; van der Velden et al., 2015; Vøllestad, Nielsen, & Nielsen, 2012), all of which overlap with PTSD, both in terms of diagnostic criteria and high frequency of comorbidities (APA, 2013; Kessler, Wai, Demler, & Walters, 2005; Kobayashi, Boarts, & Delahanty, 2007; Panagioti et al., 2012).

Two recent systematic reviews and meta-analyses of randomized controlled trials (RCTs) concluded that CIH interventions significantly improve symptoms of PTSD. The larger of the two included 19 RCTs (mindfulness-based approaches (10 studies), meditation/mantrum-based approaches (6 studies), yoga-movement based approaches (4 studies), and combination approaches (1 study)) and found support for a small-medium effect size on PTSD, with effect sizes larger for smaller studies (< 30 sample size) (Gallegos, Crean, Pigeon, & Heffner, 2017). Similarly, the smaller of the two included 10 RCTs (mindfulness-based approaches (5 studies), yoga-movement based approaches (3 studies), and meditation/mantrum-based approaches (2 studies)) and found support for a small-medium effect size on PTSD and depression (Hilton et al., 2017). However, a consistent theme across these systematic reviews and meta-analyses is the paucity of high-quality, well-controlled efficacy studies of CIH interventions for PTSD, with existing studies containing biases such as small sample size, inadequate control/comparison group, non-random allocation, non-blinding, high attrition rates, or a failure to report on these aspects of study design.

VA hospitals are mandated to provide certain CIH interventions (including meditation and yoga) that have preliminary evidence suggesting at least the potential for benefit (Gaudet & Shulkin, 2016). At the same time, the VA/DoD states that currently there is insufficient evidence to formally recommend CIH interventions as first-line treatments for PTSD (HAIG, 2015; VA/DoD, 2017). To inform a formal recommendation, studies must address the biases and poor quality highlighted in the two recent systematic reviews and meta-analyses outlined above. The ideal study design is a large RCT with an active control comparison group rather than case studies or non-controlled studies (IOM, 2005). Non-inferiority design RCTs are recommended for testing the hypothesis that a novel intervention (e.g., a CIH intervention) is no worse than an

established standard intervention (e.g., trauma-focused therapy) at treating the target condition (e.g., PTSD) (Greene, Morland, Durkalski, & Frueh, 2008). This design is particularly appropriate when the novel intervention may be preferable to the standard intervention for reasons other than efficacy, such as lower costs, greater acceptability, lower drop-out rates, etc. SKY is a promising CIH meditation intervention for PTSD;(?) it has been shown to reduce symptoms of PTSD, depression, and anxiety in several uncontrolled or small pilot RCTs, including several involving veterans with a history of trauma (Brown & Gerbarg, 2005; Carter et al., 2013; Descilo et al., 2010; Seppälä et al., 2014; Walker & Pacik, 2017). Our clinical research team at the VA Palo Alto Health Care System recently launched a RCT with a non-inferiority parallel group design comparing a breathing meditation intervention (Sudarshan Kriya Yoga [SKY]) to an evidence-based psychotherapy (CPT) for PTSD in veterans ("Breathing Meditation Intervention for Post-Traumatic Stress Disorder" (PI Bayley); VA RR&D Merit Review; ClinicalTrials.gov NCT02366403). The aim of this manuscript is to outline the study design and protocol for this ongoing, 4-year RCT. The primary aim of the RCT is to test the hypothesis that SKY breathing meditation is non-inferior to CPT as a treatment for veterans with clinically significant symptoms of PTSD. As such, we will compare PTSD symptoms pre- versus post-treatment, as well as pre-treatment versus 1-month and 1-year follow-up. We also aim to assess whether dropout rates at post-treatment differ between SKY and CPT. We have carefully chosen a combination of clinical interview, self-report, experimental, and physiological outcome measures to assess treatment-related changes across each of the four PTSD symptom clusters of re-experiencing, avoidance, negative cognitions or mood, and hyperarousal/reactivity.

Methods and analyses

Patient and Public Involvement

In May 2016, the VA issued a Memorandum entitled "Advancing Complementary and Integrative Health in VHA", mandating that all VA hospitals provide CIH interventions – such as meditation and yoga – to Veterans (Gaudet & Shulkin, 2016), emphasizing the VA's commitment to providing these services. The Memorandum was jointly authored by Tracy Gaudet, M.D., Director Office of Patient Centered Care & Cultural Transformation, and David J. Shulkin, M.D., Under Secretary for Health. The Office of Patient Centered Care & Cultural Transformation is charged with transforming the VA Health Care System into a patient-centered, patient-driven, personalized approach. This RCT is in direct alignment with this Memorandum.

Study design

A non-inferiority parallel group design RCT is being used to test the hypothesis that SKY breathing meditation is non-inferior to CPT as a treatment for veterans with clinically significant symptoms of PTSD. Participants who meet inclusion criteria are randomly assigned to one of two groups (SKY or CPT) and receive treatment over a 6-week period. Random allocation occurs at a 1:1 (SKY:CPT) ratio and participants blindly draw their group out of a hat consisting of sealed envelopes created by the study coordinator. The primary outcome measure is change in PTSD symptoms, as measured by the Posttraumatic Stress Disorder Checklist-Civilian Version (PCL-C) and assessed at pre-treatment, post-treatment, 1-month follow-up, and 1-year follow-up. The secondary outcome measures utilize a multi-methodological approach assessing a wide range of subjective and objective PTSD-related symptoms assessed pre- and post-treatment. This combination of clinical interview, self-report, experimental, and physiological outcome measures were chosen to assess treatment-related changes across each of the four PTSD

symptom clusters of re-experiencing, avoidance, negative cognitions or mood, and hyperarousal/reactivity (APA, 2013) (Table 1, Figure 1). In this way, we are also able to examine potential differences in mechanisms of treatment action (e.g., SKY may work via bottom-up (physiological arousal and regulation) processes whereas CPT may exert more top-down (cognitive, self-regulatory) influences).

Setting

All in-person assessments and treatment interventions occur at the War Related Illness and Injury Study Center (WRIISC) at the Veterans Affairs Palo Alto Health Care System (VAPAHCS) in Palo Alto, California, USA. All screening interviews, assessments, and the CPT intervention are conducted in private clinical interview rooms. The SKY intervention is conducted in a large conference room.

Participants

This RCT is funded by a Department of Veterans Affairs RR&D Merit Review ("Breathing Meditation Intervention for Post-Traumatic Stress Disorder" (PI Bayley); ClinicalTrials.gov NCT02366403) and the RCT is only open to veterans. To ensure the greatest generalizability for dissemination of meditation for treating PTSD, participants are any veteran of any age or sex who demonstrate clinically significant symptoms of PTSD. Participants are community-dwelling outpatient adult veterans who reside in the San Francisco Bay Area and those from outer areas who are willing and able to visit the VA Palo Alto for assessment and treatment. A recent study among Vietnam veterans suggests that most ethnic minority veteran groups have a higher rate of PTSD than Caucasian veterans (Loo, 2007). Therefore, we are seeking an ethnically diverse population of male and female veterans, with combat and non-combat PTSD.

Exclusion criteria. Individuals are excluded if they (i) are participating in a concurrent RCT; (ii) are unable to attend study visits and sessions at the VA Palo Alto; (iii) intend to begin a new trauma-focused therapy (e.g., CPT, PE, IE, EMDR) during the study period; (iv) have experienced mania or psychosis for any reason within the past 6-months (e.g., bipolar, schizophrenia, drug-induced psychosis, as the effects of SKY on more severe mental health disorders are unknown); (v) endorse suicidal or homicidal intent within the past 60 days (those that do are referred for VA psychiatric care); (vi) endorse substance dependence (other than nicotine) within the past 30 days; (vii) have an unmanaged seizure disorder; (viii) have a severe traumatic brain injury; (ix) or have initiated psychotropic medication within 8 weeks prior to screening (all medication use is closely tracked throughout the duration of the RCT). Study candidates who express imminent intent to harm self or others at any point in the study are referred for VA emergency care. Participants who exhibit clinically meaningful symptoms of PTSD but are eliminated due to screening failure, or elect not to participate in this research program, are referred to their local mental health clinic.

Sample size (power analysis). The minimum clinically meaningful difference on the PCL-C is estimated to be 10-points (Jacobson & Truax, 1991; Monson et al., 2008) and is the threshold criterion to determine whether SKY reaches non-inferiority to CPT[1]. In a large study of 374 veterans with PTSD treated with CPT, the mean change in PCL scores following treatment was 18.9 (SD = 12.3 (Dr. K. Chard, Personal Communication); Chard, Ricksecker,

[1]While some PTSD treatment studies have used non-inferiority thresholds of 10-points on the CAPS (Greene et al., 2008), treatment-related changes on the CAPS are typically two-thirds to three quarters of those observed on the PCL (Monson et al., 2008), so our choice of a 10-point threshold on the PCL-C is conservative.

Healy, Karlin, & Resick, 2012). As recommended for non-inferiority trials, we set the power to 80% and Type I error to p = 0.025 (Greene et al., 2008).

When designing the study protocol, dropout rates from PTSD treatment studies delivering CPT ranged from 17-22% in non-VA studies (Schottenbauer et al., 2008) and were approximately 20% in VA studies (Monson et al., 2006). A pilot study of SKY for PTSD reported a dropout rate of 9% (1 of 11 veterans) at 1-year follow-up (Seppälä et al., 2014).

Power analyses determined that a minimum of 30 participants per group are needed. We took the highest (most conservative) dropout rate of 22% and aimed to recruit a total of 76 participants (n = 38 per group), which should allow for the minimum of n = 30 per group at 1-year follow-up. However, more recent PTSD treatment studies have higher dropout rates (25-30%; Forbes et al., 2012; Steenkamp et al., 2015). Therefore, if our study has high dropout[2] we will continue to recruit participants until we reach the appropriately powered number of 30 participants per treatment group.

Recruitment

Participants are recruited through a multifaced outreach strategy including direct outreach to veterans, clinician referral, direct mail, and local advertisements. Study staff coordinate mass mailing of a flyer to local veterans who have reported symptoms of PTSD, give presentations about the study to veterans at various outpatient and community groups, liaise with clinicians to educate them about the study and obtain referrals, have information desks at VAPAHCS, and post flyers at VAPAHCS and surrounding community based outpatient clinics.

[2]Consistent with previous RCTs of PTSD, we define treatment dropout as completion of <75% of the treatment sessions for either CPT or SKY (Rizvi, Vogt, & Resick, 2009).

Procedure

Initial screening is performed by the study coordinator over telephone using the PCL-5[3] to confirm presence/absence of clinically meaningful symptoms of PTSD. Candidates who meet this criteria are given an appointment at the study site in which the study coordinator administers the Mini International Neuropsychiatric Interview (MINI 7.0) (Sheehan, 2014) to assess exclusion criteria. Eligible participants are guided through informed consent (RCT participation, data collection, future contact for other research studies) by the study coordinator and complete demographic and health histories. Each participant then undergoes pre-treatment assessment and is randomly assigned to one of two treatment groups. Participants are also assessed at post-treatment, 1-month follow-up, and 1-year follow-up (Figure 2). Pre- and post-treatment assessments require visits on consecutive days and an overnight assessment in between. Participants have the option of overnight accommodation in a local hotel to enable them to conveniently undergo the evening and morning assessments. Participants are reimbursed for their participation in the study, with half of the payment made at the post-treatment visit and the other half made at the end of the 1-year follow-up.

[3]The PCL-5 is a 20-item self-report measure that assesses current PTSD symptom severity according to the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed; DSM-5) diagnostic criteria (Weathers et al., 2013). When this RCT commenced, the PCL-5 had only recently been released and a clinical cut-off score of 38 was proposed (which we are implementing here). Psychometrics were recently completed, and a clinical cut-off score of 31-33 is now recommended as having the highest convergent validity with the CAPS-5 (Bovin et al., 2016; NCPTSD, 2017). Therefore, our screening cut-off score of 38 is a conservative estimate of clinically meaningful symptoms of PTSD.

Interventions

Cognitive processing therapy (CPT)[4]. CPT is an evidence-based, trauma-focused CBT. It has been shown to be as efficacious as PE in treating PTSD and comorbid symptoms of depression (Resick, Nishith, Weaver, Astin, & Feuer, 2002), with effects maintained at least 5-10 years post-treatment (Resick, Williams, Suvak, Monson, & Gradus, 2012). Sessions are rigorously structured, with content, materials, and home practice assignments dictated by a manual (Resick et al., 2014a, 2014b). CPT consists of twelve 50- to 60-minute sessions given twice per week for a duration of 6-weeks. Sessions focus on developing cognitive "restructuring" skills and then applying them to challenge negative beliefs ("stuck points") related to responsibility for the traumatic event(s) and five additional key areas (safety, trust, power/control, esteem, and intimacy) (Table 2). Home practice is assigned following each session, and a significant amount of in-session time is spent reviewing home practice. All CPT

[4]Note that for this RCT, we are employing the "cognitive only" version of CPT which does not include a written account of the trauma. The manual we are using refers to this version as "CPT-C" (Resick, Monson, & Chard, 2014a, 2014b), however, the latest version of the manual (Resick, Monson, & Chard, 2017) now uses the term "CPT" to refer to the version that does not include a written trauma account (i.e., the previous "CPT-C"), whereas "CPT-A" now refers to the version that includes the written trauma account (i.e., the previous "CPT"). This change in terminology and standard practice stems from the dismantling study conducted in 2008 that demonstrated equivalent efficacy in treating PTSD between both versions of CPT (with/without the written trauma account), though the version *without* the written trauma account demonstrated faster symptom improvement across the 6-weeks of treatment and lower dropout rates than the version with the written trauma account (22% vs. 34%) (Resick et al., 2008).

sessions are delivered by a licensed or postdoctoral clinical psychologist trained in CPT. All CPT providers were certified via the VA's CPT rollout initiative. Sessions are audio recorded to determine adherence.

Sudarshan Kriya Yoga (SKY). SKY is provided in a group format and incorporates controlled cyclical breathing exercises, gentle yoga postures, and periods of discussion (*Project Welcome Home Troops*; www.pwht.org). It has been shown to reduce symptoms of PTSD, depression, and anxiety in individuals with a history of trauma (Brown & Gerbarg, 2005; Carter et al., 2013; Descilo et al., 2010; Seppälä et al., 2014; Walker & Pacik, 2017), with effects maintained at 6-months (Brown & Gerbarg, 2005; Descilo et al., 2010) and 1-year (Seppälä et al., 2014) post-treatment. All SKY protocols used in research consist of four different controlled breathing components (Sanskrit: *pranayama*), performed in a seated position, eyes closed or gaze focused down, breathing through the nostrils: (i) alternate nostril breath[5] (*nadi sodhana*), (ii) three-stage victory breath (*ujjayi*), (iii) bellows breath (*bhastrika*), and (iv) Sudarshan Kriya. Alternate nostril breathing, victory breath (inhale:hold:exhale:hold at 4:4:6:2 counts), and bellows breath are practiced in many schools of yoga. Sudarshan Kriya or SKY breath, the central component of SKY, is a cyclical breathing exercise consisting of consecutive slow (8-14 cycles per minute), medium (30 cycles per minute), and fast (100-180 cycles per minute) rates. The in session (instructor-led) version of SKY is longer than the home practice version. Sessions close with five deep breaths inhaled through the nose and exhaled through the mouth with pursed

[5]We use the non-Sanskrit names (alternate nostril breath, victory breath, bellows breath, SKY breath) in groups to allow greater accessibility to veterans, consistent with *Project Welcome Home Troops* and the *International Association of Human Values* (IAHV).

lips (as if breathing through a straw) and a 5-min meditation/rest phase to ensure participants are safe and grounded.

We use a SKY protocol consisting of a 5-day intensive group class (3 hours/) (Table 3). This is followed by 10, 60-minute sessions given twice per week for a duration of 5-weeks. Thus, the SKY treatment is a total of six weeks long and is equivalent in duration to the CPT condition and involve 25 hours of group contact time, which is greater than CPT's 12 hours of contact time. Home practice is optional and strongly encouraged. All SKY sessions are led by an experienced, certified SKY instructor[6] from *Project Welcome Home Troops*, a project of IAHV (www.iahv.org). Sessions are video recorded to determine adherence.

Outcome measures

Posttraumatic Stress Disorder Checklist-Civilian Version (PCL-C)[7]. The PCL-C (Weathers, Litz, Herman, Huska, & Keane, 1994) is a 17-item self-report measure that assesses current PTSD symptom severity corresponding to the DSM-IV diagnostic criteria for PTSD (APA, 1994). It is the primary outcome measure.

Clinician-Administered PTSD Scale for DSM-5 past month version (CAPS-5). The CAPS-5 (Weathers et al., 2015) is the gold standard semi-structured clinical diagnostic interview

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[6]As some breathing components have important contraindications such as pregnancy, high blood pressure, or seizures, SKY should only be taught by experienced instructors trained in appropriate delivery and individual modification.

[7]Due to our non-inferiority design, it is crucial for the primary outcome measure to have an established margin of a clinically meaningful change. At the time of commencement of this RCT, the psychometric properties of the newer PCL-5 were unknown.

for the assessment of PTSD (Weathers, Keane, & Davidson, 2001). CAPS-5 items correspond to DSM-5 (APA, 2013) symptom definitions. It is a secondary clinical outcome measure to confirm PTSD diagnostic status and severity.

Mini International Neuropsychiatric Interview (MINI 7.0). The MINI 7.0 (Sheehan, 2014) is a brief (15-min) structured clinical interview designed to screen for current and lifetime DSM-5 and ICD-10 mental health disorders. It is being used here to assess exclusion criteria.

Beck Depression Inventory II (BDI-II). The BDI-II (Beck, Steer, & Brown, 1996) is a 21-item self-report measure that assesses current depression symptom severity. Items are rated on a 4-point scale according to how much the symptom bothered the respondent over the prior two weeks.

Beck Scale for Suicide Ideation (BSS). The BSS (Beck & Steer, 1991) is a 21-item self-report measure that assesses the extent of thought, planning, and intent to engage in self-directed harm over the past week.

Positive and Negative Affect Schedule (PANAS). The PANAS (Watson, Clark, & Tellegen, 1988) is a 20-item self-report measure that assesses positive and negative mood states. Items are rated on a 5-point Likert scale according to the extent to which participants experienced each of 20 emotions over the past few weeks.

Daily sleep and home practice compliance log. Participants record an estimate of the duration of their sleep each night and the extent to which they complete their assigned home practice each day.

Cambridge Neuropsychological Test Automated Battery (CANTAB). The CANTAB (Cambridge Cognition; www.cambridgecognition.com) is a computerized neuropsychological

assessment system. It is the most well-validated and widely used cognitive research software (e.g., Aslam et al., 2018; Gonçalves et al., 2015; Lowe & Rabbitt, 1998; Luciana, 2003; Olff, Polak, Witteveen, & Denys, 2014). We utilize tasks assessing learning, visual memory, spatial working memory, and sustained attention.

Actigraphy. Participants wear a Motionlogger Actigraph (Ambulatory Monitoring, Inc.) wrist watch overnight at pre- and post-treatment that records ambulatory movement to measure sleep patterns. It provides an objective, robust, and valid measure of sleep quality, including total sleep time, sleep onset, and wakefulness (Morgenthaler, Alessi, et al., 2007; Morgenthaler, Lee-Chiong, et al., 2007).

Heart Rate. Participants wear the ActiWave (CamNtech) heart rate monitor on their chest overnight at pre- and post-treatment to assess physiological arousal (Balzarotti, Biassoni, Colombo, & Ciceri, 2017; Holzman & Bridgett, 2017).

Multivariate Apnea Prediction Index (MAPI). The MAPI (Maislin et al., 1995) is a 13-item self-report measure that yields a percentage likelihood that each participant has clinically meaningful sleep apnea. This measure will be used to ensure the actigraphy sleep data are not confounded by artifacts due to sleep apnea.

Restless Legs Syndrome Diagnostic Index (RLS-DI). The RLS-DI (Beneš & Kohnen, 2009) is a standardized diagnostic tool developed from a combination of data from polysomnography, neurological reports, and clinical interviews to diagnose restless legs syndrome according to current international diagnostic criteria. This measure will be used to ensure the actigraphy sleep data are not confounded by artifact due to restless legs syndrome.

Data collection and blinding

All in-person assessments (i.e., clinical interviews, outcome measures, experimental assessments) are conducted by an assessor blinded to treatment group (SKY, CPT) to protect the integrity of assessment and prevent assessor bias. Data entry is also blinded and data collection is ongoing. Data are deidentified and stored on the secure VA network and REDCap. Demographics information are stored separately from data on the secure VA network and are password protected to ensure confidentiality. No analyses will occur prior to the completion of the RCT and closure to recruitment. Once the RCT is completed, data analysis will be conducted by a statistician blind to treatment group. Long-term access to the final RCT dataset will be maintained by the principal investigator (PJB).

Data analysis plan

The RCT will employ a 2 Group (SKY, CPT) x 4 Time (pre-treatment, post-treatment, 1-month follow-up, 1-year follow-up) design for each outcome measure. Primary analyses will use both an intent-to-treat (ITT) data sample (i.e., all randomized participants, including those who drop-out) and a per-protocol or "treatment completers"[8] procedure (i.e., only participants who complete the protocol/treatment). In the ITT analyses, we will use the "last observation carried forward" methodology, which is considered a conservative approach for handling missing data (Little & Kang, 2015; Piaggio, Elbourne, Altman, Pocock, & Evans, 2006; Piaggio, Elbourne, Pocock, Evans, & Altman, 2012; Streiner & Geddes, 2001). In a non-inferiority design, ITT favors the alternative hypothesis (i.e., no difference between treatments), because it minimizes the difference between groups, therefore, using both analyses (ITT, per-protocol/treatment

[8]Consistent with previous RCTs of PTSD, we define treatment completers as those who complete ≥75% of the treatment sessions for either CPT or SKY (Rizvi et al., 2009).

completers) is the most rigorous approach to non-inferiority designs (Greene et al., 2008). Lowering the alpha level to correct for multiple comparisons is not appropriate in non-inferiority designs as it has the same effect as increasing the alpha level in traditional (superiority) designs. Provided that adequate randomization occurs, the two treatment groups (SKY, CPT) are not expected to differ on key demographic variables (e.g., age, sex, ethnicity, education, PTSD severity, psychiatric comorbidity). If significant differences occur, these will be covaried in analyses. We will use both confidence interval (95% CI) and hypothesis testing (one-sided t-test; α=.025) to compare the mean change (Greene et al., 2008) in outcome measure scores from pre- to post-treatment for the SKY versus CPT treatment groups. in December 2019.

Ethics and dissemination

Ethical considerations

This RCT protocol is approved by Stanford University Institutional Review Board. All participants provide written informed consent prior to participation (see Appendices). Consent forms are audited annually by the VA. Annual continuing reviews are also conducted by Stanford University Institutional Review Board and the Department of Veterans Affairs.

Safety policy

All participants are routinely followed-up by telephone by the study coordinator (JST) to monitor serious adverse events and unanticipated problems. Any serious adverse events and unanticipated problems will be recorded and reported to Stanford University Institutional Review Board and VA within the reporting deadlines. Suicide risk is comprehensively assessed throughout the study and a safety plan exists (led by a licensed clinical psychologist; RJS-H) to

be employed in respond to reports of thoughts about or intent to harm oneself or others. The interviewer will assess whether the participant has a viable plan and means to carry out the plan

Dissemination policy

The datasets generated and/or analyzed during the current study are not publicly available due to privacy restrictions at the Department of Veterans Affairs. De-identified electronic data sets will be made available upon written request to the principal investigator (PJB). Once the RCT is completed, outcomes will be published in international peer-reviewed journals, regardless of the direction of effects.

Trial registration

This RCT was first registered online at ClinicalTrials.gov (identifier NCT02366403) on 19 February 2015. The first participant was recruited in March 2016. Recruitment is expected to continue until December 2018 with 1-year follow-up to be completed in December 2019.

Discussion

PTSD is a debilitating, highly prevalent condition in both general and veteran populations (Bryan et al., 2015; Fulton et al., 2015; Gates et al., 2012; Kessler, Berglund, et al., 2005; Panagioti et al., 2012; Pietrzak et al., 2011; Reynolds et al., 2016; Spottswood et al., 2017; Tarrier & Gregg, 2004). Current national and international clinical practice guidelines recommend evidence-based, trauma-focused psychotherapy (e.g., CPT, PE, I.E., EMDR) as the first-line treatment for PTSD (ACPMH, 2013; Benedek et al., 2009; ISTSS, 2008; NICE, 2005; VA/DoD, 2017; WHO, 2013). Despite the relative success of these treatments (Bradley et al., 2005; Lee et al., 2016), the majority of those who begin treatment retain a diagnosis of PTSD

post-treatment (Schottenbauer et al., 2008; Steenkamp et al., 2015). For these and other reasons (e.g., personal preference, stigma, accessibility to treatment, cost-effectiveness) healthcare consumers and providers have begun to seek more holistic, mind-body, CIH interventions for a variety of conditions (Wynn, 2015). However, there remains a paucity of high-quality, active controlled efficacy studies of CIH interventions for PTSD, which precludes their formal recommendation by institutions such as the VA and DoD (VA/DoD, 2017).

The aim of this RCT is to address this gap in the field. Here, we present the protocol for an ongoing, 4-year non-inferiority parallel group design RCT comparing the efficacy of SKY (a breathing meditation intervention) to CPT (an evidence-based psychotherapy) for treating PTSD among veterans. If non-inferiority of SKY compared to CPT is suggested this will provide an empirical rationale for a larger multi-site RCT to evaluate the efficacy of SKY in multiple treatment settings across different veteran populations. This will also provide the impetus to explore cost-effectiveness of SKY versus trauma-focused therapy, evaluate implementation issues (e.g., setting (hospital vs. community center), target population demographics (e.g., veteran vs. non-veteran)), and investigate the efficacy of SKY for other mental health conditions with high comorbidity with PTSD (e.g., depression, chronic pain, substance use). Such a study would inform evidence-based formal recommendations regarding the implementation of CIH interventions in the VA Health Care System.

Declarations

Competing interests

Not applicable.

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Author's contributions

DCM was responsible for writing the manuscript with significant contributions from all other authors. PJB is principal investigator and executive manager of this RCT. PJB and EMS conceptualized the study. JST is the study coordinator and one of the SKY instructors. DCM, RJS-H, and TJA are the CPT providers. RJS-H is the supervising licensed clinical psychologist. All authors read and approved the final manuscript.

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Table 1

Outcome measures and assessment time points

Measure	Phone Screen	On Site Screen	Pre-treatment	Post-treatment	1-month follow up	1-year follow up
PCL-5*	x					
MINI*		x				
PCL-C			x	x	x	x
CAPS-5*			x	x		
BDI-II			x	x		
BSS			x	x		
PANAS			x	x	x	x
CANTAB			x	x		
Actigraphy			x	x		
Heart Rate			x	x		
MAPI			x	x		
RLS-DI*			x	x		

Note. PCL-5 = Posttraumatic Stress Disorder Checklist-Version 5; MINI = Mini International Neuropsychiatric Interview; PCL-C = Posttraumatic Stress Disorder Checklist-Civilian Version; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5 past month version; BDI-II = Beck Depression Inventory II; BSS = Beck Scale for Suicide Ideation; PANAS = Positive and Negative Affect Schedule; CANTAB = Cambridge Neuropsychological Test Automated Battery; MAPI = Multivariate Apnea Prediction Index; RLS-DI = Restless Legs Syndrome Diagnostic Index.

*proctored

Table 2

Summary of session content for CPT

Session	Content	Home practice assignment
1	Introduction and education phase	Describe event's impact
2	Meaning of the event	ABC worksheets
3	Identifying thoughts and feelings	ABC worksheets
4	Identifying "stuck points"	Practice challenging questions
5	Challenging questions	Identify problematic thinking patterns
6	Problematic thinking	Practice challenging beliefs
7	Challenging beliefs	Evaluate safety beliefs
8	Safety issues	Evaluate trust beliefs
9	Trust issues	Evaluate power/control beliefs
10	Power/control issues	Evaluate esteem beliefs Give/receive compliments Pleasant/positive activities
11	Esteem issues	Revise description of event's impact Evaluate intimacy beliefs Give/receive compliments Pleasant/positive activities
12	Intimacy issues; revisiting meaning of the event	Continue using worksheets

Note. CPT = cognitive processing therapy. ABC worksheets = preliminary cognitive restructuring exercise involving identification of Activating event, Belief, and Consequences of belief.

Table 3

Summary of session content for SKY

Session	Content	Daily home practice
1	Introductory SKY practices	5 min breathwork
	Guided meditation	Reflection questions
2	Introductory SKY practices	15 min breathwork
	Guided meditation	Reflection questions
3	SKY breathing and accompanying	20 min breathwork
	practices	Reflection questions
4	SKY breathing and accompanying	20 min breathwork
	practices	Reflection questions
5	SKY breathing and accompanying	30 min breathwork
	practices	Reflection questions
6,8,10,12	SKY breathing and accompanying	30 min breathwork daily
	practices	
7,9,11,13	SKY home practice program	30 min breathwork daily
	Guided meditation	

Figure Legends

Figure 1. Graphical representation of outcome measures by PTSD symptom clusters.

Figure 2. CONSORT flow diagram.

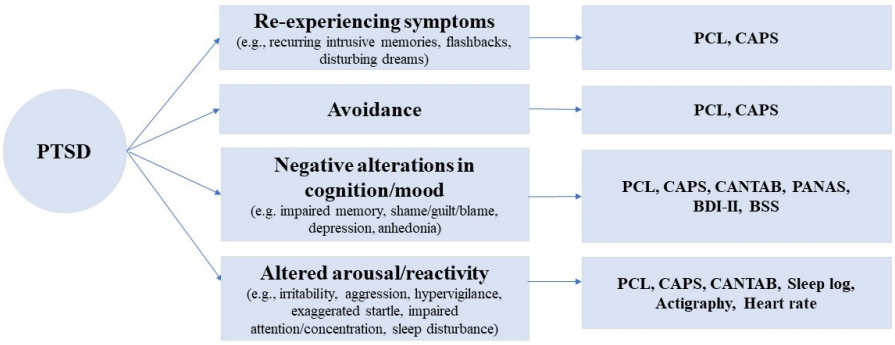

Figure 1. Graphical representation of outcome measures by PTSD symptom clusters.

338x190mm (96 x 96 DPI)

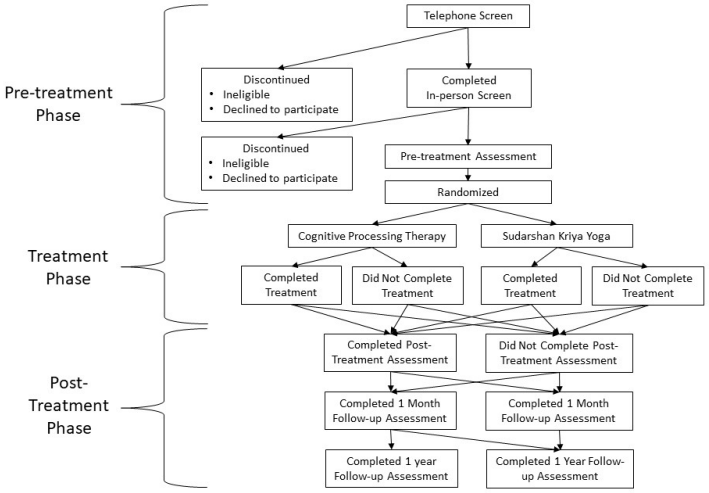

Figure 2. CONSORT flow diagram.

338x190mm (96 x 96 DPI)

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RESEARCH CONSENT FORM

Title of Study: Breathing Meditation Intervention for Posttraumatic Stress Disorder	
Principal Investigator: **Dr Peter J. Bayley**	VAMC: VA Palo Alto HCS

Breathing Meditation Intervention for Posttraumatic Stress Disorder

Informed Consent

Are you participating in other research studies? ___Yes ___No

PURPOSE OF RESEARCH

You are invited to participate in a research study to compare the efficacy of a breathing meditation to Cognitive Processing Therapy in treating symptoms of Posttraumatic Stress Disorder (PTSD). You were selected as a possible participant in this study because: 1) you are a Veteran; and 2) you have symptoms of PTSD.

This study is being done by researchers at VA Palo Alto, and is sponsored by the Department of Veterans Affairs (VA).

This research study is looking for 76 Veterans who exhibit symptoms of PTSD.

The primary aim for this study is to compare two different ways of treating PTSD in Veterans. One way involves treatment with a breathing-based meditation in a group setting. The other involves a therapy commonly used by the VA to treat PTSD called Cognitive Processing Therapy. Apart from changes in your symptoms of PTSD, we will also be assessing whether there are related changes to your memory, attention, mood, sleep, medication and heart rate.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but you may withdraw your consent later and stop being in the study without any loss of benefits or medical care you are entitled to.

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DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 4 years. Participants will be assigned to either a meditation treatment group or a one-on-one Cognitive Processing Therapy treatment. Participants in the meditation group will undergo a treatment program consisting of a 5-day group class (3 hours/day) followed by five weeks of sessions twice per week (1hr/session). Participants given Cognitive Processing Therapy treatment will be given 12 one-hour sessions twice per week over the course of 6 weeks. At the end of treatment all participants will be tested again. Follow up tests will be given at one-month and 12-months post-treatment.

PROCEDURES

Patients who sign this informed consent and meet the study eligibility criteria will be enrolled into the study and will be randomized to one of two treatment groups: a meditation treatment group or a one-on-one Cognitive Processing Therapy treatment.

If you choose to participate, Dr. Bayley and his research staff will ask you to participate in the activities described below. All study procedures will be completed by trained professionals and research staff. This study has 4 phases: baseline and randomization (1 day), intervention (6 weeks), end of treatment (1 day), 4) follow-up at one month (one hour) and one year (one hour).

1. BASELINE AND RANDOMIZATION PHASE

If you agree to be in this study, you will complete a number of tests to make sure that you are eligible. You will read and sign this informed consent form before you begin the baseline phase. The baseline phase will take place over two half-days (an afternoon and a morning) and will involve overnight measurements of memory, heart rate and sleep. To conveniently undergo the afternoon and morning assessments you will be accommodated overnight in a local hotel.

During the baseline phase and before you are given any treatments, the following will happen:

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- We will ask for some general information, and give you questionnaires about your mental health, mood, and sleep.
- You will be given computerized tests of cognition to measure your memory and attention.
- Study staff will review with you any drugs (prescriptions, "natural food products" and "over the counter" supplements) that you are taking. During the study, you will be able to take medications. You will also be given a questionnaire about any non-medical use of drugs over the past year.
- You will complete self-report questionnaires about the symptoms of PTSD which will be reviewed by study staff in an interview.
- On the overnight visit, you be asked to wear a heart rate monitoring device and an actigraph motion logger on your wrist. The heart rate monitor and motion logger will be fitted in the evening and you will be asked to keep wearing them for the next 12 hours. You will also be assessed to see how well you remember some information overnight using computer-based tests. For these you will be trained in the afternoon and retested the next morning.

If you agree and are eligible to participate in this research study, you will be randomized to either the breathing meditation treatment or to the Cognitive Processing Therapy treatment. Randomization is a process that is similar to flipping a coin where one side of the coin is breathing meditation and the other side is the Cognitive Processing Therapy. There is a 50:50 chance of being randomized to either treatment. Both groups will receive all the same measurements and tests.

2. INTERVENTION PHASE

BREATHING MEDITATION GROUP

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This treatment will be given in a group setting at VA Palo Alto and will last 6 weeks. The class meets 3 hours per day for the first five days, followed by five weeks of sessions given twice per week (one hour per session). There will be a maximum class size of ten..The meditation will include several types of breathing exercises involving arousal and attentional control. Initial breathing exercises are designed to be calming and focusing. Subsequent breathing exercises are more fully energizing, allowing you to focus more fully. All are soothing and present-focused. You will be encouraged to learn all the breathing exercises, and to utilize the ones that seem most appropriate to your needs. During the six weeks of treatment, you will be encouraged to engage in optional home practice. This will consist of seeking venues that you have been avoiding in order to practice the meditation techniques in those environments. You will be encouraged to start with situations that are less arousing, and progress to more difficult situations. At each class you will have the opportunity to share your experiences, and discuss ways to continue to incorporate the exercises into your daily lives. You will also be asked to keep a daily log to record whether you practiced the intervention, your estimated hours of sleep, and any changes to medications.

COGNITIVE PROCESSING THERAPY

This treatment will be given individually as a series of office visits at VA Palo Alto and will last for six weeks. Each session will last around forty-five minutes and there will be two sessions per week. Sessions will include reviewing homework from the previous session, focusing on specific issues, learning new therapeutic techniques and setting up homework for the following session including real-life application of learned techniques.

In the first few sessions you will be told more about the theory behind the treatment. You will be taught the connection between events, thoughts, and

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feelings and begin to identify places where you can focus on thinking about past emotionally traumatic events. Later, skills will be taught, including looking at the evidence for and against some of your beliefs, and examining the context from which the belief was formed. You will be asked to focus on five key areas, including safety, trust, power/control, esteem, and intimacy. Finally, you will be asked to look to the future and identify areas that may be problematic and discuss ways that you can manage these issues. You will also be asked to keep a daily log to record whether you practiced the intervention, your estimated hours of sleep, and any changes to medications.

3. END OF TREATMENT PHASE

When you finish treatment, you will be given most of the same tests and questionnaires as you received during the baseline phase:

- We will give you questionnaires about your mental health, mood, and sleep.
- You will be given computerized tests of cognition to measure your memory and attention.
- Study staff will review with you any drugs (prescriptions, “natural food products” and “over the counter” supplements) that you are taking. You will also be given a questionnaire about any non-medical use of drugs over the past year.
- You will complete self-report questionnaires about the symptoms of PTSD which will be reviewed by study staff in an interview.
- On the overnight visit, you will be asked to wear a heart rate monitoring device and an actigraph motion logger on your wrist. The heart rate monitor and motion logger will be fitted in the evening and you will be asked to keep wearing them for the next 12 hours. You will also be assessed to see how well you remember some information using

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computer-based tests. For these you will be trained in the afternoon and retested the next morning.

4. FOLLOW-UP PHASE

Two follow-ups visits are scheduled following treatment at 1) one month, and 2) one year. The amount of time required to complete each follow-up should be around 1 hour. During the follow-up, study staff will ask you to complete three self-assessments about your mood and current PTSD symptoms.

5. FOR ALL STUDY PHASES

- It is important for study staff to be aware of any changes in your medications during your participation in the study.
- You will interact with members of the entire study team. The study takes place at the VA Palo Alto Health Care System (VAPAHCS). If asked, we will provide a note for your employer that you were receiving medical treatment. We will not compensate for missed work time.
- You will be asked about adverse events whenever you are seen by study staff for treatment, evaluation, and follow-up visits. An adverse event is anything bad that happens with you and may or may not be related to your participation in this study. An independent committee will be told about all adverse events at least once every six months. If they believe that any aspect of this study is unsafe, they will recommend that changes be made to eliminate the safety problem.

6. OPTIONAL STUDY PHASES

If you agree to take part in the study described above, you will be offered the option to participate in the additional (optional) study phases described below. These will occur during Baseline, End of Treatment, and Follow-Up.

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☐ Magnetic Resonance Imaging (MRI) scans of the head:

The MRI phase will be done at the Stanford Center for Cognitive and Neurobiological Imaging (CNI) and will take 1 hour.

The MRI scan uses a strong magnet and radiofrequency magnetic fields to create pictures of the structure and function of the brain. The scanning procedure is like an X-ray or CT scan but you will not be exposed to x-rays. You will not feel anything. The hardest part of the scan is the need to lie still for the duration. You will lie on a table and be slid into a tunnel. Your head and shoulders lie in a plastic rounded tray which makes it more comfortable and easier to lie still. You will hear repetitive tapping noises from the scanner as it collects data to make the pictures of the brain. You will be required to wear earplugs. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling.

The MRI in this study is not harmful. The scanner and associated equipment are approved by the FDA. However, the scanner uses a strong magnet that will attract metals and affect some electronic devices. If you have a cardiac pacemaker, any other biomedical device (surgical clips, devices, or implants) in or on your body, a history of head or eye injury involving metal fragments, have ever worked in a metal shop, if you could be pregnant, or have kidney trouble, you must you tell the MRI operator/investigator before entering the MRI room, as it may be decided that should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be given a secure place to store such objects prior to the MRI scan. There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is expected and should not be painful. There is a small risk the scanner will heat up, so tell the operator if

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you start to feel heat. Dizziness or nausea may occur if you move your head rapidly within the scanner.

If you feel discomfort at any time, notify the operator and the exam will be stopped.

The MRI scans performed in this study are for specific research purposes and are not optimized to find medical abnormalities. Our research scans do not qualify as a clinical diagnostic scan. The investigators for this project may not be trained to perform medical diagnosis. The investigators are not responsible for failure to find existing abnormalities with these MRI scans. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal. If this occurs, we will follow CNI's protocol for incidental findings. In this case, the research scans are referred to an approximately qualified individual (neuroradiologist) designated by the CNI Board for further review. The reviewer will determine if the potential abnormality merits further investigation and will inform the Principal Investigator of the action to be taken. The CNI operations team promptly provides a DVD with the scans in question or in another way that makes the images available to the reviewer to be read "as is". If follow-up is recommended, the investigator will contact you with the appropriate information. Because the images are taken using research settings, they will not be made available for clinical purposes. Finding out that you may have a medical abnormality that you had not been aware of before could cause psychological stress to you or your family and possibly affect your health insurance coverage in the future.

The safety protocol for the Stanford CNI does not require a pregnancy test because MRI does not use ionizing radiation (high-energy radiation that can potentially cause damage to DNA, such as with x-rays used in CT scans). There are currently no known harmful side-effects associated with temporary exposure to the strong magnetic field used by MRI scanners. However, because MRI may

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involve risks to the subject (or the embryo, fetus, or nursing infant if the subject is or may become pregnant), which are currently unknown and unforeseeable, if you are pregnant, or suspect you might be, or there is a chance you are, or you are currently breast feeding, you may not participate in this part of the study.

☐ Electroencephalography (EEG) and psychophysiological assessment:

The EEG phase will be done at the Palo Alto VA and will take 1.5 hours, including time spent setting-up the cap and removing it/washing hair.

EEG is a test that measures and records the electrical activity of the brain. To collect this information we will ask you to wear a cap on your head similar to a swimming cap. The cap has special sensors attached to it and is hooked by wires to a computer. Sensors will also be attached to your face and hands with a sticky paste to record facial movements, eye-blinks, heart rate, and skin conductance. The sensors only record activity, they do not produce any sensation. The hardest part of the EEG assessment is the need to minimize any movement including jaw movements, coughing, sneezing, yawning.

A computer will be set up to provide visual stimulation while you are in a shielded EEG room. Simple sounds or pictures will be projected onto a computer and headphones. You will be asked simple questions relating to these sounds or pictures. Your responses to these questions will be recorded using EEG specific equipment such as a computer-amplifier interface system. You will be given a hand-held control box or joystick to manually respond to the questions. Some pictures or words may provoke emotional responses such as fear, disgust, or sadness.

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If you choose to undergo the optional phases, you will be asked to complete each of these assessments three times: before treatment, after treatment, and at 1-year follow-up.

The EEG performed in this study is for specific research purposes and is not optimized to find medical abnormalities. Our research tests do not qualify as clinical diagnostic tests. The investigators for this project may not be trained to perform medical diagnosis. The investigators are not responsible for failure to find existing abnormalities with these EEG data. However, on occasion the investigator may notice a finding on an EEG wave that seems abnormal. If this occurs, a doctor will be asked to look at the raw EEG to see if any medical follow-up is needed. If so, the investigator will contact you and recommend you inform your doctor about the findings. Because the wave signals are collected using research settings, they will not be made available for clinical purposes.

PARTICIPANT'S RESPONSIBILITIES

You should:

- Follow the instructions of the investigators and study staff.
- Complete your questionnaires as instructed. You are free to skip any questions that you prefer not to answer.
- Ask questions as you think of them.
- Tell the investigator or research staff if you change your mind about staying in the study.
- While participating in this research study, do not take part in any other research study without approval from the investigators. Taking part in other research studies without approval from the investigators may invalidate the results of this research, as well as that of the other studies.

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- Keep your study appointments. If it is necessary to miss an appointment, please contact the investigator or study staff to reschedule as soon as you know you will miss the appointment.
- It is important that you not give false, incomplete, or misleading information about your medical history, including past and present drug use.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are **free to withdraw** your consent and stop your participation at any time. If you decide to withdraw from the study, you will not lose any benefits to which you would otherwise be entitled and your decision will not affect your ability to receive medical care for your condition.

The investigators may also withdraw you from the study without your consent for one or more of the following reasons:

o Failure to follow the instructions of the investigators and/or study staff.

o The investigators decide that continuing your participation could be harmful to you.

o Pregnancy

o The study is cancelled.

o Other administrative reasons.

o Unanticipated circumstances.

If you want to stop being in the study you should tell the investigators or study staff. You can do this by phone by calling Dr. Bayley at (650) 493-5000 x68653, or the Study Coordinator at (650) 785-6661

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POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Study Director if you have any questions. This study involves the following risks, discomforts, and possible inconveniences:

There are few risks involved in the treatments. However, because the treatments deal with painful feelings, emotions and experiences you may feel emotionally uncomfortable at times. You may even experience a temporary increase in your symptoms of PTSD during treatment which usually resolves as treatment progresses. Risks of the behavioral testing and measurements include possible anxiety that can be associated with any test. It is possible that you might also become tired or frustrated by some of our testing. You may find answering the questionnaires annoying, boring, or repetitive. If this happens, please tell us and we will take a break or skip a particularly difficult test.

For the heart rate monitor and the actigraph motion logger there is the possibility of developing a skin rash where they touch the skin. If this were to occur, the devices can be moved to a different location and lotion can be applied to the rash. We may request to remove obstructive chest hair with an electric razor in order to ensure a proper heart-rate reading.There are no other known risks associated with wearing the devices, other than the inconvenience of wearing them

All breathing meditation classes will be given in a group setting. As a consequence you should keep in mind that anonymity is not possible. However, all tests and assessments will be given individually and your results will not be shared with the group.

Risks of the usual care you receive are not risks of the research. They are not included in this consent form. You should talk with your health care providers about risks of usual care.

Optional phases:

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MRI Risks. There are no known significant risks with this procedure at this time because the radiofrequency magnetic field(s) and magnetic fields, at the strengths used, are thought to be without harm. However, metallic objects may experience a strong attraction to the magnet, so it is very important that you notify the researcher of any metal objects, devices, or implants that are in or on your body before entering the magnet room. This includes biomedical devices such as pacemakers and aneurysm clips, prostheses, and any other metallic objects embedded in the body such as bullets, buckshot, shrapnel, and any metal fragments from working around metal.

If you have any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop, if you have some type of implanted electrical device (such as a cardiac pacemaker), if you have severe heart disease (including susceptibility to arrhythmias), if you are wearing metal braces on your teeth, or (for women) if you could be pregnant or are breast feeding, you should not have an MRI scan.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful. Please report any heating sensation immediately. Dizziness and nausea may occur if the head is moved rapidly within the bore of the magnet.

If you feel discomfort at any time, notify the operator and the exam will be stopped.

EEG Risks. EEG experiments are non-invasive and painless. However, some people do experience mild and temporary skin irritation from: i) skin preparation where skin debris (dead skin cells) is removed from the area directly on the outer area of the eyes with a pad, or ii) slight itchiness from conductive paste that is used during application of the cap and sensors.

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If you feel discomfort at any time, notify the operator and the exam will be stopped.

VIDEO RECORDING

Video recording will be used to monitor treatment delivery. Recordings will be made of treatment providers, and not the participants. All recordings will be stored indefinitely in accordance with VA guidelines.

POTENTIAL BENEFITS

We can't promise that you will get any benefits from taking part in this research study. However, possible benefits may include being able to deal better with thoughts and memories associated with PTSD. The information that is obtained during this study may be scientifically useful and may lead to greater knowledge about the treatment of PTSD.

The testing done in this study could reveal a condition that you might not have previously been aware of and for which you may need treatment. Study staff will refer you for additional treatment if such problems are identified but the study will not pay for the treatment of any such identified problems.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY DIRECT BENEFITS FROM THIS STUDY.

ALTERNATIVES

You may choose not to participate in this study. If this is your decision, there are other choices including the standard treatments provided by a local clinic. Your study investigator will discuss any alternatives with you before you agree to participate in this study. Alternative treatments include medication and behavioral therapy.

ClinicalTrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not

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include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

PARTICIPANT'S RIGHTS

Your participation is voluntary. You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. You have the right to refuse to answer particular questions.

If you decide not to participate, tell the Protocol Director. You will still receive care for any disease and will not lose any benefits to which you would otherwise be entitled.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

CONFIDENTIALITY

Your identity will be kept as confidential as possible as required by law. Except as required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Your research records may be disclosed outside of the VA, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel. The responses to questions concerning illegal drug use could be self-incriminating and harmful to you if they became known outside the study. As explained in the confidentiality statement of the consent, we do not intend to disclose this information.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed.

Federal agencies as required, including the Department of Defense, the VA Office of Research Oversight or the VA Office of the Inspector General may have access to your information and research records.

Department of Veterans Affairs

RESEARCH CONSENT FORM

Title of Study: Breathing Meditation Intervention for Posttraumatic Stress Disorder	
Principal Investigator: **Dr Peter J. Bayley**	VAMC: VA Palo Alto HCS

FINANCIAL CONSIDERATIONS

Payments

You will receive a payment of $400.00 for successful completion of the study.

- $200 will be paid after the completion of the Treatment Phase.
- $200 will be paid after the completion of the Follow-Up Phase.
- $50 will be paid for each session (Baseline, End of Treatment) of the optional study phase (MRI, EEG), after completion of the Treatment Phase.
- $50 will be paid for each session of the optional study phase (MRI, EEG), after completion of the Follow-Up Phase.
- If you withdraw from the study early, your payment will be prorated for the proportion of the study completed.

These payments will be mailed in the form of a personal check. Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work-eligible visa. You may need to provide your social security number to receive payment.

Costs

You will not have to pay anything to be in this study.

Sponsor

The Department of Veterans Affairs is providing financial support and/or material for this study.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study you should ask the Principal Investigator, Peter Bayley, Ph.D. You can call him at 650-493-5000 ext. 68653. You should also contact him/her at any time if you feel you have been hurt by being a part of this study.

Appointment Contact: If you need to change your appointment, please contact the Study Coordinator at (650) 785-6661.

IRB Use Only

Approval Date: November 30, 2016
Expiration Date: November 30, 2017

Department of Veterans Affairs

RESEARCH CONSENT FORM

Title of Study: Breathing Meditation Intervention for Posttraumatic Stress Disorder	
Principal Investigator: **Dr Peter J. Bayley**	VAMC: VA Palo Alto HCS

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, and would like to speak with a person who is independent of the research, call the Stanford Institutional Review Board (IRB) at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

May we contact you (by phone or letter) about related studies that may be of interest to you?

_____ Yes. I would like to be contacted for future research opportunities.

_____ No. Do not contact me about future research opportunities.

Signing your name means you agree to be in this study and that you were given a copy of this signed and dated consent form.

Signature of Participant Date

Print Name of Participant

Person Obtaining Consent:

Signature of Person Obtaining Consent Date

Print Name of Person Obtaining Consent

This page separates the

Informed Consent Document *(above)*

from the

HIPAA Authorization document

(below)

To preserve formatting, please

DO NOT DELETE this page

VA Palo Alto Health Care System – HIPAA Authorization Form
Protocol Title: _ Breathing Meditation Intervention for Posttraumatic Stress Disorder
Principal Investigator: ____Dr. Peter J. Bayley_____
Date of Review: December 1, 2014

Authorization To Use and Share Your Health Information For Research Purposes

HIPAA (Health Insurance Portability & Accountability Act) is a federal privacy law that protects the confidentiality of health information collected about you. The following explains how health information collected about you will be used by the investigators and who they may share your health information with as part of this research.

What is the purpose of the research study, and how will my health information be utilized in the study?

The study is to compare the effectiveness of treating posttraumatic stress disorder (PTSD) using two different methods; breathing meditation or a standard Cognitive Processing Therapy. Health information will be used in the study to monitor your progress and to evaluate the effectiveness of the treatment.

What Personal Health Information Will Be Used or Shared?

The following health information, linked to you by your name, SSN, Date of Birth, Address, email address, telephone number, will be used for this research:

- Date of visit
- Demographic information
- Physiological and Cognitive test data
- Medical history information
- Survey/questionnaire responses

Who May Use or Share Your Health Information?

By signing this document, you allow the following individuals and entities to obtain, use and share your health information for this research study:

- The Principal Investigator (Dr Bayley) and members of the VA research team.
- Departments within the VA Health Care System responsible for the oversight, administration, or conduct of research.

- The Stanford University Administrative Panel on Human Subjects in Medical Research and other Stanford University Officials responsible for the oversight, administration, or conduct of research.

Who May Receive and Use Your Health Information

The investigators may share your health information with the following individuals as part of this research study.

- Stanford University collaborating investigators and research staff.
- The Office for Human Research Protections in the U.S. Department of Health and Human Services

We will protect your health information as required by all laws, however health information shared with others may no longer be protected by Federal laws or regulations and might be shared by the parties above.

Do I have to sign this form?

No. Signing this form is voluntary. The VA may not condition treatment, payment, enrollment or eligibility for benefits based on signing this form. If you decide not to sign the form, you will not be able to take part in this study or receive any research-related treatment.

If I sign now, can I decide later not to continue in the study?

Yes. You are free to take back your permission and stop being in the study. The investigators will not collect any more information about you after you take back your permission, but they can continue to use your information that was collected before you took back your permission.

Your request to take back your permission must be done in writing. Either give your written request to the investigator or send it by mail to: Dr Peter Bayley, War Related Illness and Injury Study Center (WRIISC), 3801 Miranda Avenue, MC 151Y, Palo Alto, CA 94304-1290

Does My Permission for the use my Personal Health Information expire?

Yes. Your information cannot be used forever. Your permission related to the use and sharing of your health information expires when this research study is completed.

VA Palo Alto Health Care System – HIPAA Authorization Form

Protocol Title: _ Breathing Meditation Intervention for Posttraumatic Stress Disorder

Principal Investigator: ____Dr. Peter J. Bayley_____

Date of Review: December 1, 2014

HIPAA regulations require you to give separate written permission (signature) for the use of your protected health information.

Signature of Participant Date

Printed Name of Participant

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **Title page (p. 1)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **Abstract (p. 3) and Methods Trial Registration subsection (p. 21)**
	2b	All items from the World Health Organization Trial Registration Data Set **N/A**
Protocol version	3	Date and version identifier **N/A**
Funding	4	Sources and types of financial, material, and other support **Declarations Funding subsection (p. 23)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Title page (p. 1) and Declarations Author's contributions subsection (p. 23)**
	5b	Name and contact information for the trial sponsor **N/A**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **N/A – see Declarations Funding subsection (p. 23)**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **Declarations Author's contributions subsection (p. 23)**
Introduction		

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Introduction (p. 4-8, with question/hypotheses on p. 8)**
	6b	Explanation for choice of comparators **Introduction (p. 5, 8)**
Objectives	7	Specific objectives or hypotheses **Introduction (p. 8)**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Introduction (p. 8) and Methods Study design subsection (p. 9-10)**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Methods Setting subsection (p. 10)**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Methods Participants subsection (p. 10-11, including Exclusion criteria subsection) and Methods Interventions subsection (p. 14 paragraph 1 & p. 15-16 paragraph 2-1)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Methods Interventions subsection (p. 13-16) and Tables 2 & 3 (p. 40 & 42)**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **N/A**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **Methods Interventions subsection (p. 14 paragraph 1 & p. 16 paragraph 1)**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **Methods Participants subsection (p. 10-11)**

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Methods Study design subsection (p. 9) and Methods Outcome measures subsection (p. 16-19) and Figure 1 (Legend p. 43)**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **Methods Procedure subsection (p. 13-14) and Figure 2 (Legend p. 43)**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Methods Participants subsection (p. 11-12 Sample size (power analysis) subsection)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **Methods Recruitment subsection (p. 12-13)**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Methods Study design subsection (p. 9-10)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Methods Study design subsection (p. 9-10)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Methods Study design subsection (p. 9-10)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **Methods Data collection and blinding subsection (p. 19)**

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **N/A**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Methods Outcome measures subsection (p. 16-19) and Methods Data collection and blinding subsection (p. 19)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **Methods Participants subsection (p. 11-12 Sample size (power analysis) subsection), Methods Procedure subsection (p. 13-14), and Figure 2 (Legend p. 43)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **Methods Data collection and blinding subsection (p. 19)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Methods Data analysis plan subsection (p. 19-20)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **Methods Data analysis plan subsection (p. 19-20)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **Methods Data analysis plan subsection (p. 19-20)**
Methods: Monitoring		

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **N/A – the FDA does not mandate a DMC for our RCT design and neither does our ethics board (Stanford University Institutional Review Board) or funding body (Department of Veterans Affairs)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **Methods Participants subsection (p. 11-12 Sample size (power analysis) subsection)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **Methods Participants subsection (p. 11 Exclusion criteria subsection)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Ethics and dissemination Ethical considerations subsection (p. 20)**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Ethics and dissemination Ethical considerations subsection (p. 20)**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **Ethics and dissemination Dissemination policy subsection (p. 21)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **Methods Procedure subsection (p. 13-14)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **Methods Procedure subsection (p. 13-14)**

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **Methods Data collection and blinding subsection (p. 18-19)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **Declarations Competing interests subsection (p.23)**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **Methods Data collection and blinding subsection (p. 19)**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **N/A**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **Ethics and dissemination Dissemination policy subsection (p. 21)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **Declarations Author's contributions subsection (p.23)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **Ethics and dissemination Dissemination policy subsection (p. 21)**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **Methods Ethical considerations subsection (p. 20)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **N/A**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Study protocol for a non-inferiority randomized controlled trial of SKY breathing meditation versus cognitive processing therapy for PTSD among veterans

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Complementary medicine
Keywords:	posttraumatic stress disorder, Sudarshan Kriya, pranayama, cognitive processing therapy, non-inferiority, randomized controlled trial

Study protocol for a non-inferiority randomized controlled trial of SKY breathing meditation versus cognitive processing therapy for PTSD among veterans

Danielle C. Mathersul, PhD[1,2]*, Julia S. Tang, MS[1], R. Jay Schulz-Heik, PhD[1], Timothy J. Avery, PsyD[1,2], Emma M. Seppälä, PhD[3,4], & Peter J. Bayley, PhD[1,2]*

[1]War Related Illness and Injury Study Center, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304, United States of America

[2]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, United States of America

[3]Center for Compassion and Altruism Research and Education, Stanford University School of Medicine, Stanford, CA 94305, United States of America

[4]Yale Center for Emotional Intelligence, Yale University, New Haven, CT 06520, United States of America

*Corresponding authors. Email: dcmathersul@stanford.edu; Peter.Bayley@va.gov. Address: WRIISC VA Palo Alto Health Care System, 3801 Miranda Ave, Mail Code 151Y, Palo Alto, CA 94304, United States of America.

Author's email addresses: julia.tang@va.gov; robert.schulz-heik@va.gov; timothyavery@stanford.edu; emmasep@gmail.com.

Abstract

Introduction: Posttraumatic stress disorder (PTSD) is a debilitating, highly prevalent condition. Current clinical practice guidelines recommend trauma-focused psychotherapy (e.g., cognitive processing therapy; CPT) as the first-line treatment for PTSD. However, while these treatments show clinically meaningful symptom improvement, the majority of those who begin treatment retain a diagnosis of PTSD post-treatment. Perhaps for this reason, many individuals with PTSD have sought more holistic, mind-body, complementary and integrative health (CIH) interventions. However, there remains a paucity of high-quality, active controlled efficacy studies of CIH interventions for PTSD, which precludes their formal recommendation.

Methods and analyses: We present the protocol for an ongoing non-inferiority parallel group randomized controlled trial (RCT) comparing the efficacy of a breathing meditation intervention (Sudarshan Kriya Yoga [SKY]) to a recommended evidence-based psychotherapy (CPT) for PTSD among veterans. Assessors are blinded to treatment group. The primary outcome measure is the Posttraumatic Stress Disorder Checklist-Civilian Version and a combination of clinical, self-report, experimental, and physiological outcome measures assess treatment-related changes across each of the four PTSD symptom clusters (re-experiencing, avoidance, negative cognitions or mood, and hyperarousal/reactivity). Once the RCT is completed, analyses will use both an intent-to-treat (using the "last observation carried forward" for missing data) and a per-protocol or "treatment completers" procedure, which is the most rigorous approach to non-inferiority designs.

Ethics and dissemination: To our knowledge, this is this first non-inferiority RCT of SKY versus CPT for PTSD among veterans. The protocol is approved by Stanford University Institutional Review Board. All participants provide written informed consent prior to

participation. Results from this RCT will inform future studies including larger multi-site efficacy RCTs of SKY for PTSD and other mental health conditions, as well as exploration of cost-effectiveness and evaluation of implementation issues. Results will also inform evidence-based formal recommendations regarding CIH interventions for PTSD.

Trial registration: NCT02366403.

Keywords: posttraumatic stress disorder; Sudarshan Kriya; meditation; pranayama; cognitive processing therapy; non-inferiority; randomized controlled trial

Strengths and limitations of this study:

- There remains a paucity of high-quality, active controlled efficacy studies of complementary and integrative health interventions for posttraumatic stress disorder
- In response, here we present the protocol for an ongoing non-inferiority parallel group randomized controlled trial comparing the efficacy of Sudarshan Kriya Yoga breathing meditation to cognitive processing therapy for PTSD among veterans
- The primary outcome measure is the Posttraumatic Stress Disorder Checklist-Civilian Version (PCL-C)
- Additional outcome measures (including experimental and physiological) assess treatment-related changes across each of the four PTSD symptom clusters
- This RCT is restricted to veterans; future RCTs will explore efficacy of SKY in non-veteran populations

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating condition that develops in some individuals after exposure to a traumatic event. It is associated with four clusters of symptoms: i) re-experiencing (e.g. recurring intrusive memories, flashbacks, disturbing dreams); ii) avoidance of stimuli associated with the trauma; iii) persistent negative alterations in cognitions and mood (e.g. impaired memory, exaggerated shame/guilt/blame, depression, anhedonia), and iv) altered arousal/reactivity (e.g. irritability, aggression, hypervigilance, exaggerated startle, impaired attention/concentration, sleep disturbance)[1]. PTSD is associated with poor quality of life and increased risk of suicide[2-4], which may contribute to the alarming rise of suicidal behavior amongst returning veterans[5, 6]. The lifetime prevalence of PTSD in the general US population is estimated to be about 6.5%[7-9]. Prevalence is reported to be up to 24.5% within veteran populations[10-12]. Veterans with mental health disorders also have higher rates of comorbidity and greater severity of symptom presentation than non-veterans with mental health disorders[13, 14]. A recent systematic review revealed that the median prevalence of PTSD in primary care (across civilian and veteran populations) is equivalent to that of depression[12], though it is not typically the primary referral or complaint[15], highlighting the need for rigorous education, screening, assessment, and appropriate treatment by providers.

Cognitive behavioral therapy (CBT), an evidence-based psychotherapy, is considered the "gold standard" (strongest evidence base) mental health intervention[16]. Current clinical practice guidelines for PTSD across national and international organizations such as World Health Organization (WHO), International Society for Traumatic Stress Studies (ISTSS), Veterans Affairs/Department of Defense (VA/DoD), American Psychiatric Association (APA), National Institute for Clinical Excellence (NICE), and Australian Centre for Posttraumatic

Mental Health (ACPMH) all recommend trauma-focused therapy as the first-line treatment for PTSD[17-22]. Trauma-focused therapy for PTSD includes variations of CBT such as cognitive processing therapy (CPT), prolonged exposure therapy (PE), and imaginal exposure (IE), as well as eye-movement desensitization and reprocessing (EMDR). These evidence-based psychotherapies for PTSD show large effects compared to wait-list controls [average effect size = 1.11; 23] and supportive therapy [average effect size = 1.01; 24]. They also have significantly higher effect sizes than medications such as selective serotonin reuptake inhibitors (SSRIs; e.g., sertraline), serotonin norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine), atypical antidepressants (e.g., nefazodone), alpha-1 blockers (e.g., prazosin), antipsychotics (e.g., olanzapine, risperidone), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) [average effect size = 0.43, n.s.; 24].

Despite the relative effectiveness of trauma-focused CBT as a treatment for PTSD, these evidence-based treatments remain inadequate. First, although the majority of individuals receiving psychotherapy attain clinically meaningful symptom improvement, up to two-thirds of cases retain a PTSD diagnosis post-treatment[25, 26]. Second, treatment non-retention is a significant problem in military-related PTSD treatment; several large studies in both the VA and DoD found that only a small proportion of individuals receive a minimally adequate number of mental health encounters after PTSD diagnosis[27]. Reasons for not seeking treatment and dropout are complex and include stigma, concerns about confidentiality, time demands, perceived treatment inefficacy, and discomfort with the therapist[27].

Perhaps as a result of the numerous problems surrounding currently available treatments, there is a trend for individuals with PTSD to seek more holistic, mind-body, complementary and integrative health interventions[28]. These CIH interventions (previously referred to as

complementary and alternative medicine [CAM]) may be viewed as less stigmatizing than formal mental health interventions such as CBT[29]. Recent data show that 34% of individuals within the general US population[30] and 39% of individuals with PTSD[31] reported using at least one CIH intervention in the previous year. Outside of the PTSD field, a growing body of evidence underscores the efficacy of meditation/mindfulness-based CIH therapies for reducing suicidality[32] and insomnia[33, 34] and improving symptoms of anxiety and depression[35-42], all of which overlap with PTSD, both in terms of diagnostic criteria and high frequency of comorbidities[1, 2, 43, 44].

Two recent systematic reviews and meta-analyses of randomized controlled trials (RCTs) concluded that CIH interventions significantly improve symptoms of PTSD. The larger of the two included 19 RCTs (mindfulness-based approaches (10 studies), meditation/mantrum-based approaches (6 studies), yoga-movement based approaches (4 studies), and combination approaches (1 study)) and found support for a small-medium effect size on PTSD, with effect sizes larger for smaller studies (< 30 sample size)[45]. Similarly, the smaller of the two included 10 RCTs (mindfulness-based approaches (5 studies), yoga-movement based approaches (3 studies), and meditation/mantrum-based approaches (2 studies)) and found support for a small-medium effect size on PTSD and depression[46]. However, a consistent theme across these systematic reviews and meta-analyses is the paucity of high-quality, well-controlled efficacy studies of CIH interventions for PTSD, with existing studies containing biases such as small sample size, inadequate control/comparison group, non-random allocation, non-blinding, high attrition rates, or a failure to report on these aspects of study design.

VA hospitals are mandated to provide certain CIH interventions (including meditation and yoga) that have preliminary evidence suggesting at least the potential for benefit[47]. At the

same time, the VA/DoD states that currently there is insufficient evidence to formally recommend CIH interventions as first-line treatments for PTSD[17, 48]. To inform a formal recommendation, studies must address the biases and poor quality highlighted in the two recent systematic reviews and meta-analyses outlined above. The ideal study design is a large RCT with an active control comparison group rather than case studies or non-controlled studies[49]. Non-inferiority design RCTs are recommended for testing the hypothesis that a novel intervention (e.g., a CIH intervention) is no worse than an established standard intervention (e.g., trauma-focused therapy) at treating the target condition (e.g., PTSD)[50]. This design is particularly appropriate when the novel intervention may be preferable to the standard intervention for reasons other than efficacy, such as lower costs, greater acceptability, lower drop-out rates, etc. SKY is a promising CIH meditation intervention for PTSD; it has been shown to reduce symptoms of PTSD, depression, and anxiety in several uncontrolled or small pilot RCTs, including several involving veterans with a history of trauma[51-55]. Our clinical research team at the VA Palo Alto Health Care System recently launched a RCT with a non-inferiority parallel group design comparing a breathing meditation intervention (Sudarshan Kriya Yoga [SKY]) to an evidence-based psychotherapy (CPT) for PTSD in veterans ("Breathing Meditation Intervention for Post-Traumatic Stress Disorder" (PI Bayley); VA RR&D Merit Review; ClinicalTrials.gov NCT02366403). The aim of this manuscript is to outline the study design and protocol for this ongoing, 4-year RCT. The primary aim of the RCT is to test the hypothesis that SKY breathing meditation is non-inferior to CPT as a treatment for veterans with clinically significant symptoms of PTSD. As such, we will compare PTSD symptoms pre- versus post-treatment, as well as pre-treatment versus 1-month and 1-year follow-up. We also aim to assess whether dropout rates at post-treatment differ between SKY and CPT. The

secondary aim is to explore the potential differences in mechanisms of treatment action, for example, SKY may work via bottom-up (physiological arousal and regulation) processes whereas CPT may exert more top-down (cognitive, self-regulatory) influences. As this aim is exploratory we do not have directional hypotheses, however, we have carefully chosen a combination of clinical interview, self-report, experimental, and physiological outcome measures to assess differential treatment-related changes across each of the four PTSD symptom clusters of re-experiencing, avoidance, negative cognitions or mood, and hyperarousal/reactivity (Figure 1).

Methods and analyses

Patient and Public Involvement

In May 2016, the VA issued a Memorandum entitled "Advancing Complementary and Integrative Health in VHA", mandating that all VA hospitals provide CIH interventions – such as meditation and yoga – to Veterans [47], emphasizing the VA's commitment to providing these services. The Memorandum was jointly authored by Tracy Gaudet, M.D., Director, Office of Patient Centered Care & Cultural Transformation, and David J. Shulkin, M.D., then Under Secretary for Health. The Office of Patient Centered Care & Cultural Transformation is charged with transforming the VA Health Care System into a patient-centered, patient-driven, personalized approach. This RCT is in direct alignment with this Memorandum.

Study design

A non-inferiority parallel group design RCT is being used to test the hypothesis that SKY breathing meditation is non-inferior to CPT as a treatment for veterans with clinically significant symptoms of PTSD. Participants who meet inclusion criteria are randomly assigned to one of

two groups (SKY or CPT) and receive treatment over a 6-week period. Random allocation occurs at a 1:1 (SKY:CPT) ratio and participants blindly draw their group out of a hat consisting of sealed envelopes created by the study coordinator. The primary outcome measure is change in PTSD symptoms, as measured by the Posttraumatic Stress Disorder Checklist-Civilian Version (PCL-C) and assessed at pre-treatment, post-treatment, 1-month follow-up, and 1-year follow-up. The PCL-C was chosen as the primary outcome measure over a clinical diagnostic interview (e.g., Clinician-Administered PTSD Scale for DSM-5 [CAPS-5]) for the following reasons: (i) it can be administered over the telephone making it ideal for screening and follow-up and thus avoiding additional in-person visits by participants; (ii) it has excellent psychometric properties including high convergent validity (r = 0.93) with the CAPS[56-59]; and (iii) it was the primary outcome measure in a previous pilot study of SKY for PTSD[52], thus allowing for comparability of findings across studies.

The secondary outcome measures utilize a multi-methodological exploratory approach assessing a wide range of subjective and objective PTSD-related symptoms assessed pre- and post-treatment. This combination of clinical interview, self-report, experimental, and physiological outcome measures were chosen to assess treatment-related changes across each of the four PTSD symptom clusters of re-experiencing, avoidance, negative cognitions or mood, and hyperarousal/reactivity[1] (Table 1, Figure 1).

Setting

All in-person assessments and treatment interventions occur at the War Related Illness and Injury Study Center (WRIISC) at the Veterans Affairs Palo Alto Health Care System (VAPAHCS) in Palo Alto, California, USA. All screening interviews, assessments, and the CPT

intervention are conducted in private clinical interview rooms. The SKY intervention is conducted in a large conference room.

Participants

This RCT is funded by a Department of Veterans Affairs RR&D Merit Review ("Breathing Meditation Intervention for Post-Traumatic Stress Disorder" (PI Bayley); ClinicalTrials.gov NCT02366403) and the RCT is only open to veterans. To ensure the greatest generalizability for dissemination of meditation for treating PTSD, participants are any veteran of any age or sex who demonstrate clinically significant symptoms of PTSD. Participants are community-dwelling outpatient adult veterans who reside in the San Francisco Bay Area and those from outer areas who are willing and able to visit the VA Palo Alto for assessment and treatment. A recent study among Vietnam veterans suggests that most ethnic minority veteran groups have a higher rate of PTSD than Caucasian veterans[60]. Therefore, we are seeking an ethnically diverse population of male and female veterans, with combat and non-combat PTSD.

Exclusion criteria. Individuals are excluded if they (i) are participating in a concurrent treatment study; (ii) are unable to attend study visits and sessions at the VA Palo Alto; (iii) intend to begin a new trauma-focused therapy (e.g., CPT, PE, IE, EMDR) during the study period; (iv) have experienced mania or psychosis for any reason within the past 6-months (e.g., bipolar, schizophrenia, drug-induced psychosis, as the effects of SKY on more severe mental health disorders are unknown); (v) endorse suicidal or homicidal intent within the past 60 days (those that do are referred for VA psychiatric care); (vi) endorse substance dependence (other than nicotine) within the past 30 days; (vii) have an unmanaged seizure disorder; (viii) have a severe traumatic brain injury; (ix) or have initiated psychotropic medication within 8 weeks prior to screening (all medication use is closely tracked throughout the duration of the RCT). Study

candidates who express imminent intent to harm self or others at any point in the study are referred for VA emergency care. Participants who exhibit clinically meaningful symptoms of PTSD but are eliminated due to screening failure, or elect not to participate in this research program, are referred to their local mental health clinic.

Sample size (power analysis). The minimum clinically meaningful difference on the PCL-C is estimated to be 10-points[61, 62] and is the threshold criterion to determine whether SKY reaches non-inferiority to CPT[1]. In a large study of 374 veterans with PTSD treated with CPT, the mean change in PCL scores following treatment was 18.9 [SD = 12.3 (Dr. K. Chard, Personal Communication); 63]. As recommended for non-inferiority trials, we set the power to 80% and Type I error to p = 0.025[50].

When designing the study protocol, dropout rates from PTSD treatment studies delivering CPT ranged from 17-22% in non-VA studies[25] and were approximately 20% in VA studies[64]. A pilot study of SKY for PTSD reported a dropout rate of 9% (1 of 11 veterans) at 1-year follow-up[52].

Power analyses determined that a minimum of 30 participants per group are needed. We took the highest (most conservative) dropout rate of 22% and aimed to recruit a total of 76 participants (n = 38 per group), which should allow for the minimum of n = 30 per group at 1-year follow-up. However, more recent PTSD treatment studies have higher dropout rates[25-

[1]While some PTSD treatment studies have used non-inferiority thresholds of 10-points on the CAPS[50], treatment-related changes on the CAPS are typically two-thirds to three quarters of those observed on the PCL[61], so our choice of a 10-point threshold on the PCL-C is conservative.

30%; 26, 65]. Therefore, if our study has high dropout[2] we will continue to recruit participants until we reach the appropriately powered number of 30 participants per treatment group.

Recruitment

Participants are recruited through a multifaceted outreach strategy including direct outreach to veterans, clinician referral, direct mail, and local advertisements. Study staff coordinate mass mailing of a flyer to local veterans who have reported symptoms of PTSD, give presentations about the study to veterans at various outpatient and community groups, liaise with clinicians to educate them about the study and obtain referrals, host information desks at VAPAHCS, and post flyers at VAPAHCS and surrounding community based outpatient clinics.

Procedure

Initial screening is performed by the study coordinator over telephone using the PCL-5[3] to confirm presence/absence of clinically meaningful symptoms of PTSD. Candidates who meet

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[2]Consistent with previous RCTs of PTSD, we define treatment dropout as completion of <75% of the treatment sessions for either CPT or SKY[66].

[3]The PCL-5 is a 20-item self-report measure that assesses current PTSD symptom severity according to the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed; DSM-5) diagnostic criteria[67]. When this RCT commenced, the PCL-5 had only recently been released and a clinical cut-off score of 38 was proposed (which we are implementing here). Psychometrics were recently completed, and a clinical cut-off score of 31-33 is now recommended as having the highest convergent validity with the CAPS-5[68, 69]. Therefore, our screening cut-off score of 38 is a conservative estimate of clinically meaningful symptoms of PTSD.

this criteria are given an appointment at the study site in which the study coordinator administers the Mini International Neuropsychiatric Interview (MINI 7.0)[70] to assess exclusion criteria. Eligible participants are guided through informed consent (RCT participation, data collection, future contact for other research studies) by the study coordinator and complete demographic and health histories. Each participant then undergoes pre-treatment assessment and is randomly assigned to one of two treatment groups. Participants are also assessed at post-treatment, 1-month follow-up, and 1-year follow-up (Figure 2). Pre- and post-treatment assessments require visits on consecutive days and an overnight assessment in between. Participants have the option of overnight accommodation in a local hotel to enable them to conveniently undergo the evening and morning assessments. Participants are reimbursed for their participation in the study, with half of the payment made at the post-treatment visit and the other half made at the end of the 1-year follow-up.

Interventions

Cognitive processing therapy (CPT)[4]. CPT is an evidence-based, trauma-focused CBT. It has been shown to be as efficacious as PE in treating PTSD and comorbid symptoms of

[4]Note that for this RCT, we are employing the "cognitive only" version of CPT which does not include a written account of the trauma. The manual we are using refers to this version as "CPT-C"[71, 72], however, the latest version of the manual [73] now uses the term "CPT" to refer to the version that does not include a written trauma account (i.e., the previous "CPT-C"), whereas "CPT-A" now refers to the version that includes the written trauma account (i.e., the previous "CPT"). This change in terminology and standard practice stems from the dismantling study conducted in 2008 that demonstrated equivalent efficacy in treating PTSD between both

depression[75], with effects maintained at least 5-10 years post-treatment[76]. Sessions are rigorously structured, with content, materials, and home practice assignments dictated by a manual[71, 72]. CPT consists of twelve 50- to 60-minute sessions given twice per week for a duration of 6-weeks. Sessions focus on developing cognitive "restructuring" skills and then applying them to challenge negative beliefs ("stuck points") related to responsibility for the traumatic event(s) and five additional key areas (safety, trust, power/control, esteem, and intimacy) (Table 2). Home practice is assigned following each session, and a significant amount of in-session time is spent reviewing home practice. All CPT sessions are delivered by a licensed or postdoctoral clinical psychologist trained in CPT. All CPT providers were certified via the VA's CPT rollout initiative. Sessions are audio recorded to determine adherence.

Sudarshan Kriya Yoga (SKY). SKY is provided in a group format and incorporates controlled cyclical breathing exercises, gentle yoga postures, and periods of discussion (*Project Welcome Home Troops*; www.pwht.org). It has been shown to reduce symptoms of PTSD, depression, and anxiety in individuals with a history of trauma[51-55], with effects maintained at 6-months[51, 54] and 1-year[52] post-treatment. SKY protocols used in research typically consist of three different controlled breathing techniques, performed in a seated position, eyes closed or gaze focused down, breathing through the nostrils: (i) three-stage victory breath[5] (*ujjayi*

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versions of CPT (with/without the written trauma account), though the version *without* the written trauma account demonstrated faster symptom improvement across the 6-weeks of treatment and lower dropout rates than the version with the written trauma account (22% vs. 34%)[74].

pranayama), (ii) bellows breath (*bhastrika pranayama*), and (iii) SKY breath (*Sudarshan kriya*). Sudarshan Kriya – the central component of SKY – is a cyclical breathing exercise consisting of consecutive slow, medium, and fast breath cycle rates. Victory breath and bellows breath are practiced in many schools of yoga, though the number and rate of breath varies. Sessions close with a meditation/rest phase (*shavasana*). The in-session version of SKY contains a longer version of the SKY breath and is instructor-led for safety. The home practice version contains a shorter version of the SKY breath (with the option to use a guided audio CD), classical yoga stretches, and a guided meditation.

We use a SKY protocol designed by *Project Welcome Home Troops* specifically tailored for Veterans and adapted for clinical purposes. The protocol consists of a 5-day intensive group workshop (3 hours per day) (Table 3) followed by 10, 60-minute sessions given twice per week (alternating between a longer instructor-led [full SKY protocol] version and the shorter home practice version [in-session, instructor-led]) for a duration of five weeks. This *Project Welcome Home Troops* SKY protocol differs from the contemporary standard SKY protocol in that: (i) the initial intensive workshop is 5 days versus 3 days to allow for gradual introduction of the SKY breath (delivered on Days 4 and 5 instead of Days 1-3), thus permitting initial development of foundational breathing and meditation techniques; (ii) alternate nostril breath (*nadi sodhana*) and straw breath (deep breaths inhaled through the nose and exhaled through the mouth with pursed lips, as if breathing through a straw) are taught and practiced at the beginning and end of

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[5]We use the non-Sanskrit names (alternate nostril breath, victory breath, bellows breath, SKY breath, straw breath) in groups to allow greater accessibility to veterans, consistent with *Project Welcome Home Troops* and the *International Association of Human Values* (IAHV).

sessions, respectively; and (iii) two instructors trained in military culture facilitate the course with an emphasis on resilience, empowerment, connection, and reintegration post-service.

The SKY treatment is a total of six weeks long and, after the initial intensive workshop, is equivalent in frequency and duration to the CPT treatment. SKY, however, involves 25 hours of group contact time, which is greater than CPT's 12 hours of contact time, though CPT is arguably more "concentrated" as participants receive one-on-one treatment. In designing the RCT, we deemed that equivalent *duration* (i.e., six weeks) was most crucial for determining non-inferiority of SKY versus CPT (the primary hypothesis), as treatment dropout often increases over time. The *Project Welcome Home Troops* SKY protocol involves an initial 5-day intensive, so this feature could not be altered. If non-inferiority of SKY compared to CPT is suggested, subsequent studies could and should investigate questions regarding dosage and duration.

Home practice is optional and strongly encouraged. All SKY sessions are led by an experienced, certified SKY instructor[6] from *Project Welcome Home Troops*, a project of IAHV (www.iahv.org). Sessions are video recorded to determine adherence.

[6]As some breathing components have important contraindications such as pregnancy, high blood pressure, or seizures, SKY should only be taught by experienced instructors trained in appropriate delivery and individual modification.

Outcome measures

Posttraumatic Stress Disorder Checklist-Civilian Version (PCL-C)[7]. The PCL-C[77] is a 17-item self-report measure that assesses current PTSD symptom severity corresponding to the DSM-IV diagnostic criteria for PTSD[78]. It is the primary outcome measure (see Study design). Responses to individual items related to the four symptom clusters will also be used for the secondary exploratory analyses.

Clinician-Administered PTSD Scale for DSM-5 past month version (CAPS-5). The CAPS-5[79] is the gold standard semi-structured clinical diagnostic interview for the assessment of PTSD[80]. CAPS-5 items correspond to DSM-5 [1] symptom definitions. It is a secondary clinical outcome measure to confirm PTSD diagnostic status and severity. Responses to individual items related to the four symptom clusters will also be used for the secondary exploratory analyses.

Mini International Neuropsychiatric Interview (MINI 7.0). The MINI 7.0[70] is a brief (15-min) structured clinical interview designed to screen for current and lifetime DSM-5 and ICD-10 mental health disorders. It is being used here to assess exclusion criteria (i.e., mania, psychosis, substance dependence [see Participants]).

Beck Depression Inventory II (BDI-II). The BDI-II[81] is a 21-item self-report measure that assesses current depression symptom severity (negative alterations in mood

[7]Due to our non-inferiority design, it is crucial for the primary outcome measure to have an established margin of a clinically meaningful change. At the time of commencement of this RCT, the psychometric properties of the newer PCL-5 were unknown.

symptom cluster). Items are rated on a 4-point scale according to how much the symptom bothered the respondent over the prior two weeks.

Beck Scale for Suicide Ideation (BSS). The BSS[82] is a 21-item self-report measure that assesses the extent of thought, planning, and intent to engage in self-directed harm over the past week (negative alterations in mood symptom cluster).

Positive and Negative Affect Schedule (PANAS). The PANAS[83] is a 20-item self-report measure that assesses positive and negative mood states (negative alterations in mood symptom cluster). Items are rated on a 5-point Likert scale according to the extent to which participants experienced each of 20 emotions over the past few weeks.

Daily sleep and home practice compliance log. Participants record an estimate of the duration of their sleep each night (altered arousal symptom cluster) and the extent to which they complete their assigned home practice each day.

Cambridge Neuropsychological Test Automated Battery (CANTAB). The CANTAB (Cambridge Cognition; www.cambridgecognition.com) is a computerized neuropsychological assessment system. It is the most well-validated and widely used cognitive research software[e.g., 84, 85-88]. We utilize tasks assessing learning, visual memory, spatial working memory, and sustained attention (negative alterations in cognition and altered reactivity symptom clusters).

Actigraphy. Participants wear a Motionlogger Actigraph (Ambulatory Monitoring, Inc.) wrist watch overnight at pre- and post-treatment that records ambulatory movement to measure sleep patterns (altered arousal symptom cluster). It provides an objective, robust, and valid measure of sleep quality, including total sleep time, sleep onset, and wakefulness[89, 90].

Heart Rate. Participants wear the ActiWave (CamNtech) heart rate monitor on their chest overnight at pre- and post-treatment to assess physiological arousal (altered arousal symptom cluster)[91, 92].

Multivariate Apnea Prediction Index (MAPI). The MAPI[93] is a 13-item self-report measure that yields a percentage likelihood that each participant has clinically meaningful sleep apnea. This measure will be used to ensure the actigraphy sleep data are not confounded by artifacts due to sleep apnea.

Restless Legs Syndrome Diagnostic Index (RLS-DI). The RLS-DI[94] is a standardized diagnostic tool developed from a combination of data from polysomnography, neurological reports, and clinical interviews to diagnose restless legs syndrome according to current international diagnostic criteria. This measure will be used to ensure the actigraphy sleep data are not confounded by artifacts due to restless legs syndrome.

Data collection and blinding

All in-person assessments (i.e., clinical interviews, outcome measures, experimental assessments) are conducted by an assessor blinded to treatment group (SKY, CPT) to protect the integrity of assessment and prevent assessor bias. Data entry is also blinded and data collection is ongoing. Data are deidentified and stored on the secure VA network and REDCap. Demographics information are stored separately from data on the secure VA network and are password protected to ensure confidentiality. No analyses will occur prior to the completion of the RCT and closure to recruitment. Once the RCT is completed, data analysis will be conducted by a statistician blind to treatment group. Long-term access to the final RCT dataset will be maintained by the principal investigator (PJB).

Data analysis plan

The RCT will employ a 2 Group (SKY, CPT) x 4 Time (pre-treatment, post-treatment, 1-month follow-up, 1-year follow-up) design for each outcome measure. Primary analyses will use both an intent-to-treat (ITT) data sample (i.e., all randomized participants, including those who drop-out) and a per-protocol or "treatment completers"[8] procedure (i.e., only participants who complete the protocol/treatment). In the ITT analyses, we will use the "last observation carried forward" methodology, which is considered a conservative approach for handling missing data[95-98]. In a non-inferiority design, ITT favors the alternative hypothesis (i.e., no difference between treatments), because it minimizes the difference between groups, therefore, using both analyses (ITT, per-protocol/treatment completers) is the most rigorous approach to non-inferiority designs[50]. Lowering the alpha level to correct for multiple comparisons is not appropriate in non-inferiority designs as it has the same effect as increasing the alpha level in traditional (superiority) designs. We will use both confidence interval (95% CI) and hypothesis testing (one-sided t-test; α=.025) to compare the mean change[50] in outcome measure scores from pre- to post-treatment for the SKY versus CPT treatment groups.

Randomization allows for an unbiased distribution of potential confounding variables and as such, the two treatment groups (SKY, CPT) are not expected to differ on key demographic variables (e.g., age, sex, race, ethnicity, education, PTSD severity, psychiatric comorbidity, medication use). However, if significant group differences occur, we will explore moderators of treatment outcome[99, 100].

[8]Consistent with previous RCTs of PTSD, we define treatment completers as those who complete ≥75% of the treatment sessions for either CPT or SKY[66].

Ethics and dissemination

Ethical considerations

This RCT protocol is approved by Stanford University Institutional Review Board. All participants provide written informed consent prior to participation (see Appendices). Consent forms are audited annually by the VA. Annual continuing reviews are also conducted by Stanford University Institutional Review Board and the Department of Veterans Affairs.

Safety policy

All participants are routinely followed-up by telephone by the study coordinator (JST) to monitor serious adverse events and unanticipated problems. Any serious adverse events and unanticipated problems will be recorded and reported to Stanford University Institutional Review Board and VA within the reporting deadlines. No additional data safety and monitoring board was required by the IRB. Suicide risk is comprehensively assessed throughout the study and a safety plan exists (led by a licensed clinical psychologist; RJS-H) to be employed in respond to reports of thoughts about or intent to harm oneself or others. The interviewer will assess whether the participant has a viable plan and means to carry out the plan

Dissemination policy

The datasets generated and/or analyzed during the current study are not publicly available due to privacy restrictions at the Department of Veterans Affairs. De-identified electronic data sets will be made available upon written request to the principal investigator (PJB). Once the RCT is completed, outcomes will be published in international peer-reviewed journals, regardless of the direction of effects.

Trial registration

This RCT was first registered online at ClinicalTrials.gov (identifier NCT02366403) on 19 February 2015. The first participant was recruited in March 2016. Recruitment is expected to continue until March 2019 with 1-year follow-up to be completed in March 2020.

Discussion

PTSD is a debilitating, highly prevalent condition in both general and veteran populations[2-4, 7-12]. Current national and international clinical practice guidelines recommend evidence-based, trauma-focused psychotherapy (e.g., CPT, PE, I.E., EMDR) as the first-line treatment for PTSD[17-22]. Despite the relative success of these treatments[23, 24], the majority of those who begin treatment retain a diagnosis of PTSD post-treatment[25, 26]. For these and other reasons (e.g., personal preference, stigma, accessibility to treatment, cost-effectiveness) healthcare consumers and providers have begun to seek more holistic, mind-body, CIH interventions for a variety of conditions[28]. However, there remains a paucity of high-quality, active controlled efficacy studies of CIH interventions for PTSD, which precludes their formal recommendation by institutions such as the VA and DoD[17].

The aim of this RCT is to address this gap in the field. Here, we present the protocol for an ongoing, 4-year non-inferiority parallel group design RCT comparing the efficacy of SKY (a breathing meditation intervention) to CPT (an evidence-based psychotherapy) for treating PTSD among veterans. If non-inferiority of SKY compared to CPT is suggested this will provide an empirical rationale for a larger multi-site RCT to evaluate the efficacy of SKY in multiple treatment settings across different veteran populations. This will also provide the impetus to explore cost-effectiveness of SKY versus trauma-focused therapy, evaluate implementation

issues (e.g., setting (hospital vs. community center), target population demographics (e.g., veteran vs. non-veteran)), and investigate the efficacy of SKY for other mental health conditions with high comorbidity with PTSD (e.g., depression, chronic pain, substance use). Such a study would inform evidence-based formal recommendations regarding the implementation of CIH interventions in the VA Health Care System. Results from the secondary analyses exploring potential differences in mechanisms of treatment action may inform future studies focused on individuality of care (i.e., precision medicine).

Declarations

Competing interests

Not applicable.

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Author's contributions

DCM was responsible for writing the manuscript with significant contributions from all other authors. PJB is principal investigator and executive manager of this RCT. PJB and EMS conceptualized the study. JST is the study coordinator and one of the SKY instructors. DCM,

RJS-H, and TJA are the CPT providers. RJS-H is the supervising licensed clinical psychologist. All authors read and approved the final manuscript.

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Table 1

Outcome measures and assessment time points

Measure	Phone Screen	On Site Screen	Pre-treatment	Post-treatment	1-month follow up	1-year follow up
PCL-5*	x					
MINI*		x				
PCL-C			x	x	x	x
CAPS-5*			x	x		
BDI-II			x	x		
BSS			x	x		
PANAS			x	x	x	x
CANTAB			x	x		
Actigraphy			x	x		
Heart Rate			x	x		
MAPI			x	x		
RLS-DI*			x	x		

Note. PCL-5 = Posttraumatic Stress Disorder Checklist-Version 5; MINI = Mini International Neuropsychiatric Interview; PCL-C = Posttraumatic Stress Disorder Checklist-Civilian Version; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5 past month version; BDI-II = Beck Depression Inventory II; BSS = Beck Scale for Suicide Ideation; PANAS = Positive and Negative Affect Schedule; CANTAB = Cambridge Neuropsychological Test Automated Battery; MAPI = Multivariate Apnea Prediction Index; RLS-DI = Restless Legs Syndrome Diagnostic Index.

*proctored

Table 2

Summary of session content for CPT

Session	Content	Home practice assignment
1	Introduction and education phase	Describe event's impact
2	Meaning of the event	ABC worksheets
3	Identifying thoughts and feelings	ABC worksheets
4	Identifying "stuck points"	Practice challenging questions
5	Challenging questions	Identify problematic thinking patterns
6	Problematic thinking	Practice challenging beliefs
7	Challenging beliefs	Evaluate safety beliefs
8	Safety issues	Evaluate trust beliefs
9	Trust issues	Evaluate power/control beliefs
10	Power/control issues	Evaluate esteem beliefs Give/receive compliments Pleasant/positive activities
11	Esteem issues	Revise description of event's impact Evaluate intimacy beliefs Give/receive compliments Pleasant/positive activities
12	Intimacy issues; revisiting meaning of the event	Continue using worksheets

Note. CPT = cognitive processing therapy. ABC worksheets = preliminary cognitive restructuring exercise involving identification of Activating event, Belief, and Consequences of belief.

Table 3

Summary of session content for SKY

Session	Content	Daily home practice
1	Introductory SKY practices	5 min breathwork
	Guided meditation	Reflection questions
2	Introductory SKY practices	15 min breathwork
	Guided meditation	Reflection questions
3	SKY breathing and accompanying	20 min breathwork
	practices	Reflection questions
4	SKY breathing and accompanying	20 min breathwork
	practices	Reflection questions
5	SKY breathing and accompanying	30 min breathwork
	practices	Reflection questions
6,8,10,12	SKY breathing and accompanying	30 min breathwork daily
	practices	
7,9,11,13	SKY home practice program	30 min breathwork daily
	Guided meditation	

Figure Legends

Figure 1. Graphical representation of outcome measures by PTSD symptom clusters.

Figure 2. CONSORT flow diagram.

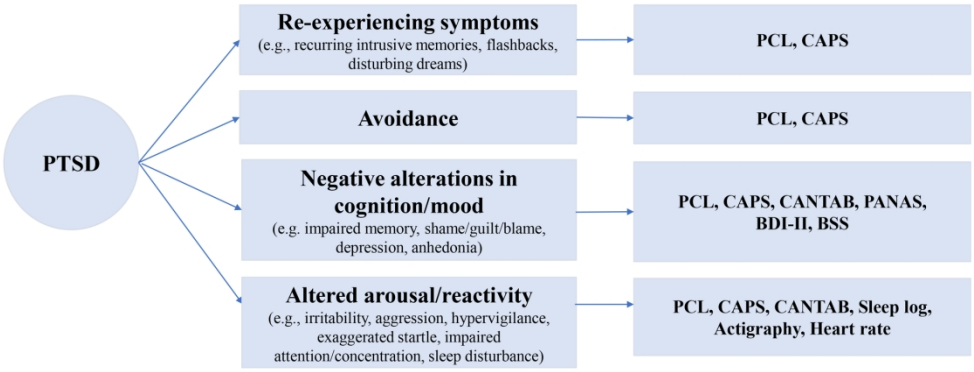

Figure 1. Graphical representation of outcome measures by PTSD symptom clusters.

173x70mm (300 x 300 DPI)

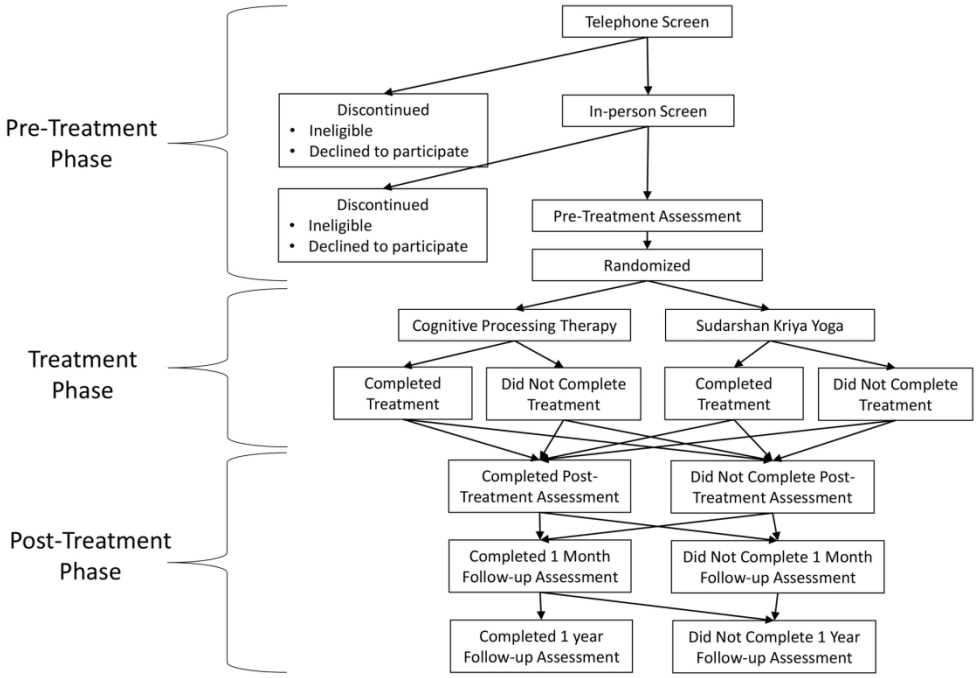

Figure 2. CONSORT flow diagram.

173x126mm (300 x 300 DPI)

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RESEARCH CONSENT FORM

Title of Study: Breathing Meditation Intervention for Posttraumatic Stress Disorder	
Principal Investigator: **Dr Peter J. Bayley**	VAMC: VA Palo Alto HCS

Breathing Meditation Intervention for Posttraumatic Stress Disorder

Informed Consent

Are you participating in other research studies? ___Yes ___No

PURPOSE OF RESEARCH

You are invited to participate in a research study to compare the efficacy of a breathing meditation to Cognitive Processing Therapy in treating symptoms of Posttraumatic Stress Disorder (PTSD). You were selected as a possible participant in this study because: 1) you are a Veteran; and 2) you have symptoms of PTSD.

This study is being done by researchers at VA Palo Alto, and is sponsored by the Department of Veterans Affairs (VA).

This research study is looking for 76 Veterans who exhibit symptoms of PTSD.

The primary aim for this study is to compare two different ways of treating PTSD in Veterans. One way involves treatment with a breathing-based meditation in a group setting. The other involves a therapy commonly used by the VA to treat PTSD called Cognitive Processing Therapy. Apart from changes in your symptoms of PTSD, we will also be assessing whether there are related changes to your memory, attention, mood, sleep, medication and heart rate.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but you may withdraw your consent later and stop being in the study without any loss of benefits or medical care you are entitled to.

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DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 4 years. Participants will be assigned to either a meditation treatment group or a one-on-one Cognitive Processing Therapy treatment. Participants in the meditation group will undergo a treatment program consisting of a 5-day group class (3 hours/day) followed by five weeks of sessions twice per week (1hr/session). Participants given Cognitive Processing Therapy treatment will be given 12 one-hour sessions twice per week over the course of 6 weeks. At the end of treatment all participants will be tested again. Follow up tests will be given at one-month and 12-months post-treatment.

PROCEDURES

Patients who sign this informed consent and meet the study eligibility criteria will be enrolled into the study and will be randomized to one of two treatment groups: a meditation treatment group or a one-on-one Cognitive Processing Therapy treatment.

If you choose to participate, Dr. Bayley and his research staff will ask you to participate in the activities described below. All study procedures will be completed by trained professionals and research staff. This study has 4 phases: baseline and randomization (1 day), intervention (6 weeks), end of treatment (1 day), 4) follow-up at one month (one hour) and one year (one hour).

1. BASELINE AND RANDOMIZATION PHASE

If you agree to be in this study, you will complete a number of tests to make sure that you are eligible. You will read and sign this informed consent form before you begin the baseline phase. The baseline phase will take place over two half-days (an afternoon and a morning) and will involve overnight measurements of memory, heart rate and sleep. To conveniently undergo the afternoon and morning assessments you will be accommodated overnight in a local hotel.

During the baseline phase and before you are given any treatments, the following will happen:

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- We will ask for some general information, and give you questionnaires about your mental health, mood, and sleep.
- You will be given computerized tests of cognition to measure your memory and attention.
- Study staff will review with you any drugs (prescriptions, "natural food products" and "over the counter" supplements) that you are taking. During the study, you will be able to take medications. You will also be given a questionnaire about any non-medical use of drugs over the past year.
- You will complete self-report questionnaires about the symptoms of PTSD which will be reviewed by study staff in an interview.
- On the overnight visit, you be asked to wear a heart rate monitoring device and an actigraph motion logger on your wrist. The heart rate monitor and motion logger will be fitted in the evening and you will be asked to keep wearing them for the next 12 hours. You will also be assessed to see how well you remember some information overnight using computer-based tests. For these you will be trained in the afternoon and retested the next morning.

If you agree and are eligible to participate in this research study, you will be randomized to either the breathing meditation treatment or to the Cognitive Processing Therapy treatment. Randomization is a process that is similar to flipping a coin where one side of the coin is breathing meditation and the other side is the Cognitive Processing Therapy. There is a 50:50 chance of being randomized to either treatment. Both groups will receive all the same measurements and tests.

2. INTERVENTION PHASE

BREATHING MEDITATION GROUP

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This treatment will be given in a group setting at VA Palo Alto and will last 6 weeks. The class meets 3 hours per day for the first five days, followed by five weeks of sessions given twice per week (one hour per session). There will be a maximum class size of ten..The meditation will include several types of breathing exercises involving arousal and attentional control. Initial breathing exercises are designed to be calming and focusing. Subsequent breathing exercises are more fully energizing, allowing you to focus more fully. All are soothing and present-focused. You will be encouraged to learn all the breathing exercises, and to utilize the ones that seem most appropriate to your needs. During the six weeks of treatment, you will be encouraged to engage in optional home practice. This will consist of seeking venues that you have been avoiding in order to practice the meditation techniques in those environments. You will be encouraged to start with situations that are less arousing, and progress to more difficult situations. At each class you will have the opportunity to share your experiences, and discuss ways to continue to incorporate the exercises into your daily lives. You will also be asked to keep a daily log to record whether you practiced the intervention, your estimated hours of sleep, and any changes to medications.

COGNITIVE PROCESSING THERAPY

This treatment will be given individually as a series of office visits at VA Palo Alto and will last for six weeks. Each session will last around forty-five minutes and there will be two sessions per week. Sessions will include reviewing homework from the previous session, focusing on specific issues, learning new therapeutic techniques and setting up homework for the following session including real-life application of learned techniques.

In the first few sessions you will be told more about the theory behind the treatment. You will be taught the connection between events, thoughts, and

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feelings and begin to identify places where you can focus on thinking about past emotionally traumatic events. Later, skills will be taught, including looking at the evidence for and against some of your beliefs, and examining the context from which the belief was formed. You will be asked to focus on five key areas, including safety, trust, power/control, esteem, and intimacy. Finally, you will be asked to look to the future and identify areas that may be problematic and discuss ways that you can manage these issues. You will also be asked to keep a daily log to record whether you practiced the intervention, your estimated hours of sleep, and any changes to medications.

3. END OF TREATMENT PHASE

When you finish treatment, you will be given most of the same tests and questionnaires as you received during the baseline phase:

- We will give you questionnaires about your mental health, mood, and sleep.
- You will be given computerized tests of cognition to measure your memory and attention.
- Study staff will review with you any drugs (prescriptions, “natural food products” and “over the counter” supplements) that you are taking. You will also be given a questionnaire about any non-medical use of drugs over the past year.
- You will complete self-report questionnaires about the symptoms of PTSD which will be reviewed by study staff in an interview.
- On the overnight visit, you will be asked to wear a heart rate monitoring device and an actigraph motion logger on your wrist. The heart rate monitor and motion logger will be fitted in the evening and you will be asked to keep wearing them for the next 12 hours. You will also be assessed to see how well you remember some information using

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computer-based tests. For these you will be trained in the afternoon and retested the next morning.

4. FOLLOW-UP PHASE

Two follow-ups visits are scheduled following treatment at 1) one month, and 2) one year. The amount of time required to complete each follow-up should be around 1 hour. During the follow-up, study staff will ask you to complete three self-assessments about your mood and current PTSD symptoms.

5. FOR ALL STUDY PHASES

- It is important for study staff to be aware of any changes in your medications during your participation in the study.
- You will interact with members of the entire study team. The study takes place at the VA Palo Alto Health Care System (VAPAHCS). If asked, we will provide a note for your employer that you were receiving medical treatment. We will not compensate for missed work time.
- You will be asked about adverse events whenever you are seen by study staff for treatment, evaluation, and follow-up visits. An adverse event is anything bad that happens with you and may or may not be related to your participation in this study. An independent committee will be told about all adverse events at least once every six months. If they believe that any aspect of this study is unsafe, they will recommend that changes be made to eliminate the safety problem.

6. OPTIONAL STUDY PHASES

If you agree to take part in the study described above, you will be offered the option to participate in the additional (optional) study phases described below. These will occur during Baseline, End of Treatment, and Follow-Up.

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☐ Magnetic Resonance Imaging (MRI) scans of the head:

The MRI phase will be done at the Stanford Center for Cognitive and Neurobiological Imaging (CNI) and will take 1 hour.

The MRI scan uses a strong magnet and radiofrequency magnetic fields to create pictures of the structure and function of the brain. The scanning procedure is like an X-ray or CT scan but you will not be exposed to x-rays. You will not feel anything. The hardest part of the scan is the need to lie still for the duration. You will lie on a table and be slid into a tunnel. Your head and shoulders lie in a plastic rounded tray which makes it more comfortable and easier to lie still. You will hear repetitive tapping noises from the scanner as it collects data to make the pictures of the brain. You will be required to wear earplugs. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling.

The MRI in this study is not harmful. The scanner and associated equipment are approved by the FDA. However, the scanner uses a strong magnet that will attract metals and affect some electronic devices. If you have a cardiac pacemaker, any other biomedical device (surgical clips, devices, or implants) in or on your body, a history of head or eye injury involving metal fragments, have ever worked in a metal shop, if you could be pregnant, or have kidney trouble, you must you tell the MRI operator/investigator before entering the MRI room, as it may be decided that should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be given a secure place to store such objects prior to the MRI scan. There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is expected and should not be painful. There is a small risk the scanner will heat up, so tell the operator if

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Title of Study: Breathing Meditation Intervention for Posttraumatic Stress Disorder	
Principal Investigator: **Dr Peter J. Bayley**	VAMC: VA Palo Alto HCS

you start to feel heat. Dizziness or nausea may occur if you move your head rapidly within the scanner.

If you feel discomfort at any time, notify the operator and the exam will be stopped.

The MRI scans performed in this study are for specific research purposes and are not optimized to find medical abnormalities. Our research scans do not qualify as a clinical diagnostic scan. The investigators for this project may not be trained to perform medical diagnosis. The investigators are not responsible for failure to find existing abnormalities with these MRI scans. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal. If this occurs, we will follow CNI's protocol for incidental findings. In this case, the research scans are referred to an approximately qualified individual (neuroradiologist) designated by the CNI Board for further review. The reviewer will determine if the potential abnormality merits further investigation and will inform the Principal Investigator of the action to be taken. The CNI operations team promptly provides a DVD with the scans in question or in another way that makes the images available to the reviewer to be read "as is". If follow-up is recommended, the investigator will contact you with the appropriate information. Because the images are taken using research settings, they will not be made available for clinical purposes. Finding out that you may have a medical abnormality that you had not been aware of before could cause psychological stress to you or your family and possibly affect your health insurance coverage in the future.

The safety protocol for the Stanford CNI does not require a pregnancy test because MRI does not use ionizing radiation (high-energy radiation that can potentially cause damage to DNA, such as with x-rays used in CT scans). There are currently no known harmful side-effects associated with temporary exposure to the strong magnetic field used by MRI scanners. However, because MRI may

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involve risks to the subject (or the embryo, fetus, or nursing infant if the subject is or may become pregnant), which are currently unknown and unforeseeable, if you are pregnant, or suspect you might be, or there is a chance you are, or you are currently breast feeding, you may not participate in this part of the study.

☐ Electroencephalography (EEG) and psychophysiological assessment:

The EEG phase will be done at the Palo Alto VA and will take 1.5 hours, including time spent setting-up the cap and removing it/washing hair.

EEG is a test that measures and records the electrical activity of the brain. To collect this information we will ask you to wear a cap on your head similar to a swimming cap. The cap has special sensors attached to it and is hooked by wires to a computer. Sensors will also be attached to your face and hands with a sticky paste to record facial movements, eye-blinks, heart rate, and skin conductance. The sensors only record activity, they do not produce any sensation. The hardest part of the EEG assessment is the need to minimize any movement including jaw movements, coughing, sneezing, yawning.

A computer will be set up to provide visual stimulation while you are in a shielded EEG room. Simple sounds or pictures will be projected onto a computer and headphones. You will be asked simple questions relating to these sounds or pictures. Your responses to these questions will be recorded using EEG specific equipment such as a computer-amplifier interface system. You will be given a hand-held control box or joystick to manually respond to the questions. Some pictures or words may provoke emotional responses such as fear, disgust, or sadness.

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If you choose to undergo the optional phases, you will be asked to complete each of these assessments three times: before treatment, after treatment, and at 1-year follow-up.

The EEG performed in this study is for specific research purposes and is not optimized to find medical abnormalities. Our research tests do not qualify as clinical diagnostic tests. The investigators for this project may not be trained to perform medical diagnosis. The investigators are not responsible for failure to find existing abnormalities with these EEG data. However, on occasion the investigator may notice a finding on an EEG wave that seems abnormal. If this occurs, a doctor will be asked to look at the raw EEG to see if any medical follow-up is needed. If so, the investigator will contact you and recommend you inform your doctor about the findings. Because the wave signals are collected using research settings, they will not be made available for clinical purposes.

PARTICIPANT'S RESPONSIBILITIES

You should:

- Follow the instructions of the investigators and study staff.
- Complete your questionnaires as instructed. You are free to skip any questions that you prefer not to answer.
- Ask questions as you think of them.
- Tell the investigator or research staff if you change your mind about staying in the study.
- While participating in this research study, do not take part in any other research study without approval from the investigators. Taking part in other research studies without approval from the investigators may invalidate the results of this research, as well as that of the other studies.

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- Keep your study appointments. If it is necessary to miss an appointment, please contact the investigator or study staff to reschedule as soon as you know you will miss the appointment.
- It is important that you not give false, incomplete, or misleading information about your medical history, including past and present drug use.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are **free to withdraw** your consent and stop your participation at any time. If you decide to withdraw from the study, you will not lose any benefits to which you would otherwise be entitled and your decision will not affect your ability to receive medical care for your condition.

The investigators may also withdraw you from the study without your consent for one or more of the following reasons:

o Failure to follow the instructions of the investigators and/or study staff.

o The investigators decide that continuing your participation could be harmful to you.

o Pregnancy

o The study is cancelled.

o Other administrative reasons.

o Unanticipated circumstances.

If you want to stop being in the study you should tell the investigators or study staff. You can do this by phone by calling Dr. Bayley at (650) 493-5000 x68653, or the Study Coordinator at (650) 785-6661

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POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Study Director if you have any questions. This study involves the following risks, discomforts, and possible inconveniences:

There are few risks involved in the treatments. However, because the treatments deal with painful feelings, emotions and experiences you may feel emotionally uncomfortable at times. You may even experience a temporary increase in your symptoms of PTSD during treatment which usually resolves as treatment progresses. Risks of the behavioral testing and measurements include possible anxiety that can be associated with any test. It is possible that you might also become tired or frustrated by some of our testing. You may find answering the questionnaires annoying, boring, or repetitive. If this happens, please tell us and we will take a break or skip a particularly difficult test.

For the heart rate monitor and the actigraph motion logger there is the possibility of developing a skin rash where they touch the skin. If this were to occur, the devices can be moved to a different location and lotion can be applied to the rash. We may request to remove obstructive chest hair with an electric razor in order to ensure a proper heart-rate reading.There are no other known risks associated with wearing the devices, other than the inconvenience of wearing them

All breathing meditation classes will be given in a group setting. As a consequence you should keep in mind that anonymity is not possible. However, all tests and assessments will be given individually and your results will not be shared with the group.

Risks of the usual care you receive are not risks of the research. They are not included in this consent form. You should talk with your health care providers about risks of usual care.

Optional phases:

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MRI Risks. There are no known significant risks with this procedure at this time because the radiofrequency magnetic field(s) and magnetic fields, at the strengths used, are thought to be without harm. However, metallic objects may experience a strong attraction to the magnet, so it is very important that you notify the researcher of any metal objects, devices, or implants that are in or on your body before entering the magnet room. This includes biomedical devices such as pacemakers and aneurysm clips, prostheses, and any other metallic objects embedded in the body such as bullets, buckshot, shrapnel, and any metal fragments from working around metal.

If you have any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop, if you have some type of implanted electrical device (such as a cardiac pacemaker), if you have severe heart disease (including susceptibility to arrhythmias), if you are wearing metal braces on your teeth, or (for women) if you could be pregnant or are breast feeding, you should not have an MRI scan.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful. Please report any heating sensation immediately. Dizziness and nausea may occur if the head is moved rapidly within the bore of the magnet.

If you feel discomfort at any time, notify the operator and the exam will be stopped.

EEG Risks. EEG experiments are non-invasive and painless. However, some people do experience mild and temporary skin irritation from: i) skin preparation where skin debris (dead skin cells) is removed from the area directly on the outer area of the eyes with a pad, or ii) slight itchiness from conductive paste that is used during application of the cap and sensors.

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If you feel discomfort at any time, notify the operator and the exam will be stopped.

VIDEO RECORDING

Video recording will be used to monitor treatment delivery. Recordings will be made of treatment providers, and not the participants. All recordings will be stored indefinitely in accordance with VA guidelines.

POTENTIAL BENEFITS

We can't promise that you will get any benefits from taking part in this research study. However, possible benefits may include being able to deal better with thoughts and memories associated with PTSD. The information that is obtained during this study may be scientifically useful and may lead to greater knowledge about the treatment of PTSD.

The testing done in this study could reveal a condition that you might not have previously been aware of and for which you may need treatment. Study staff will refer you for additional treatment if such problems are identified but the study will not pay for the treatment of any such identified problems.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY DIRECT BENEFITS FROM THIS STUDY.

ALTERNATIVES

You may choose not to participate in this study. If this is your decision, there are other choices including the standard treatments provided by a local clinic. Your study investigator will discuss any alternatives with you before you agree to participate in this study. Alternative treatments include medication and behavioral therapy.

ClinicalTrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not

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include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

PARTICIPANT'S RIGHTS

Your participation is voluntary. You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. You have the right to refuse to answer particular questions.

If you decide not to participate, tell the Protocol Director. You will still receive care for any disease and will not lose any benefits to which you would otherwise be entitled.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

CONFIDENTIALITY

Your identity will be kept as confidential as possible as required by law. Except as required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Your research records may be disclosed outside of the VA, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel. The responses to questions concerning illegal drug use could be self-incriminating and harmful to you if they became known outside the study. As explained in the confidentiality statement of the consent, we do not intend to disclose this information.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed.

Federal agencies as required, including the Department of Defense, the VA Office of Research Oversight or the VA Office of the Inspector General may have access to your information and research records.

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FINANCIAL CONSIDERATIONS

Payments

You will receive a payment of $400.00 for successful completion of the study.

- $200 will be paid after the completion of the Treatment Phase.
- $200 will be paid after the completion of the Follow-Up Phase.
- $50 will be paid for each session (Baseline, End of Treatment) of the optional study phase (MRI, EEG), after completion of the Treatment Phase.
- $50 will be paid for each session of the optional study phase (MRI, EEG), after completion of the Follow-Up Phase.
- If you withdraw from the study early, your payment will be prorated for the proportion of the study completed.

These payments will be mailed in the form of a personal check. Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work-eligible visa. You may need to provide your social security number to receive payment.

Costs

You will not have to pay anything to be in this study.

Sponsor

The Department of Veterans Affairs is providing financial support and/or material for this study.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study you should ask the Principal Investigator, Peter Bayley, Ph.D. You can call him at 650-493-5000 ext. 68653. You should also contact him/her at any time if you feel you have been hurt by being a part of this study.

Appointment Contact: If you need to change your appointment, please contact the Study Coordinator at (650) 785-6661.

IRB Use Only

Approval Date: November 30, 2016
Expiration Date: November 30, 2017

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Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, and would like to speak with a person who is independent of the research, call the Stanford Institutional Review Board (IRB) at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

May we contact you (by phone or letter) about related studies that may be of interest to you?

_____ Yes. I would like to be contacted for future research opportunities.

_____ No. Do not contact me about future research opportunities.

Signing your name means you agree to be in this study and that you were given a copy of this signed and dated consent form.

Signature of Participant Date

Print Name of Participant

Person Obtaining Consent:

Signature of Person Obtaining Consent Date

Print Name of Person Obtaining Consent

This page separates the

Informed Consent Document *(above)*

from the

HIPAA Authorization document

(below)

To preserve formatting, please

DO NOT DELETE this page

VA Palo Alto Health Care System – HIPAA Authorization Form
Protocol Title: _ Breathing Meditation Intervention for Posttraumatic Stress Disorder
Principal Investigator: ____Dr. Peter J. Bayley_____
Date of Review: December 1, 2014

Authorization To Use and Share Your Health Information For Research Purposes

HIPAA (Health Insurance Portability & Accountability Act) is a federal privacy law that protects the confidentiality of health information collected about you. The following explains how health information collected about you will be used by the investigators and who they may share your health information with as part of this research.

What is the purpose of the research study, and how will my health information be utilized in the study?

The study is to compare the effectiveness of treating posttraumatic stress disorder (PTSD) using two different methods; breathing meditation or a standard Cognitive Processing Therapy. Health information will be used in the study to monitor your progress and to evaluate the effectiveness of the treatment.

What Personal Health Information Will Be Used or Shared?

The following health information, linked to you by your name, SSN, Date of Birth, Address, email address, telephone number, will be used for this research:

- Date of visit
- Demographic information
- Physiological and Cognitive test data
- Medical history information
- Survey/questionnaire responses

Who May Use or Share Your Health Information?

By signing this document, you allow the following individuals and entities to obtain, use and share your health information for this research study:

- The Principal Investigator (Dr Bayley) and members of the VA research team.
- Departments within the VA Health Care System responsible for the oversight, administration, or conduct of research.

- The Stanford University Administrative Panel on Human Subjects in Medical Research and other Stanford University Officials responsible for the oversight, administration, or conduct of research.

Who May Receive and Use Your Health Information

The investigators may share your health information with the following individuals as part of this research study.

- Stanford University collaborating investigators and research staff.
- The Office for Human Research Protections in the U.S. Department of Health and Human Services

We will protect your health information as required by all laws, however health information shared with others may no longer be protected by Federal laws or regulations and might be shared by the parties above.

Do I have to sign this form?

No. Signing this form is voluntary. The VA may not condition treatment, payment, enrollment or eligibility for benefits based on signing this form. If you decide not to sign the form, you will not be able to take part in this study or receive any research-related treatment.

If I sign now, can I decide later not to continue in the study?

Yes. You are free to take back your permission and stop being in the study. The investigators will not collect any more information about you after you take back your permission, but they can continue to use your information that was collected before you took back your permission.

Your request to take back your permission must be done in writing. Either give your written request to the investigator or send it by mail to: Dr Peter Bayley, War Related Illness and Injury Study Center (WRIISC), 3801 Miranda Avenue, MC 151Y, Palo Alto, CA 94304-1290

Does My Permission for the use my Personal Health Information expire?

Yes. Your information cannot be used forever. Your permission related to the use and sharing of your health information expires when this research study is completed.

VA Palo Alto Health Care System – HIPAA Authorization Form

Protocol Title: _ Breathing Meditation Intervention for Posttraumatic Stress Disorder

Principal Investigator: ____Dr. Peter J. Bayley_____

Date of Review: December 1, 2014

HIPAA regulations require you to give separate written permission (signature) for the use of your protected health information.

Signature of Participant Date

Printed Name of Participant

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **Title page (p. 1)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **Abstract (p. 3) and Methods Trial Registration subsection (p. 21)**
	2b	All items from the World Health Organization Trial Registration Data Set **N/A**
Protocol version	3	Date and version identifier **N/A**
Funding	4	Sources and types of financial, material, and other support **Declarations Funding subsection (p. 23)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Title page (p. 1) and Declarations Author's contributions subsection (p. 23)**
	5b	Name and contact information for the trial sponsor **N/A**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **N/A – see Declarations Funding subsection (p. 23)**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **Declarations Author's contributions subsection (p. 23)**
Introduction		

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Introduction (p. 4-8, with question/hypotheses on p. 8)**
	6b	Explanation for choice of comparators **Introduction (p. 5, 8)**
Objectives	7	Specific objectives or hypotheses **Introduction (p. 8)**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Introduction (p. 8) and Methods Study design subsection (p. 9-10)**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Methods Setting subsection (p. 10)**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Methods Participants subsection (p. 10-11, including Exclusion criteria subsection) and Methods Interventions subsection (p. 14 paragraph 1 & p. 15-16 paragraph 2-1)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Methods Interventions subsection (p. 13-16) and Tables 2 & 3 (p. 40 & 42)**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **N/A**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **Methods Interventions subsection (p. 14 paragraph 1 & p. 16 paragraph 1)**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **Methods Participants subsection (p. 10-11)**

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Methods Study design subsection (p. 9) and Methods Outcome measures subsection (p. 16-19) and Figure 1 (Legend p. 43)**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **Methods Procedure subsection (p. 13-14) and Figure 2 (Legend p. 43)**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Methods Participants subsection (p. 11-12 Sample size (power analysis) subsection)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **Methods Recruitment subsection (p. 12-13)**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Methods Study design subsection (p. 9-10)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Methods Study design subsection (p. 9-10)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Methods Study design subsection (p. 9-10)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **Methods Data collection and blinding subsection (p. 19)**

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **N/A**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Methods Outcome measures subsection (p. 16-19) and Methods Data collection and blinding subsection (p. 19)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **Methods Participants subsection (p. 11-12 Sample size (power analysis) subsection), Methods Procedure subsection (p. 13-14), and Figure 2 (Legend p. 43)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **Methods Data collection and blinding subsection (p. 19)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Methods Data analysis plan subsection (p. 19-20)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **Methods Data analysis plan subsection (p. 19-20)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **Methods Data analysis plan subsection (p. 19-20)**
Methods: Monitoring		

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **N/A – the FDA does not mandate a DMC for our RCT design and neither does our ethics board (Stanford University Institutional Review Board) or funding body (Department of Veterans Affairs)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **Methods Participants subsection (p. 11-12 Sample size (power analysis) subsection)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **Methods Participants subsection (p. 11 Exclusion criteria subsection)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Ethics and dissemination Ethical considerations subsection (p. 20)**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Ethics and dissemination Ethical considerations subsection (p. 20)**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **Ethics and dissemination Dissemination policy subsection (p. 21)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **Methods Procedure subsection (p. 13-14)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **Methods Procedure subsection (p. 13-14)**

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **Methods Data collection and blinding subsection (p. 18-19)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **Declarations Competing interests subsection (p.23)**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **Methods Data collection and blinding subsection (p. 19)**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **N/A**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **Ethics and dissemination Dissemination policy subsection (p. 21)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **Declarations Author's contributions subsection (p.23)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **Ethics and dissemination Dissemination policy subsection (p. 21)**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **Methods Ethical considerations subsection (p. 20)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **N/A**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.