Mechanisms of Change in Yoga and Physical Activity for Veterans

NCT03509909

August 16, 2022

Background and Significance

Posttraumatic stress disorder (PTSD) is a chronic, debilitating disorder that broadly impacts the life of affected individuals. Existing treatment approaches have clinically meaningful positive effects on PTSD symptoms, yet the majority of patients who receive our best treatments continue to have a diagnosable disorder after treatment (Steenkamp, Litz, Hoge, & Marmar, 2015), pointing to the need for more robust recovery plans. Clinically significant residual PTSD symptoms and individual preferences have led many patients seek alternatives to psychotherapy and pharmacotherapy (Clarke, Black, Stussman, Barnes, & Nahin, 2015). Consequently, VA facilities currently offer a wide array of complementary and alternative approaches (Libby, Pilver, & Desai, 2012), despite a paucity of evidence about their effectiveness for the treatment of PTSD (Lang, Strauss, & Schnurr, 2016). Current empirically-supported therapies emphasize habituation of fear/arousal and change in dysfunctional beliefs about the trauma (e.g., Schumm, Dickstein, Walter, Owens, & Chard, 2015). PTSD, however, is also characterized impaired emotion regulation (Seligowski, Lee, Bardeen, & Orcutt, 2015) and cognitive processing deficits (Bomyea & Lang, 2015), suggesting additional mechanisms by which PTSD may be addressed. *An intervention that reduces barriers to care, complements current first-line approaches, and/or targets mechanisms that maintain PTSD may ameliorate the broad range of negative effects of this disorder; yoga may accomplish all of these.* The acceptabilility of yoga is readily apparent. It is widely offered within VA PTSD programs (Libby, Reddy, Pilver, & Desai, 2012), and surveys suggest that interest in yoga continues to grow, with over 30 million Americans engaged in some type of yoga practice (Ipsos Public Affairs, 2016). We argue herein that yoga potentially impacts transdiagnostic mechanisms that are not only connected to the etiology and maintenance of PTSD but also may increase one's ability to tolerate trauma-focused psychotherapy.

The two largest randomized controlled trials of yoga for civilian PTSD suggest that the practice leads to meaningful change in PTSD symptoms from pre- to post-treatment; in both cases this effect was greater than the control condition with effect sizes in the range of 1.07-1.65 (Jindani, Turner, & Khalsa, 2015; van der Kolk et al., 2014). Although these two trials suggest optimism, the broader literature on yoga for PTSD is highly variable and of inconsistent quality, thus limiting the conclusions that can be drawn. Several studies show no difference between yoga and a control condition (e.g., Mitchell et al., 2014; Thordardottir, Gudmundsdottir, Zoega, Valdimarsdottir, & Gudmundsdottir, 2014), and one very small study found negligible effect on PTSD symptoms among Veterans (Staples, Hamilton, & Uddo, 2013). Whereas methodology may be one factor in the variability in outcomes observed in yoga studies, another likely source is the fact that yoga practice varies widely, ranging from quite vigorous to highly relaxing and including no to heavy emphasis on physical asanas (postures), meditative practices, spirituality or breath control. *Just as trying to establish whether or not "psychotherapy" is effective for PTSD would be untenable because of the broad range of procedures encompassed by that term, it is unlikely that "yoga" will be proven efficacious or not. The quest for effective psychotherapeutic strategies was driven by a conceptual understanding of processes that create or maintain psychopathology and the use of techniques to modify those mechanisms. Similarly, we suggest that delivering efficacious yoga-based interventions will depend on understanding mechanisms of change and targeting those variables in the therapeutic teaching of yoga.*

Accordingly, the **primary aim** of this randomized clinical trial is to examine the efficacy of a manualized hatha yoga protocol as compared to a supportive physical activity control in a sample of Veterans with PTSD, thus adding to the evidence base in this understudied area. The proposed study incorporates "gold standard" requirements for PTSD treatment trials, including clearly defined target symptoms; reliable and valid measures; use of blind evaluation of outcome; systematic assessor training; manualized, replicable, specific treatment programs; unbiased assignment to condition; and measurement of treatment adherence (Foa & Meadows, 1997). The larger published and ongoing trials of yoga have used wait list, group health education and psychotherapy as control conditions, but none have addressed the important question of whether or not yoga confers more benefit than other types of physical activity; this project answers that need. The yoga literature continues to develop, with recent work showing positive clinical effects when applying Trauma Sensitive Yoga for women (Kelly et al., 2021). This project will contribute to the literature by examining a more typical hatha yoga practice in a diverse sample.

A **secondary aim** of this project is to understand the mechanisms by which clinical change may occur when Veterans with PTSD practice yoga. *This aspect of the study extends our current knowledge as there is no comprehensive model of yoga's impact on PTSD.* Out of this understanding, we envision developing guidelines for the therapeutic application of yoga. Given the tens of thousands of people teaching yoga (Bachman, 2015) and the wide range of settings in which Veterans may practice, trying to disseminate a particular protocol may be infeasible. More realistically, we would aim to extend current trauma-sensitive yoga
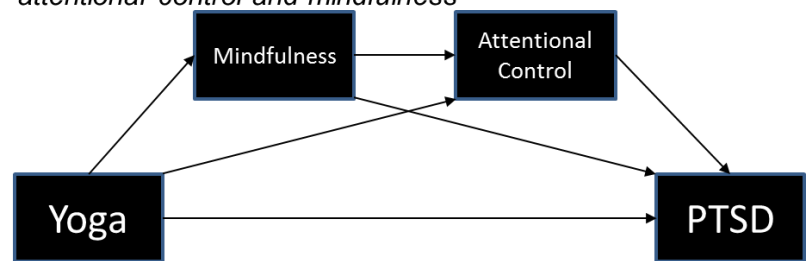
guidelines, which focus largely on the acceptability of the practice (Emerson, Sharma, Chaudhry, & Turner, 2009), to highlight key principles and postures that support recovery. In doing so, we could create a consumer's guide for yoga for PTSD so that Veterans can apply yoga to work on key concepts wherever they choose to practice. *In doing so, we would greatly enhance the disseminability of effective yoga practice.* Further, we believe that this work has the potential to inform the application of yoga to other mental health conditions, as the mechanisms we propose to examine have applicability to other disorders.

Mechanisms of change. Proposed herein are two models through which yoga may impact PTSD: the attention model and the coping model. These transdiagnostic concepts have well-established links to psychopathology, and some early evidence that they may be modifiable through yoga. Thus it is an important next step to determine whether attentional functioning and coping are modified through yoga practice and whether these changes explain observed clinical benefits.

Attention model. PTSD is characterized by deficits in aspects of cognitive processing. Compared to individuals without a psychiatric diagnosis, those with PTSD demonstrate specific deficits in attention and executive function (Vasterling & Brailey, 2005). These deficits are observed both when individuals are required to utilize cognitive processes in the context of neutral information (e.g., Falconer et al., 2008) and emotionally-valenced information (e.g., disengaging attention from threat stimuli; Pineles et al., 2009), and may correspond to subjective symptoms observed in the disorder (e.g., hypervigilance, cognitive avoidance, concentration difficulties; Aupperle et al., 2011). Neurobiologically, individuals with PTSD demonstrate hypoactivation of prefrontal cortical regions that underlie performance on complex attention and executive function tasks (e.g., dorsolateral prefrontal cortex, anterior cingulate, ventromedial prefrontal cortex; Falconer et al., 2008; Francati, Vermetten, & Bremner, 2007).

Yoga frequently involves active and deliberate regulation of attention to a fixed point (known as a *drishti*), which creates a focused attention mindfulness practice (Lutz, Slagter, Dunne, & Davidson, 2008). Both studies of expert meditators and of training in novices show that focused attention mindfulness is linked to enhanced attentional functioning (e.g., Lutz et al., 2008; Moore & Malinokski, 2009), leading to a "significant decrease in emotionally reactive behaviors

Figure 1: Path diagram for the multiple mediation model of attentional control and mindfulness

that are incompatible with stability of concentration" (Lutz et al., 2008, p. 3). Such findings drive the suggestion that this aspect of yoga practice drives cognitive benefits above and beyond the benefits of physical exercise (Gothe & McAuley, 2016). Empirical studies across diverse samples (e.g., older adults, children, patients with multiple sclerosis, patients with schizophrenia) also demonstrate yoga's beneficial effects on cognition as assessed using objective cognitive assessment batteries (e.g., Hariprasad et al., 2013). The cognitive systems utilized to hone focused attention are likely the same systems that govern cognitive performance more broadly speaking; thus, yoga may improve more global cognitive indices by way of enhancing performance and efficiency of attention (Gothe, Kramer, & McAuley, 2014; Gothe & McAuley, 2016). Work in our lab recently showed that a computer-based attentional control training successfully reduced reexperiencing symptoms with a medium-large effect size (Bomyea, Stein, & Lang, 2015). As depicted in Figure 1, we will examine a multiple mediation model (Wang et al., 2012), whereby one mediator (mindfulness) can affect the other (attentional control). Thus, we will examine the model that yoga increases mindfulness, which increases attentional control, which in turn reduces PTSD symptoms. We will compare the fit of this model to the models including only one of these mediators, i.e., mindfulness mediates the relationship between yoga and PTSD symptoms and attentional control mediates the relationship between yoga and PTSD symptoms.

Coping model. Distress following exposure to trauma is a normal human experience that typically fades with the passage of time. Current models of PTSD suggest that one factor that drives the development and maintenance of the disorder (i.e., normal distress does not resolve) is pathological coping. Consistent with this, a recent meta-analysis of 57 studies showed that strategies such as rumination, thought suppression and experiential avoidance are strongly associated with PTSD (Seligowski, Lee, Bardeen, & Orcutt, 2015). There is evidence to suggest that yoga and other focused meditation approaches reduce the use of such maladaptive coping strategies. A recent pilot study of yoga (vs assessment only control) in women found that yoga was associated with reduced suppression of emotion, although this the change was not associated with change in

PTSD symptoms in this small sample (*n* = 38; Dick, Niles, Street, DiMartino, & Mitchell, 2014). Such mediation has been observed, however; focused meditation as compared to relaxation and wait list was associated with increased use of effective emotion regulation strategies, which, in turn, correlated with reduced trait anxiety (Menezes & Bizarro, 2015). Mindfulness meditation as compared to a relaxation control was associated with decreased use of distraction and rumination; change in rumination partially mediated observed changes in distress (Jain et al., 2007). Thus, yoga may reduce PTSD symptoms by directly reducing maladaptive coping (refer to Figure 2).

Yoga may also support positive coping by increasing tolerance of discomfort. Yoga provides physical experiences in which to learn non-reactivity. For example, yoga differentiates between pain and discomfort such that pain signals the need to respond (e.g., withdrawing a hand from a hot surface) whereas discomfort does not (e.g., remaining in an uncomfortable situation and simply observing one's reaction). This increased capacity has been demonstrated experimentally. For example, individuals with a long history of yoga practice were able to tolerate induced pain in the laboratory setting about twice as long as controls without a yoga practice (Villemure, Ceko, Cotton, & Bushnell, 2014). Thus, we suggest that yoga can change one's tolerance

Figure 2: Path diagram for the multiple mediation model of tolerance of discomfort and coping
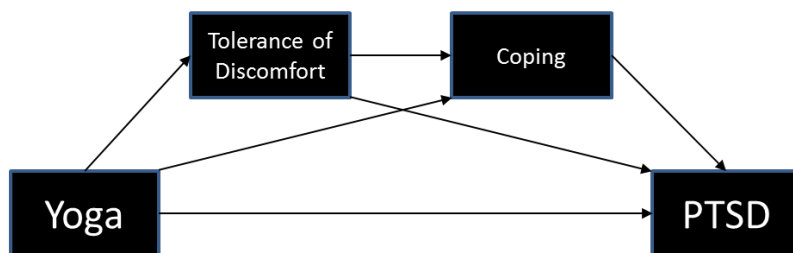
of discomfort. Tolerance of discomfort has been described in multiple ways in the literature and has been associated with PTSD. The term "distress tolerance" is used to describe the ability to tolerate uncomfortable emotions (Simons & Gaher, 2005). Distress tolerance inversely correlates with PTSD severity; specifically, those with poorer distress tolerance have more re-experiencing symptoms and emotional numbing (Vujanovic et al., 2013). The idea that increased tolerance of discomfort may ameliorate PTSD is supported by studies of "anxiety sensitivity (AS)," which is the fear of anxiety symptoms (physiological, cognitive and social). AS is not only related to the development and maintenance of the PTSD (Lang, Kennedy, & Stein, 2002), but change in AS predicts change in PTSD symptoms. Further, interventional studies show that reducing AS ameliorates PTSD (Allan, Short, Albanese, Keough, & Schmidt, 2015). Further, Medina et al. (2015) showed that hatha yoga increased distress tolerance (specifically an aspect of distress tolerance called distress absorption), which led to more adaptive coping (namely less emotionally-driven eating in response to stress). A direct extension of these data is a multiple mediation model for PTSD involving tolerance of discomfort and coping, as diagrammed in Figure 2. We will examine the model that yoga increases tolerance of discomfort, which improves coping, which in turn reduces PTSD symptoms. We will compare the fit of this model to the models including each of the mediators alone. To inform future work, we additionally will explore whether any combination of the Attention and Coping Models explains more variance than either one alone.

Summary. In light of the evidence presented, we predict that yoga will be associated with clinically significant change in PTSD symptoms and that the change associated with yoga will be significantly greater than the change associated with physical activity because of the meditative nature of the practice. We will secondarily assess the impact of the two interventions on symptoms that are commonly associated with PTSD and examine the clinical utility of both interventions (Smart, 2006) with the ultimate goal of guiding the clinical application of the practice. Further, we have described two models that link yoga practice to change in PTSD symptoms. The fit of the proposed Attention and Coping Models will be assessed and compared.

Yoga is a highly popular practice, which is increasingly being leveraged as a part of Veterans' PTSD recovery programs. Although initial evidence suggests the usefulness of this strategy, it is urgent that we gather more evidence as to its efficacy for Veterans and understand its mechanisms of action. Such information is critical if we are to find ways to replicably deliver yoga to Veterans for symptom management. By focusing on key mechanistic variables that are linked to the development and maintenance of PTSD and are impacted by yoga, we believe that we will be able to identify pathways to change. This information, in turn, can be used to optimize practice and create delivery guidelines. This project therefore represents an important next step in yoga intervention research.

Preliminary Studies and Current Status of the Field

We relied on three primary sources of preliminary information in designing the proposed study: clinical data from ongoing yoga groups at a VA San Diego, ongoing and past studies at our facility of yoga and other complementary interventions, and extant literature on yoga for PTSD.

Acceptability

Clinical data supports the acceptability of yoga for PTSD among Veterans at this facility. There has been a "Yoga, Nutrition and Meditation" group for "pain and suffering" at the Oceanside Community Based Outpatient Clinic since 2015. Offered in 8-week group meetings, the group features gentle hatha yoga with some adaptions for physical limitations (e.g., availability of seated poses). In FY 16, 66 unique Veterans took advantage of this offering, accounting for 330 visits. In FY17 to date, there have been 53 unique participants with a total of 294 encounters. Thus, patients on average are completing 5-6 of the 8 sessions.

Successful past research also speaks to the acceptability yoga and similar complementary approaches in San Diego. Co-Investigator Erik Groessl has been conducting yoga research at VA San Diego since 2004, establishing the feasibility of conducting yoga research at this facility. Dr. Groessl's most recent RCT of yoga for VA patients with chronic low back pain easily enrolled the target of 150 VA patients within 30 months (Groessl et al., 2017). This study, which utilized the protocol to be used herein, compared hatha yoga delivered immediately or after a delay. Participants attended an average of 13 (median 15) of 24 classes, and 80% were retained at 6- and 12-weeks, with 73% retention at 6-months. Both groups showed significant change on the primary outcome measure, the Roland-Morris Disability Questionnaire. Mental health outcomes were not measured in this study, but Dr. Groessl's past work with pain patients showed significant change in depression and mental health related quality of life (Groessl, Weingart, Aschbacher, Pada, & Baxi, 2008).

The acceptabililty of a yoga and physical activity trial is also suggested by successful trials at this facility utilizing other complementary and alternative treatments for PTSD. Dr. Lang recently completed a feasibility and proof of concept study of compassion meditation (CM) for Veterans with PTSD. CM focuses on the heartfelt wish that others be free of suffering based on cultivation of a common sense of humanity. This NCCIH R34 (PI Lang) involves iterative refinement of the meditation protocol based on quantitative and qualitative data followed by a small randomized controlled trial comparing CM to a relaxation-based control. Pooled data from the nonrandomized refinement phase, which enrolled 36 participants in 4 groups, shows meaningful change in PTSD (partial eta squared = 0.27) and depression (partial eta squared = 0.19). The subsequent randomized pilot study enrolled 38 participants in CM or a relaxation condition; results are not yet available. Dr. Lang was also a co-investigator on Dr. Jill Bormann's mantram repetition trials. The first enrolled 66 Veterans with PTSD in a group format (Bormann, Liu, Thorp & Lang, 2012), and the second enrolled 118 Veterans in a randomized trial that delivered care one-on-one (manuscript submitted for publication). Finally, Dr. Tom Rutledge recently randomized 203 Veterans with PTSD to Transcendental Meditation, Prolonged Exposure or health education (personal communication).

Thus, the successful track record of implementing clinical and research programs using complementary approaches at the VASDHS, is strong evidence for the acceptability of this type of study at this facility.

Feasibility

Although we initially projected being able to enroll approximately 6 Veterans per month in the trial for a sample of 144 completers, this has not proven to be realistic. In 38 months of active recruitment, we have screened 326 individuals (~9/month) of whom 51% consented to participation and 26% were randomized (~2.5/month). We believe that these lower-than expected rates of participation and randomization are partly related to competition with many other opportunities to engage in recorded or live-streamed yoga/exercise classes. As a result, we plan to enroll approximately 96 Veterans in the trial (48/group).

Pilot Effect Sizes

Effect sizes in studies of yoga for PTSD vary widely (0.08 to 1.65; Wells, Lang, Schmalzl, Groessl, & Strauss, 2016), perhaps because of variability in practice types and the populations studied. The largest randomized controlled trial of yoga for PTSD to date compared a "trauma sensitive" version of Kundalini yoga to a wait list control in an 80-person civilian sample (Jindani et al., 2015). Greater decreases in PTSD symptoms (Cohen's *d* = 1.65), insomnia, stress and anxiety were observed in the yoga group. In addition, yoga was associated with increased in positive affect and resilience. No significant changes in depression or negative affect were observed. This trial is limited, however, by the lack of an active control and a high rate of

attrition. It's generalizability to Veterans is also unknown. The other relatively large randomized evaluation of yoga included 64 women with chronic, treatment-resistant PTSD (van der Kolk et al., 2014). As compared to a health-education class, yoga was associated with greater change in PTSD symptoms (Cohen's d = 1.07). It is unknown, however, how these findings generalize to men. One uncontrolled trial involved Kripalu yoga, a form of hatha yoga, for active duty and Veteran participants. They observed large effect size pre-post change in symptoms (Cohen's d = .77), although this change was less than a benchmark that the authors calculated based on meta-analysis of published studies of active PTSD treatments (Johnston et al., 2015). In contrast, smaller studies have found no difference between yoga and a control condition (Mitchell et al., 2014; Thordardottir et al., 2014) or negligible effect on PTSD symptoms in Veterans (n = 12; Staples et al., 2013). Weighting the larger studies more heavily, we have powered the study to detect a medium to large effect size.

Ongoing Research

The proposed study differs in important ways from ongoing studies in Veterans. Dr. Bayley's (VAMC Palo Alto) VA-funded study of Sudarshan Kriya Yoga (SKY; a breathing-based meditation technique) does not include physical asanas, so likely differs in terms of the way in which it impacts PTSD and may hold different appeal. SKY also requires specific certification, which may limit dissemination. The comparison condition in the Bayley study, Cognitive Processing Therapy, allows the investigators to address the efficacy of yoga as compared to gold standard PTSD treatment. This project examines a different question, namely whether yoga performs differently than physical activity, allowing us to determine whether the meditative (as opposed to physical) component of yoga is an active change agent. Dr. Davis's (VAMC Indianapolis) study of a Holistic Yoga Program is much broader than the proposed protocol, including not only yogic postures and breathing but also deep muscle contraction and relaxation. The broader nature of the holistic program is appropriate to their aim of comparing the interventions' impact on PTSD symptoms, but is less well suited to the type of mechanistic questions that will be addressed herein. Dr. Kelly's (VAMC Atlanta) comparison of yoga to Cognitive Processing Therapy is limited to women, whereas this study will represent the VA population more broadly. None of these projects includes this type of mechanistic analysis to lay a groundwork for identifying commonalities among approaches, thus enhancing the disseminability and ultimately clinical utility of yoga for PTSD.

Innovation. The present study extends and compliments previous yoga research. Much of the current yoga literature is limited by small sample sizes and poor methodological rigor. In response to this need, the proposed study includes a randomized controlled design, with an active control condition that is matched for time/attention, social group interactions, attention, and expectancy. It features standardized and psychometrically sound assessment instruments, including blinded evaluation, and addresses the limited generalizability of previous samples by including both men and women with broad inclusion/exclusion criteria. Finally, it is set in a Veteran population, which is an understudied group in the published literature and may differ in important ways from non-military populations. Furthermore, the yoga intervention is a manualized Hatha yoga, which has been implemented in prior studies at this facility, and is reviewed for fidelity. Thus, the proposed project addresses an important need for high quality studies of yoga for PTSD. *The greatest innovation, however, lies in the evaluation and comparison of the Attention and Coping Models. Examination of these mechansim will advance our understanding of the way in which a guided asana practice may impact PTSD, but will also inform yoga-based mental health treatment more broadly as these transdiagnostic processes are applicable to other mental health concerns.*

Research Design and Methods

The proposed study is a randomized controlled trial of Hatha yoga as compared to supportive physical activity in Veterans with PTSD. A sample of approximately 96 recruited (refer to Sample Size). Longitudinal outcome assessment will take place over approximately a 6 month period; refer to Table 1 for an overview of measures at each time point. A 3-month follow-up is planned because information about maintenance of change following the completion of a yoga intervention is important given the long-term follow-up data from the van der Kolk trial, which suggest that ongoing practice is critical continued clinical effects (Rhodes, Spinazzola, & van der Kolk, 2016).

Procedures

Potential participants will be recruited from VA clinics (including primary care and mental health) and the community, following procedures that have been proven successful in our previous meditation and yoga trials. The initial contact for potential participants will be with a study recruiter/assessor, who will complete informed consent and conduct the evaluation for eligibility (see *Assessment*). After eligibility and consent are confirmed, the participant will complete the baseline assessment and then will have brief safety assessments every class ; they will be asked to complete a total of 12 classes within 14 weeks. A follow-up will occur 12 weeks after the completion of the final class. No shows will receive a telephone follow-up. Participants will receive a payment for each assessment session ($50 baseline part 1, $50 baseline part 2, $50 post-treatment part 1, $50 post-treatment part 2, $50 follow-up part 1, $50 follow-up part 2 for a total of $300; refer to Table 1).

Randomization will be done by the study statistician. In the initial phase of the trial, this was a 2:1 allocation to yoga and physical activity and took place at the individual level. Uneven allocation was planned to allow for sufficient power to accomplish the modeling proposed in Aim 2 (refer to *Sample Size*); given pandemic-related difficulties with accrual, however, the allocation will be reversed to 1:3 for the final months of the study to accomplish a minimum of 48/cell. The randomization table will be prepared prior to start of the study and revised for the new allocation strategy. Using an individual randomization strategy and continual group enrollment allows patients to begin treatment more quickly (i.e., as soon as the baseline evaluation is complete), which reduces attrition. This continual enrollment strategy is possible because the yoga and physical activity classes do not build from week to week; rather, every class provides multiple options for each pose/exercise to allow for individual differences, as is consistent with typical practice in the community. Further, sharing of personal information is minimized in this type of class, so newcomers are unlikely to cause discomfort among group members. Further, this strategy may support better retention. By allowing participants 14 weeks in which to complete 12 classes, participants will be able to make up missed classes to receive the full "dose."

Participants. Participants will be Veterans with a diagnosis of PTSD, aged 18 or older, who are able to consent and willing to participate. Co-occurring disorders such as depression, anxiety, or treated substance abuse or dependence problems are permitted provided that PTSD is the primary presenting complaint. Heterogeneity within the group of Veterans (e.g., gender, era of service, type of trauma) is allowed for greater generalizability of the results from this sample as well as to facilitate recruitment. Trauma sensitive principles (Emerson et al., 2009) will be employed to maximize participants' comfort, particularly for individuals with concerns about personal safety/bodily integrity. The following are criteria for **exclusion**: (1) serious suicidality or homicidality that has required urgent or emergent evaluation or treatment within the past three months, (2) a known, untreated substance abuse or dependence problem (inclusion is possible if there is evidence that the individual has been afforded and is complying with treatment for the substance problem), (3) serious mental disorders, such as psychotic disorders or bipolar type I, or serious dissociative symptoms (4) cognitive impairment that would interfere with treatment, (5) circumstances that lead to recurrent traumatization (e.g., engaged in a violent relationship), (6) any medical condition for which yoga is contraindicated, including pregnancy, (7) concurrent enrollment in any other treatment specifically targeting PTSD symptoms or social functioning (e.g., couples therapy) or in any meditative or mind-body intervention (including yoga practice >1 class/month in the preceding 6 months). Participants can continue current pharmacological treatment (provided they have stabilized on medication, i.e., no additional treatment response is expected, and no changes are anticipated during the study period) or any supportive or nonspecific therapy. These selection criteria are intentionally broad so as to represent as fully as possible Veterans who may seek alternative interventions for their PTSD. The sample may have limited generalizability to non-military populations.

Assessment

Instrument selection for this trial is based on psychometric properties, past use with mental health populations and/or yoga, conceptual fit with our model and minimizing participant burden.The sample will be characterized at baseline in terms of relevant **demographic characteristics** (age, gender, race/ethnicity, relationship status, years of education, SES/income/living situation, occupation/work status, branch of service/highest rank, service connection/disability status), clinical characteristics that could affect treatment response (e.g., depression, alcohol use), and exercise tolerance (**Veterans Specific Activity Questionnaire**; Myers, Bader, Madhavan & Froelicher, 2001). The **Alcohol Use Disorders Identification Test (AUDIT**;

Babor, Biddle-Higgins, Saunders, & Monteiro, 2001) will be used to track problematic alcohol use for eligibility and clinical monitoring purposes. A score of 4 or above has excellent sensitivity for detecting current alcohol abuse or dependence (.90 and 1.0 respectively) but lower specificity (.60). At a score of 8, the specificity rises to .94 (Rumpf, Hapke, Meyer, & John, 2002). The **Life Events Checklist** portion of the PCL-5/CAPS-5 (see below) will describe the type and number of traumas to which an individual has been exposed, including identifying current circumstances that may preclude study involvement. To the extent there is heterogeneity in the sample, these data additionally may be used to explore differences in treatment response based on the nature of trauma exposure.

Eligibility. The **Montreal Cognitive Assessment (MoCA**; Nasreddine et al., 2005) is a brief (~10 minutes) clinician-administered cognitive screening test, which will be used to screen for cognitive impairment. If the score is < 22, which has been identified an as appropriate cutoff for psychiatric patients (Gierus et al., 2015), patients will be referred for additional evaluation and excluded, unless a qualified clinician provides clearance to participate. The **PTSD Checklist – 5 (PCL-5**; Weathers, Litz, et al., 2013) will be used to quantify PTSD symptoms; individuals with a score of 33 or greater, the currently recommended cutoff for the instrument (National Center for PTSD, 2016), will be eligible for enrollment. Individuals with lower initial PCL-5 scores will be additionally evaluated using the CAPS if they carry a clinical diagnosis of PTSD. This self-report measure of PTSD is well-established for monitoring treatment-related change and has well-documented strong psychometric properties. The PCL-5 will be repeated at each assessment point for ongoing participant safety evaluation. Given that the TBN instructors will not be mental health professionals, Dr. Lang, who is a privileged and licensed clinical psychologist with specialized training and 18 years of experience in treating Veterans with PTSD, will review these data (blinded to condition) on an ongoing basis to monitor adverse reactions. Absence of serious mental illness, untreated substance dependence, serious suicidality will be evaluated using the **Mini International Neuropsychiatric Interview (MINI 7.0**; Sheehan et al 1998), which has been validated against the SCID and CIDI. The interview takes 15-30 minutes to complete and will be supplemented with questions to assess homicidality. Finally, the participant will be queried about use of mental health services, including pharmacotherapy, psychotherapy (type, modality, frequency and duration), complementary and alternative approaches and hospitalization using the **Emory Treatment Resistance Interview for PTSD (ETRIP**; Dunlop, Kaye, Youngner, & Rothbaum, 2014). Psychotropic medication information will be collected and cross-checked against the electronic medical record. Mental health utilization will be used to characterize the sample and also to characterize behavioral changes associated with study participation at follow-up (e.g., continued yoga or exercise).

Clinical outcomes. The **Clinician Administered PTSD Scale (CAPS-5**; Weathers, Blake, et al., 2013) will be used to establish the PTSD diagnosis and quantify severity. This clinician-rated measure of PTSD is the "gold standard" for assessing PTSD and takes 45-60 minutes to complete. The CAPS has high internal consistency (for the DSM-IV version, alphas of 0.87 and 0.88 for the three PTSD symptom clusters and 0.95 for PTSD symptoms overall) and validity (sensitivity, specificity, efficiency, and agreement). The CAPS total score will be used as the primary measure of clinical outcome. Given our interest in exploring the effect of these interventions on symptoms that commonly co-occur with PTSD, we will also assess depression severity as measured by the 20-item **Center for Epidemiologic Studies Depression Scale Revised (CESD-R**; Eaton, Muntaner, Smith, Tien, & Ybarra, 2004), general anxiety as measured by the 40-item **State-Trait Anxiety Inventory (STAI**; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), anger as measured by the 35-item **State-Trait Anger Expression Inventory – II (STAXI-II**; Spielberger, 1991) and sleep problems as measured by the 7-item **Insomnia Severity Index (ISI**; Bastien, Vallieres, & Morin, 2001), a 7-item instrument that assesses the consequences of and distress related to insomnia, will be included as well. Finally, the **Sheehan Disability Scale (SDS**; Sheehan, Harnett-Sheehan, & Raj, 1996), a 3-item measure of impairment in work, social and family settings, will be included. This widely-used but low-burden measure of disability has been shown to change with treatment in similar population samples (e.g., Lang, Schnurr, et al., 2016).

Clinical utility. Clinical utility can be defined as the usefulness of an intervention in clinical practice and is considered to have four major dimensions (Smart, 2006). The **appropriateness** of yoga for PTSD depends on its efficacy (addressed in Aim 1) but also on the successful integration of the intervention into current care practices. **Accessibility** involves the factors involved in making yoga available to Veterans. Issues such as the usability of the manual and the way in which training can be conducted speak to **practicality**. Finally, the **acceptability** of yoga depends on its reception by key stakeholders, including Veterans and clinicians. Aspects

of clinical utility will be assessed by examining recruitment/retention data and feedback from referring clinicians and Veterans in preparation for future implementation of practice guidelines.

Mechanisms of change: Attention model. The **Philadelphia Mindfulness Scale (PMS**; Cardaciotto, Herbert, Forman, Moitra, & Farrow, 2008) is a 21-item measure that assesses present-moment awareness and acceptance and has good internal consistency (Cronbach's α .75) and validity (e.g., corresponds highly with other measures of mindfulness but not with measures of psychopathology or social desirability) in psychiatric samples.

To fully characterize the nature of yoga's impact on attention, we will utilize multi-modal assessment including two tasks with an affectively neutral context, as well as two tasks that include affective stimuli to allow for an assessment of the ability to deploy attentional resources in emotional contexts. The **Digit Span** test from the Wechsler Adult Intelligence Scale 4th edition (WAIS-IV) will be used as a standardized neuropsychological measure of attention and working memory (Wechsler, Coalson, & Raiford, 2008). This test includes Digit Span Forward, wherein the participant is read a sequence of numbers and recites the numbers back in the same order; Digit Span Backwards, wherein the participant is read a sequence of numbers and must recite them back in reverse order; and Digit Span Sequencing, wherein the participant is read a sequence of numbers and must recite them back in numerically ascending order. Digit Span is a well validated assessment with established norms, and has been shown to be sensitive to change in a study using a yoga intervention (Brunner et al., 2017). Each subtest is scored based on the number of items correctly recited on each trial.

Mechanisms of change: Coping model. Again, we hope to identify a latent variable indicating maladaptive coping strategies that are associated with PTSD through use of a set of indicators. The **Ruminative Thought Style Questionnaire (RTSQ)** is a 20-item, Likert-based (1-7) scale with good psychometric properties (Cronbach's α .92, strong correlations with measures of depression, anxiety and repetitive thought) and demonstrated separability from mood (Brinker & Dozois, 2009). The **Emotion Regulation Questionnaire (ERQ**; Gross & John, 2003) is a 10-item measure of reappraisal and expressive suppression, which are thought to be effective and ineffective emotion regulation strategies respectively. The ERQ expressive suppression subscale has previously been shown to be impacted by yoga in PTSD patients (Dick et al., 2014) and has good convergent and discriminant validity and internal consistency (Gross & John, 2003). Experiential avoidance will be quantified using the **Brief Experiential Avoidance Questionnaire (BEAQ**; Gamez et al., 2014). This 15-item Likert-based (1-6) measure was developed to improve on the Acceptance and Action Questionnaire – II (AAQ-II), which has been shown to be highly reflective of general distress (Wolgast, 2014). The BEAQ has good internal consistency (Cronbach's α .86) and is more strongly related to measures of avoidance than negative affect.

To assess the construct of tolerance of discomfort, we will use the **Distress Tolerance Scale (DTS)**, a 15-item, Likert-based (1-5) scale with good internal consistency (Cronbach's α .75) and test-retest reliability (*r* = .61). The DTS has been shown to be associated with PTSD (Vujanovic et al., 2013), prospectively predict problematic alcohol use (Simons & Gaher, 2005) and be modified by hatha yoga (Medina et al., 2015).

Assessment schedule. The assessment schedule presented in Table 1 is designed to balance depth of understanding with participant burden. Constructs with a greater degree of fluctuation (e.g., mental health symptoms) are administered more frequently, whereas those that change more slowly are assessed less frequently (e.g., functioning).

Table 1: Summary of Assessments

	Instrument	Aim	Baseline	Weekly	Mid-treatment	Post-treatment	Follow-up	Assessment session
Descriptives, Eligibility, Covariates	Demographics		X					1
	Veterans Specific Activity Questionnnaire		X					1
	Alcohol Use Disorders Identification Test		X	X	X	X	X	1
	Life Events Checklist		X					1
	HRV		X			X	X	2
	Montreal Cognitive Assessment		X					1
	PTSD Checklist-5		X	X	X	X	X	1
	Mini International Neuropsychiatric Interview		X					1
	Emory Treatment Resistance Interview for PTSD		X			X	X	1
Clinical Outcomes	Clinician Administered PTSD Scale 5	1a	X			X	X	1
	Center for Epidemiologic Studies Depression Scale	1b	X	X	X	X	X	1
	State-Trait Anxiety Inventory	1b	X		X State only	X	X	1
	State-Trait Anger Expression Inventory	1b	X		X	X	X	1
	Insomnia Severity Index	1b	X		X	X	X	1
	Sheehan Disability Scale	1b	X		X	X	X	1
Mechanisms of Change	Attention Model							
	Philadelphia Mindfulness Scale	2a	X			X	X	1
	Digit Span	2a	X			X	X	2
	Coping Model							
	Ruminative Thought Style Questionnaire	2b	X			X	X	1
	Emotion Regulation Questionnaire	2b	X			X	X	1
	Brief Experiential Avoidance Questinnaire	2b	X			X	X	1
	Distress Tolerance Scale	2b	X			X	X	1

Intervention

Yoga. The proposed yoga program is a classical Hatha practice, which is currently used at the VA San Diego. Hatha yoga refers to practice of physical asanas, or poses, as opposed to practices that are limited to breath-work or are primarily meditative. The program is designed to minimize the risk of injury and make the poses accessible to a wide range of people (Iyengar, 1979). The manualized program (see the manual and

home practice guide presented in the *Appendix*) includes 23 asanas (32 total variations), which are conducted at a slow-moderate pace in the context of a positive intention. Asanas are aligned with the breath, and the instructor describes/demonstrates optimal alignment. In addition, participants are encouraged to focus on an intention (a goal or positive direction for their yoga practice). Sessions are structured as follows: breath-based meditation (5 minutes), basic postures to warm-up the body (Poses 1-8; 10 minutes), standing poses (Poses 9-14; 15 minutes), floor poses (Poses 15-22; 15 minutes), "savasana" (i.e., complete relaxation; 10 minutes). The manual contains pictures and a description of how to perform each pose with typical instructor dialogue to maximize consistency across instructors. Participants are cautioned to stop if any pose becomes painful (as opposed to uncomfortable) and to consult with the instructor individually about any problems that arise. Although this program has not been specifically applied to PTSD, we selected it because it employs commonly used asanas, has been successfully applied at this facility, is known to be safe, and impacts mental health. In addition, it requires no specialized training beyond basic yoga certification so would be easily disseminable. *There is no current empirical basis for the selection of any particular practice type or asanas for the treatment of PTSD; this project would provide such guidance.*

The 12-class program will be delivered in one 60-minute yoga class/week for 12-14 consecutive weeks with at home practice of 15-20 minutes/day. This frequency/length of intervention was chosen because it is similar to other PTSD interventions (e.g., CPT; Voelkel, Pukay-Martin, Walter, & Chard, 2015) and similar to the "dose" in successful yoga clinical trials, e.g., 8 90-minute sessions Jindani et al., 2015) or 10 60-minute sessions (van der Kolk et al., 2014). The importance of attending all sessions and practicing between sessions is stressed throughout. Text reminders will be sent before all classes, a strategy which has had a positive effect on attendance in our current compassion meditation trial. Participants who miss a session without notifying the instructor will be contacted to check on the reason for non-attendance and to encourage them to resume participation as soon as possible. Fidelity to the manual will be assessed using video recordings of sessions. All yoga sessions will be video-recorded with instructor/participant consent. Ten percent of the sessions will be randomly selected for review by an independent certified yoga instructor. Sessions will be rated using an adherence checklist for each procedure or instruction.

The instructor will be certified (minimum of RYT-200; Yoga Alliance, 2016) and trained in trauma-sensitive yoga principles, which is a set of adaptations to enhance the comfort of trauma survivors. Trauma-sensitive practice involves using invitatory (as opposed to commanding) language, providing a space where clients feel less vulnerable (e.g., lighting should not be too dark), allowing patients to opt out of postures, minimizing physical assists until trust is established, and creating an overall welcoming and approachable environment (Emerson et al., 2009).

Yoga is fundamentally an experiential intervention, but it may be useful to tailor the practice to increase the likelihood of certain types of experiences or to provide guidance to Veterans as to how to apply what is learned through yoga practice to the management of PTSD. Such tailoring will depend on the mechanisms that are identified as important for symptom change. For example, if we find that affective reactivity and emotion regulation are mediators of the relationship between yoga and PTSD, it may be worthwile to increase the focus on mindfulness (i.e., nonjudgmental awareness) during the yoga practice. Mindfulness alone has been shown to impact emotion regulation strategies such as rumination and distraction (Jain et al., 2007) and may also contribute to distress tolerance (Feldman, Dunn, Stemke, Bell, & Greeson, 2014). Thus, these processes may be further targeted by increasing the amount of teaching and practice of mindfulness within the class and homework. In addition, it has been suggested that guiding attention to one's internal experience during yoga and differentiating pain from other senstations may increase the capacity to tolerate discomfort (Schmalzl et al., 2015). Similarly, if cognitive processes, such as attentional control, appear to have an important clinical effect, both the breath and the drishti (gaze) can be used to train attention during yoga practice (Schmalzl et al., 2015). Increasing explicit instruction about attention or using poses that require heightened attention (e.g., balancing) may augment change in this area. Finally, practice characteristics could be modified to enhance physiological changes. Higher intensity movement and slow, rhythmic breathing may increase parasympathetic activity (Schmalzl et al., 2015) and specific poses (e.g., inversions; Papp et al., 2013) may foster these changes as well.

Physical activity. The physical activity control condition was designed to meet Centers for Disease Control (CDC) anaerobic exercise recommendations. The manualized stretching-strengthening class will be held in 60-minute sessions weekly for 12-14 weeks with home conditioning for 15-20 minutes per day, matching the time spent in yoga practice. Each class will consist of a warm-up, exercises and cool-down periods. Participants will generally complete 10-12 repetitions of 8-10 different exercises targeting whole-body

conditioning. Each exercise can be modified to meet the needs of individual participants. The classes will be conducted by certified personal trainers. This control group was selected because of its past use as a control condition for Hatha yoga. This type of exercise program was comparable to Hatha yoga in terms of gains in functional fitness (Gothe & McAuley, 2016) but less effective at improving cognition (Gothe, Kramer, & McAuley, 2014) in community-dwelling samples of older adults.

Analytic Plan

Descriptive statistics will be obtained for all variables, including distributions, means, medians, variances, standard deviations, skewness, kurtosis, ranges, and quartiles. Tests of normality of continuous measures will be made using the Shapiro-Wilk W and the Kolomogorov D statistics in conjunction with plots of the distribution of data and descriptive measurements. The data will also be examined for homogeneity of variance. An appropriate statistical method will be employed to correct for any abnormalities. Missing data values will be minimized by intensive training of the assessors in techniques of clarifying answers and checking questionnaires while participants are on-site. When missing values are identified, we will employ several approaches to reduce their influences. If at all possible, participants will be rescheduled or a telephone call will be made within 24 hours of completion of tests or interviews. The pattern of missing data will be examined according to the procedure recommended by Little and Rubin (1987), which includes comparing group differences in the primary outcomes of subjects with versus without missing data. We will also test whether the drop-outs are random or systematic by comparing the drop-outs with the study completers on the baseline data. An absence of significant differences would support the random nature of drop-outs. Effect of drop-outs will be minimized by including all subjects in the analyses and by including any effect of systematic differences between the drop-outs and completers in the model as a covariate when applicable.

Each outcome variable will be graphed versus time for each subject for all available time points (baseline, mid-treatment, post-treatment, follow-up) to evaluate what function of time best describes the data. Hypotheses 1a and 1b will be tested using the Mixed Effect Model (Hedeker, Gibbons, & Waternaux, 1999). This method is robust with respect to drop-out and missing data. These mixed models allow us to assess whether important estimates are dependent on missing data patterns, and provide overall estimates of effects by averaging over the various missing-data patterns (Hedeker et al., 1999). In addition, we will use the extension of the Pattern-Mixture Models (Guo, Ratcliffe and Ten Have, 2004), which allows subject-to-subject heterogeneity and assess if there is bias due to drop out or missing data. The Mixed Effect method has several advantages over more traditional analytic approaches such as a change score, end-point or repeated measures analysis of variance. It allows the inclusion of subjects with missing data or those who were terminated early in the study, without relying on data imputation procedures. This method provides an estimate of the individual variability around the population trend, the variability of the individual intercepts (baseline values) and slopes (changes across time), and the correlation between them. We will include a random intercept, a random effect for assessment time, and fixed effects for comparison groups and group-by-time interaction in the model. A fully saturated treatment by time model will be utilized for inference. Co-variance structure will be chosen based on Akaikes Information Criterion (AIC). Random group level treatment effects will also be evaluated for importance based on the model AIC. This allows for any group level effects to be incorporated into the model. Denominator degrees of freedom will be calculated using the Kenward-Roger small sample correction. Statistical significance will be determined by $p < .05$ for hypothesis 1a and $p < .01$ (.05/5 to correct for multiple comparisons) for hypothesis 1b.

Hypotheses 2a.1, 2a.2, 2b.1 and 2b.2 initially will be tested using the same mixed model procedure identified in Hypothesis 1a and 1b. To test for mediation effect, we will utilize the analytic strategy described by Krull and MacKinnon (1999, 2001). In this approach, four conditions must be met: a) a significant relationship between the independent variable (treatment) and the dependent variable (PTSD symptoms as measured by CAPS), b) a significant relationship between the independent variable and the proposed mediator (Attention Model: mindfulness and attentional control; Coping Model: tolerance of discomfort and coping), c) a significant relationship between the mediators and the outcome, and d) the relationship between the independent variable and outcome must be significantly lower after controlling for the proposed mediator. The multiple-mediation model includes a multiple-path mediating effect through both mediators (i.e. mindfulness and attentional control or tolerance of discomfort and maladaptive coping), which allows one mediator (e.g., mindfulness) to causally affect the other mediator (e.g., attentional control). Multimodal assessment is used for Attentional Control, Tolerance of Discomfort and Coping based on the theoretical models discussed previously. The relation among these variables and their individual contribution to the construct of interest will be examined in order to

remove variables or create composites. Correlation coefficients among the outcomes for each mediator will be examined. Furthermore, the main effect of each outcome will be examined in the mixed effect model. Low correlated outcomes or outcomes that are highly (greater than .8) correlated with each other and/or low contribution in the model will be consider to be dropped from the model. The effect of mediators in the model can be calculated based on either the difference between two regression parameters ($\tau - \tau^2$) or the multiplication of two regression parameters ($\alpha\beta$) (MacKinnon, Warsi, & Dwyer, 1995). The variance estimates produced by the various methods are quite similar to each other and to the true value of the variance in situations involving continuous multivariate normal data and a continuous independent variable (MacKinnon et al., 1995). Although there is some evidence that the least model in the case-control study design setting this approach could provide biased estimations for the indirect effects (Wang et al., 2012), we believe the Sobel (1982) procedure to test for significant mediation is most appropriate approach for this study. Next we will use the formula provided by MacKinnon and Dwyer (1993) to determine the percentage of the intervention condition to primary outcome path that was accounted for by change in our mediator. We acknowledge that this method may not be supportable given the need to reduce sample size. If the study biostatistician determines that this is the case, she will utilize other strategies to analyze available data and generate testable hypotheses for future studies. The exploratory aim will be analyzed using similar approach. Data will be analyzed from all randomized subjects on whom we have a baseline assessment and at least one post-baseline evaluation. All statistical tests will be two-tailed. We will adjust p-values for multiple testing as appropriate.

Sample size. We used the method provided by Hedeker, Gibbons, & Waternaux (1999) for the Random Regression Model and the RMASS program provided by Hedeker (2016) to estimate needed sample size for Aim 1. Medium effect size was selected based on finding from previous yoga trials (Wells et al., 2016) and was defined as a between-group difference increasing linearly from 0 at baseline to .5 SD units at the last time point. The minimum power estimation is based on sample size calculation for 10% and 20% attrition, correlations of 0.2, 0.5, and 0.8 between the repeated measures, and for medium and large effect sizes. We are confident that with the proposed total sample size of at least 48/arm would be sufficient to achieve a minimum 80% power for the primary aim.

Management

Management of this single-site study will be Dr. Lang's responsibility. She has considerable experience in research management from small developmental grants (e.g., NCCIH R34) to a large multi-site consortium (INTRuST PTSD/TBI Clinical Consortium Deputy Director) and center of excellence (VASDHS CESAMH Associate Director). Administrative aspects of the project will be supported by Ms. Robinson, who has been Dr. Lang's lead coordinator for more than a decade. Dr. Lang will coordinate scientific aspects of the project, holding regular meetings with the investigative team. Dr. Golshan, the study biostatistician, will work closely with Dr. Lang around data management and analysis. Dr. Groessl will draw on his experience with yoga research to help with issues of recruitment, enrollment and retention. Drs. Bomyea (attention) and Herbert (pain) will provide guidance in their relative areas of expertise. Dr. Lang, who is a licensed clinical psychologist, also will be responsible for clinical oversight. The timeline of major study activities is presented in Table 2.

Table 2. Study Timeline

Year 1 (2018-2019)	Year 2 (2019-2020)	Year 3 (2020-2021)	Year 4 (2021-2022)	Year 5 (2022-2023)
Original Timeline				

Set-up Regulatory Hiring Training Recruitment	Recruitment (approx. 6/month x 30 mos) Assessment Intervention delivery, fidelity (12 groups) Data management DSMB reporting	Follow-up, data lock	Dissemination	Analyses	■■■
Revised Timeline					
✓ Set-up ✓ Regulatory Hiring Training	Recruitment (approx. 6/month x 30 mos) Assessment Intervention delivery, fidelity (12 groups) Data management DSMB reporting	Follow-up, data lock	Dissemination	Analyses	
Revised Timeline 2022					
✓ Set-up ✓ Regulatory Hiring Training	In person recruitment → Transition → Remote recruitment Assessment Intervention delivery, fidelity Data management, including QA/QC and data lock DMC reporting			Analyses, Dissemination	

Data Management

Data management and statistical analysis will be supervised by Dr. Liu. Dr. Liu is a biostatistician at the VASDHS and an Assistant Adjunct Professor in the UCSD Department of Family Medicine and Public Health. She has prior experience in VA clinical trials, including studies of yoga and PTSD, and has previously collaborated with Dr. Lang. Dr. Golshan will oversee the development of the study database, which allows for automated data validation and auditing. Data will be maintained on the secure VA research server. Participant names will be held separate from data. Subjects will be assigned a unique ID number, and the single name-to-ID relational file will be kept in an encrypted form electronically and in a locked filing cabinet physically. Statistical analysis will be conducted using SPSS, R and SAS software packages. All statistical transfer routines are inherently secure via their operating platform and they contain no patient names or personal data.