

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

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ABSTRACT

Introduction Post-traumatic stress disorder (PTSD) is a debilitating, highly prevalent condition. Current clinical practice guidelines recommend trauma-focused psychotherapy (eg, 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 randomised 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 PTSD 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 the best of our knowledge, this is this first non-inferiority RCT of SKY versus CPT for PTSD among veterans. The protocol is approved by the Stanford University Institutional Review Board. All participants provided 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.

Strengths and limitations of this study

- There remains a paucity of high-quality, active controlled efficacy studies of complementary and integrative health interventions for post-traumatic stress disorder (PTSD).
- In response, here we present the protocol for an ongoing non-inferiority parallel group randomised controlled trial (RCT) comparing the efficacy of Sudarshan Kriya Yoga (SKY) breathing meditation to cognitive processing therapy for PTSD among veterans.
- The primary outcome measure is the PTSD Checklist-Civilian Version.
- 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 the efficacy of SKY in non-veteran populations.

Trial registration number NCT02366403; Pre-results.

INTRODUCTION

Post-traumatic 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: (1) re-experiencing (eg, recurring intrusive memories, flashbacks and disturbing dreams); (2) avoidance of stimuli associated with the trauma; (3) persistent negative alterations in cognitions and mood (eg, impaired memory, exaggerated shame/guilt/blame, depression and anhedonia) and (4) altered arousal/reactivity (eg, irritability, aggression, hypervigilance, exaggerated startle, impaired attention/concentration and 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 behaviour among 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 behavioural 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 organisations, such as World Health Organisation (WHO), International Society for Traumatic Stress Studies, Veterans Affairs/Department of Defense (VA/DoD), American Psychiatric Association, National Institute for Clinical Excellence and Australian Centre for Posttraumatic Mental Health, 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 therapy (IE), as well as eye movement desensitisation and reprocessing (EMDR). These evidence-based psychotherapies for PTSD show large effects compared with 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 (eg, sertraline), serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine), atypical antidepressants (eg, nefazodone), alpha-1 blockers (eg, prazosin), antipsychotics (eg, olanzapine and risperidone), tricyclic antidepressants and monoamine oxidase inhibitors (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 the 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 (CIH) interventions.²⁸ These CIH interventions (previously referred to as complementary and alternative medicine [CAM]) may be viewed as less stigmatising than formal mental health interventions, such as CBT.²⁹ Recent data show that 34% of individuals within the general US population³⁰ and 39% of individuals with PTSD³¹ 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 suicidality³² 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 randomised 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/mantram-based approaches [six studies], yoga-movement based approaches [four studies] and combination approaches [one 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 [five studies], yoga-movement based approaches [three studies] and meditation/mantram-based approaches [two 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 (eg, a CIH intervention) is no worse than an established standard intervention (eg, trauma-focused therapy) at treating the target condition (eg, 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 dropout rates, etc. Sudarshan Kriya Yoga (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 (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). 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-treatment 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 and 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 emphasising the VA's commitment to providing these services. The memorandum was jointly authored by Tracy Gaudet, MD, Director, Office of Patient Centered Care & Cultural Transformation, and David J Shulkin, MD, 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-centred, patient-driven, personalised 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 PTSD 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 (eg, Clinician-Administered PTSD Scale for DSM-5 [CAPS-5]) for the following reasons: (1) it can be administered over the telephone making it ideal for screening and follow-up and thus, avoiding additional in-person visits by participants; (2) it has excellent psychometric properties including high convergent validity ($r=0.93$) with the CAPS^{56–59} and (3) 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 utilise a multi-methodological exploratory approach assessing a wide range of subjective and objective PTSD-related symptoms

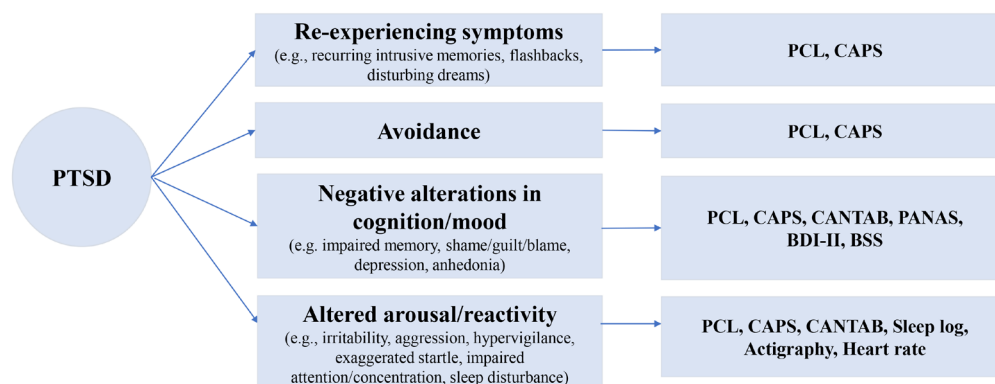


Figure 1 Graphical representation of outcome measures by post-traumatic stress disorder symptom clusters. BDI-II, Beck Depression Inventory II; BSS, Beck Scale for Suicide Ideation; CANTAB, Cambridge Neuropsychological Test Automated Battery; CAPS, Clinician-Administered PTSD Scale for DSM-5 past month version; PANAS, Positive and Negative Affect Schedule; PCL, Post-traumatic Stress Disorder Checklist; PTSD, post-traumatic stress disorder.

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		

*Proctored.

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

assessed pre-treatment 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/reactivity¹ (table 1, figure 1).

Setting

All in-person assessments and treatment interventions occur at the War Related Illness and Injury Study Center 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 the Department of Veterans Affairs RR&D Merit Review ('Breathing Meditation Intervention for Post-Traumatic Stress Disorder' [PI Bayley]; ClinicalTrials.gov) and the RCT is only open to veterans. To ensure the greatest generalisability 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 (1) are participating in a concurrent treatment study; (2) are unable to attend study visits and sessions at the VA Palo Alto; (3) intend to begin a new trauma-focused therapy (eg, CPT, PE, IE and EMDR) during the study period; (4) have experienced mania or psychosis for any reason within the past 6 months (eg, bipolar, schizophrenia and drug-induced psychosis, as the effects of SKY on more severe mental health disorders are unknown); (5) endorse suicidal or homicidal intent within the past 60 days (those that do are referred for VA psychiatric care); (6) endorse substance dependence (other than nicotine) within the past 30 days; (7) have an unmanaged seizure disorder; (8) have a severe traumatic brain injury or (9) 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 programme, 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 (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). 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% to 22% in non-VA studies²⁵ 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%–30%).^{26 65} Therefore, if our study has high dropout, we will continue to recruit participants until we reach the appropriately powered number of 30 participants per treatment group (consistent with previous RCTs of PTSD, we define treatment dropout as completion of <75% of the treatment sessions for either CPT or SKY⁶⁶).

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 to confirm presence/absence of clinically meaningful symptoms of PTSD. 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* (fifth 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. 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)⁷⁰ to assess exclusion criteria. Eligible participants are guided through informed consent (RCT

participation, data collection and future contact for other research studies) by the study coordinator and complete demographic and health histories. Each participant then undergoes a 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-treatment 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)

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,⁷¹ with effects maintained at least 5–10 years post-treatment.⁷² Sessions are rigorously structured, with content, materials and home practice assignments dictated by a manual.^{73 74} CPT consists of twelve 50–60 min 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. (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’^{73 74}; however, the latest version of the manual⁷⁵ now uses the term ‘CPT’ to refer to the version that does not include a written trauma account (ie, the previous ‘CPT-C’), whereas ‘CPT-A’ now refers to the version that includes the written trauma account (ie, 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%)⁷⁶

Sudarshan Kriya Yoga (SKY)

SKY is provided in a group format and incorporates controlled cyclical breathing exercises, gentle yoga

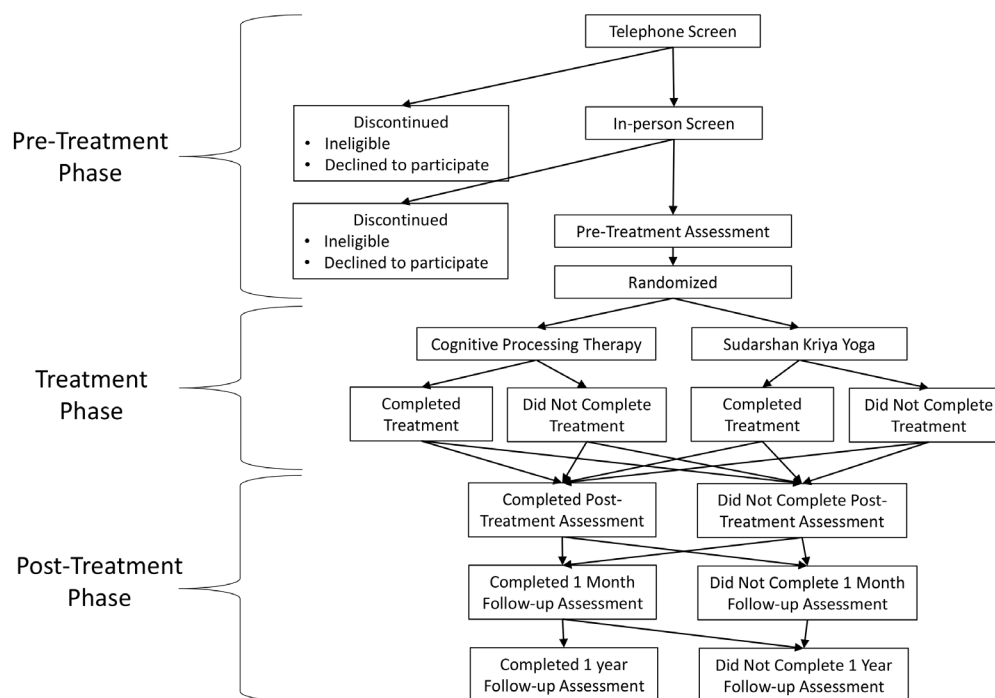


Figure 2 CONSORT flow diagram. CONSORT; Consolidated Standards of Reporting Trials.

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 year⁵² 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: (1) three-stage victory breath (*ujjayi pranayama*); (2) bellows breath (*bhastrika pranayama*); and (3) SKY breath (*Sudarshan Kriya*). (We use the non-Sanskrit names (alternate nostril breath, victory breath, bellows breath, SKY breath and straw breath) in groups to allow greater accessibility to veterans, consistent with *Project Welcome Home Troops* and the *International Association of Human Values* [IAHV].) 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 practised in many schools of yoga, though the number and rate of breath vary. 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 ten 60 min 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 5 weeks. This *Project Welcome Home Troops* SKY protocol differs from the contemporary standard SKY protocol in which: (1) 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; (2) 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 practised at the beginning and end of sessions, respectively, and (3) 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 6 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 (ie, 6 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 group 'retreat', so this feature could not be altered. If non-inferiority of SKY compared with CPT is suggested, subsequent studies could and should investigate questions regarding dosage and duration.

Table 2 Summary of session content for cognitive processing therapy (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

ABC worksheets, preliminary cognitive restructuring exercise involving identification of Activating event, Belief and Consequences of belief.

Table 3 Summary of session content for Sudarshan Kriya Yoga (SKY)

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

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

Outcome measures

PTSD Checklist-Civilian Version (PCL-C)

The PCL-C⁷⁷ 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. (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.)

Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) past month version

The CAPS-5⁷⁹ is the gold standard semi-structured clinical diagnostic interview for the assessment of PTSD.⁸⁰ CAPS-5 items correspond to DSM-5¹ 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 7.0⁷⁰ is a brief (15min) structured clinical interview designed to screen for current and lifetime DSM-5 and International Classification of Diseases (ICD-10) mental health disorders. It is being used here to assess exclusion criteria (ie, mania, psychosis and substance dependence [see Participants]).

Beck Depression Inventory II (BDI-II)

The Beck Depression Inventory-II⁸¹ is a 21-item self-report measure that assesses current depression symptom severity (negative alterations in mood symptom cluster). Items are rated on a four-point scale according to how much the symptom bothered the respondent over the prior 2 weeks.

Beck Scale for Suicide Ideation (BSS)

The BSS⁸² 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 PANAS⁸³ 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 five-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 computerised neuropsychological assessment system. It is the most well-validated and widely used cognitive research software.^{84–88} We utilise 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.) wristwatch overnight at pre-treatment 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-treatment and post-treatment to assess physiological arousal (altered arousal symptom cluster).^{91 92}

Multivariate Apnea Prediction Index (MAPI)

The MAPI⁹³ 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 artefacts due to sleep apnea.

Restless Legs Syndrome-Diagnostic Index (RLS-DI)

The RSL-DI⁹⁴ is a standardised 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 artefacts due to restless legs syndrome.

Data collection and blinding

All in-person assessments (ie, clinical interviews, outcome measures and experimental assessments) are conducted by an assessor blinded to treatment group (SKY and CPT) to protect the integrity of assessment and prevent assessor bias. Data entry is also blinded and data collection is ongoing. Data are de-identified and stored on the secure VA network and REDCap. Demographics information is 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 and CPT) × 4 time (pre-treatment, post-treatment, 1-month follow-up and 1-year follow-up) design for each outcome measure. Primary analyses will use both an intent-to-treat (ITT) data sample (ie, all randomised participants, including those who dropout) and a per-protocol or ‘treatment completers’ procedure (ie, only participants who complete the protocol/treatment). 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 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 favours the alternative hypothesis (ie, no difference between treatments), because it minimises the difference between groups; therefore, using both analyses (ITT and 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 95% CI and hypothesis testing (one-sided t-test; $\alpha=0.025$) to compare the mean change⁵⁰ in outcome measure scores from pre-treatment to post-treatment for the SKY versus CPT treatment groups.

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

ETHICS AND DISSEMINATION

Ethical considerations

The protocol is approved by the Stanford University Institutional Review Board. All participants have provide written informed consent prior to participation (see online supplementary appendices). Consent forms are audited annually by the VA. Annual continuing reviews are also conducted by the Stanford University Institutional Review Board (IRB) 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 the Stanford University IRB and the VA within the reporting deadlines. No additional data safety and monitoring board were 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 analysed during the current study are not publicly available due to privacy restrictions at the Department of Veterans Affairs. De-identified electronic datasets will be made available on 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 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 (eg, CPT, PE, IE and 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 (eg, personal preference, stigma, accessibility to treatment and 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 the 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 with CPT is suggested then 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 (eg, setting [hospital vs community centre], target population demographics (eg, veteran vs non-veteran) and investigate the efficacy of SKY for other mental health conditions with high comorbidity with PTSD (eg, depression, chronic pain and 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 the individuality of care (ie, precision medicine).

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Contributors DCM was responsible for writing the manuscript with significant contributions from all the 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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Competing interests None declared.

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