Protocol:
Outcomes of a Holistic Yoga Program Designed to Relieve PTSD (RELIEVE trial)

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1.0 **Background**

Overview of the Problem: PTSD affects 7-12% of the general population[15] or approximately 21 million Americans[16] who will use health care services frequently for many years. The annual cost of anxiety disorders such as PTSD is substantial, estimated at about $42.3 billion in the United States.[14] Furthermore, individuals with PTSD are among the most frequent users of healthcare services, with nonpsychiatric direct medical costs (e.g., doctor and hospital visits) estimated at approximately $23 billion a year.[14] Societal costs include both psychiatric and nonpsychiatric medical treatment, indirect workplace costs, and mortality costs. More than half of these costs are attributed to repeat use of healthcare services to relieve anxiety-related symptoms that mimic those of other physical conditions. Therefore, PTSD is a source of chronic disability for veterans and civilians and costly for the US government in terms of treatment as well as disability payments. Despite some success with currently used medications, many PTSD patients report little meaningful improvement in their symptoms. Furthermore, veterans whose PTSD symptoms have been present for many years pose the particularly complex challenge of being more resistant to the beneficial effects of medications for PTSD symptoms.[28] Medications currently used to treat PTSD are of limited effectiveness as they were not designed to target the unique pathophysiology of PTSD, and remain one of many challenges in PTSD treatment.[33] Although there are effective, available PTSD-specific treatments such as Cognitive Processing Therapy and Prolonged Exposure, many PTSD sufferers delay seeking professional help for years to decades.[4] Such factors as avoidance (one of the three PTSD symptom clusters), fears that directly addressing the trauma will only make matters worse, and the stigma related to PTSD and mental health treatment, are thought to contribute to this reluctance to engage in treatment.[5] In addition, dropout rates are high for current PTSD treatments and they may not be effective for all evidenced by the significant number who remain symptomatic despite pharmacotherapy and psychotherapy.[6] Although there are now psychological treatments that can effectively treat individuals with PTSD, the majority of individuals with PTSD, including active duty military personnel, veterans, and civilians, receive treatments of unknown efficacy.[34] Unresolved or untreated trauma has been associated with the development of multiple, severe, and persistent physical and mental health problems, substance abuse, future criminal behavior, and social problems.[35] Thus there is a need for more effective PTSD treatments options, particularly which do not require direct verbal processing of the trauma but can calm the hyperactive threat system typical of PTSD.

Other treatments are needed when PTSD symptoms are not relieved: The lack of relief from existing treatments can be extremely frustrating to patients who may feel that they have exhausted all options for PTSD treatment. This is also frustrating for VA and other mental health providers concerned about the limited efficacy of medications and lack of additional treatment options. Therefore, novel treatment approaches are needed that have potential for application across multiple VA clinical settings and in the community, to supplement existing services for PTSD care. Increasingly, patients are interested in complementary and alternative medicine (CAM) treatment options.[36] This growing interest in CAM is likely multifactorial, involving concerns about limited efficacy of conventional medicine, adverse effects of medications, and avoidance-beliefs related to medications or mental health treatments. CAM treatment options typically have minimal physical and emotional risks, and may allow patients to take a more active role in managing their illness.

Yoga holds promise for PTSD as it combines physical and mental techniques: Yoga therapy is defined by the International Association of Yoga Therapists as “the process of empowering individuals to progress toward improved health and well-being through the application of the philosophy and practice of yoga”.[38] Although there are many types of yoga, all involve a combination of stretching exercises and postures with breathing and meditative practices aimed at: (1) lengthening and toning muscles; (2) maintaining flexibility in the joints and spine; (3) increasing oxygenation of the brain; and, (4) training attention and concentration.[39] Accumulating research evidence supports yoga as an acceptable and efficacious intervention for those who have experienced trauma, reducing clinician rated[9] and self-reported PTSD symptoms symptoms,[10-12] depression[12], anxiety.[12] Research evidence also supports the benefits of yoga in those with other physical and mental health conditions for challenges typical of those with PTSD including increased resiliency to chronic and acute stress[43,44], anger-hostility,[13,45] disturbed sleep.[46,47] Studies of Mindfulness-Based Stress Reduction (MBSR), an intervention that combines mindfulness meditation with gentle hatha yoga, also provide evidence to support the use of yoga for treatment of trauma.

A trial evaluating holistic yoga for PTSD is timely and needed: Although there has been increased military and VA interest in CAM approaches, such as yoga and meditation, which do not require trauma

processing, research has been limited although promising in terms of acceptability and efficacy.[7] Our recent search of the ClinicalTrials.com website revealed a total of 10 studies of yoga as an intervention for PTSD (5 completed and 5 current), with such limitations as small samples, uncontrolled or waitlist/usual care controls, and much variation in the style of yoga and components of yoga studied. Thus, randomized controlled trials with large samples to evaluate a standardized traditional holistic yoga intervention are urgently needed to inform VA policy makers and clinicians of what outcomes to expect from a yoga intervention for PTSD. We believe that the proposed trial, "Outcomes of a Holistic Yoga Program Designed to Relieve PTSD" (RELIEVE trial), designed as a large randomized controlled efficacy study of a standardized, traditional holistic yoga intervention (postures, breathing practices, deep muscle contraction practices, relaxation practices), is a significant step beyond previous studies that have evaluated a variety of yoga approaches and/or one yoga component such as relaxation, or yoga as only a part of a mind-body intervention such as Mindfulness-Based Stress Reduction. The Holistic Yoga Program will be documented in a treatment manual and will be taught by teachers registered at least at the 200 hour level with the Yoga Alliance. Additional standardized training and supervision will be provided by an experienced yoga therapist. Thus, if found to be effective, the Holistic Yoga Program and teacher training will have been documented and tested, allowing for swift dissemination and implementation within the VA system.

Significance: PTSD poses enormous public health challenges due to its effects on mental and physical health, and functioning, including interpersonal, social and occupational.[34] PTSD is also a critical mental health problem among veterans and constitutes a substantial proportion of the burden of illness among veterans affecting as many as 14 to 16%.[17] Apart from the significant psychological cost to individuals with PTSD and their families, there is a steep financial cost to society, in terms of entitlements and lost productivity. PTSD is the most common psychiatric disorder for which veterans seek and receive compensation and most common cause of disability within the VA system and the U.S.[2] Although individuals suffering from PTSD desire relief, it is difficult for them to present for treatment due to the avoidance, a hallmark symptom of the disorder. Additional research is desperately needed to find more effective approaches to assisting individuals with PTSD to engage in treatment earlier by providing treatment options that relieve symptoms yet do not require the feared trauma processing. Armed with new skills and some symptom relief from less intense treatment options, those with PTSD may feel more confident to pursue the more intense evidence-based treatments such as Cognitive Processing Therapy, Prolonged Exposure and Cognitive-Behavioral Conjoint Therapy for PTSD.

Yoga, in its traditional, holistic form, is aimed at improving physical, mental and spiritual well-being and involves teaching individuals skills they can practice at home. Yoga has been found to reduce trauma-related symptoms, and thereby may improve the ability of individuals with PTSD to attend to and become aware of their cognitive, emotional and physical states, including dysfunctional thinking and behavioral patterns that contribute to emotional suffering and interfere with effective functioning. Until recently, those who have PTSD have been largely ignored in yoga research. Our proposal is significant as it will be the first large, rigorously designed, randomized, controlled trial comparing a holistic yoga intervention tailored for individuals with PTSD to an attention control. Results of the proposed study may scientifically validate the therapeutic value of yoga as an intervention for veterans with PTSD, in particular, revealing what kinds of clinical and rehabilitation benefits can be expected from augmenting current VA PTSD treatment with a yoga intervention, e.g. reduced PTSD and PTSD-related symptoms, improved well-being, and enhanced quality of life. Results will yield scientifically sound information for policy makers and clinicians in the VA system and those outside the VA system, e.g. health insurers, healthcare delivery systems, clinical researchers, and public education systems (media). Results may provide support for investigating these procedures in other treatment settings, allowing for replication and further refinement. Enhancing current VA trauma services with a yoga intervention holds promise that many veterans may achieve gains who might otherwise fail to benefit from treatment.

2.0 **Rationale and Specific Aims**

Post Traumatic Stress Disorder (PTSD) has been recently conceptualized as a disorder of impeded recovery that is defined by the primary symptoms of re-experiencing, negative alterations in cognitions and mood, avoidance/numbing, and hyperarousal (DSM-5). While these symptoms are natural reactions to trauma, avoidance of feelings and reminders that continue to signal danger interferes with making sense of the

traumatic event and symptom remission.[1] PTSD constitutes a substantial proportion of the burden of illness among veterans.[2] The course of PTSD varies in duration of symptoms and level of disability, and many experience disabling symptoms for years.[3] Although effective PTSD-specific treatments are available (e.g. Cognitive Processing Therapy, Prolonged Exposure), many of those who have PTSD wait years to decades before seeking professional help, if they seek help at all.[4] PTSD symptoms such as avoidance, fueled by fears that directly addressing the trauma will worsen symptoms, and the stigma of PTSD and mental health treatment, contribute to delayed engagement in treatment.[5] In addition, dropout rates are high for current PTSD treatments and they may not be effective for all who suffer from PTSD, as evidenced by the significant number who remain symptomatic despite pharmacotherapy and psychotherapy.[6] As a result, there has been increased interest within the military and VA leadership, as well as active duty military and veterans, in Complementary and Alternative Medicine (CAM).[7] CAM approaches, such as yoga and meditation, do not require trauma processing, yet appear to relieve symptoms. Yoga is a holistic system of mind-body practices historically developed as a spiritual discipline that supports a mentally and physically healthy lifestyle and incorporates such elements as physical postures, breathing practices, and meditation.[8] Accumulating research evidence indicates that yoga practices are acceptable and efficacious for those who have experienced trauma, demonstrating reductions in clinician rated[9] and self-reported PTSD symptoms, [10-12] as well as depression, [12] and anxiety.[12] However, few studies exist that have evaluated yoga for PTSD and they have involved small sample sizes and are either uncontrolled or waitlist/usual care controlled. In addition, there is much variation among studies in the style and components of yoga interventions, i.e. yoga philosophy, postures (asanas), breathing practices (pranayama), relaxation practices (body scan, Yoga Nidra or yogic sleep), and/or practices that cultivate attention and concentration (meditation). [13] Thus, a fully powered and rigorous randomized controlled trial (RCT) of a standardized, traditional, holistic yoga intervention is urgently needed to inform VA policy makers and clinicians of the potential benefits of yoga as an adjunct to currently available PTSD treatments.

The Outcomes of a Holistic Yoga Program Designed to Relieve PTSD (RELIEVE trial) is a two-arm parallel group randomized clinical trial. The RELIEVE trial will include 232 individuals with PTSD randomized to one of two groups:

1) a 16-week Holistic Yoga Program (HYP) (postures, breathing practices, deep muscle contraction practices, relaxation) or
2) a 16-week Wellness Lifestyle Program (WLP) (attention control comprised of low intensity walking with didactics about wellness topics).

The Holistic Yoga Program (HYP) will be taught by experienced yoga teachers registered with the Yoga Alliance (200-hour level), who have received additional military and trauma-related training. Thus, if found to be effective, the yoga intervention and teacher training utilized in this trial will have been documented and tested, allowing for swift dissemination and implementation within the VA system.

Study Aims:

1) To compare the interventions' effects (HYP vs. WLP) on overall PTSD symptom severity at 8 weeks (early response), 4 months (immediately post intervention), and 7 months (sustained effects).

2) To compare the interventions' effects on specific PTSD symptoms (anger, sleep) and related symptoms and outcomes (well-being/quality of life, depression, anxiety, pain).

3) To manualize the Holistic Yoga Program (HYP) and procedure to train experienced yoga teachers to deliver the HYP to individuals with PTSD in order to facilitate future study and dissemination efforts.

Our primary hypothesis is that the Holistic Yoga Program (HYP) will be more effective than the Wellness Lifestyle Program (WLP) in reducing overall PTSD severity measured by the Clinician Administered PTSD Scale (CAPS) and the self-report PTSD Checklist (PCL).

Our secondary hypothesis is that the Holistic Yoga Program (HYP) will be more effective than the Wellness Lifestyle Program (WLP) in improving secondary outcomes including specific PTSD symptoms (anger, sleep), and PTSD-related symptoms and outcomes (well-being/quality of life, depression, anxiety, pain).

3.0 **Inclusion/Exclusion Criteria**

Inclusion Criteria

- 18 or older
- CAPS-confirmed PTSD diagnosis
- Access to a working telephone for ease of contact during the course of the study

Exclusion Criteria

- Severe medical conditions in which yoga is contraindicated
- Active psychosis
- Active suicidal intent
- Moderate to severe cognitive impairment as determined by the short Mini-Mental Status Examination (MMSE)
- Involvement in ongoing yoga classes and/or regular home practice of yoga in the previous 3 months
- Receiving ongoing medical or psychological treatment that includes more than one hour weekly of relaxation and mind-body based stress reduction strategies (related directly to meditation and yoga)

4.0 **Enrollment/Randomization**

Potential participants will primarily be identified by querying the VA's electronic medical record system, CPRS (Computerized Patient Record System), to create a master list of veterans who have a documented PTSD diagnosis or related diagnoses (e.g. adjustment disorder, anxiety, panic disorder), that may suggest undiagnosed PTSD. A recruitment letter and approved study brochure will be mailed to qualifying veterans who have been identified through the methods explained above to describe the study. These potential participants will be contacted by phone within a week after receipt of the letter by a trained study staff member to determine their interest in participating and if interested, an appointment will be scheduled to obtain consent. A second method will be contact of potential participants by their providers and referral to the study, which will be used at the RVAMC, the IU Psychiatry Clinic and affiliates, and with clinicians at other locations in the community as mentioned in the table below. A third method is self-referral by patients responding to word of mouth or study advertisement displayed in RVAMC elevators and clinics, community-based clinics and provider offices, military and veterans organizations, in MyHealtheVet, on tv monitors stationed throughout RVAMC facility, and on the RVAMC Facebook page. A fourth method will identify potential participants by querying medical record data from Regenstreif and IU Health (IUH), ResNet, to create initial lists of patients from each institution who have a documented PTSD diagnosis or related diagnoses that may suggest undiagnosed PTSD. After an initial list is identified, the distribution of patient information will adhere to the procedures of each institution before it will be distributed to the study staff. ResNet Research Assistants will be utilized to aid with the recruitment of study participants. ResNet will identify potential subjects at the Eskenazi outpatient clinics using Regenstrief Medical Record data (INPC). ResNet will provide the study team with recruitment information after obtaining an Authorization of Release of Health Information form. IUH ResNet will provide each individual IUH primary care practitioner information about the study and its procedures, the types of patients who would be eligible and a list of the individual patients. The providers have two weeks from the delivery of the lists, to decide if they want their patients to participate and then to review each patient's suitability, excluding those who are not a good fit. Lists are returned to IUH ResNet; patients excluded (if any) from the query. After the two weeks have expired, if IUH ResNet has not received a response from the provider, the patients are deemed eligible for recruitment. Once these procedures have been completed, staff members at Indiana CTSI will work in consultation with members of the study team to make follow-up phone calls to prospective participants and schedule consent appointments for those who are interested. All communication between staff members at Indiana CTSI and VA regarding patients and sensitive research information will be completed exclusively over the phone. A fifth method will identify subjects from the Indiana CTSI INresearch volunteer registry, IU IRB Protocol #1105005444, a website created for interested individuals to contact Indiana CTSI and sign up to

receive information about ongoing studies and is supported by the Indiana CTSI Subject Enrollment and Research Volunteer Engagement (SERVE) program. An email will be sent to INresearch volunteers who meet the study criteria. Participants are given a few days to respond to INresearch staff if they do not wish to be contacted by the study team. After 3 days, the contact information for the remaining eligible individuals is released to the study team through slashtemp secure. Only relevant information is provided to the study team such as name, contact information, and the best time to reach the participant. Participants will also have the opportunity to reach out to the study team directly. If after a week of sending the email, additional participants are needed for the study, a staff member will begin contacting the identified participants directly either by email or phone to determine their interest in participating. A sixth method is self-referral by patients responding to TV, radio or newspaper advertisement.

Table 1: Recruitment sites for RELIEVE trial	**Veterans with PTSD**	**Non-Veterans with PTSD**
RVAMC Psychiatry Service clinics (PAC, Trauma Recovery, OEF-OIF-OND) and Domiciliary	**X**	
5 RVAMC Primary Care Clinics	**X**	
3 RVAMC Community-Based Outreach Clinics (CBOCs) in Terre Haute, Bloomington, Martinsville	**X**	
Vet Center, National Guard, and Reserves	**X**	
IU School of Medicine Psychiatry Clinic and affiliated IU Health clinics	**X**	**X**
Community Mental Health Centers & University Counseling Centers	**X**	**X**
Mental Health Providers in Private Practice	**X**	**X**

Following informed consent and once a participant has been screened and meets inclusion criteria a baseline assessment will be performed. Participants will then be randomly assigned to either the holistic yoga program (HYP) or the wellness lifestyle program (WLP). The randomization process will be directed by Joanne Daggy, Ph.D. (statistician) using a program within the REDCap database. Randomization will be stratified by gender (men vs. women) and veteran/non-veteran status. Within strata, randomization with block sizes of 4 will be executed to ensure balance. Once an eligible participant has signed informed consent, been screened, and has completed the baseline measures the project coordinator will obtain the randomization from the REDCap database. The participant identifier and date are recorded. To ensure allocation concealment, only the project coordinator, Dr. Davis and Dr. Daggy will have access to the randomization function within REDCap (and will not conduct outcome assessments). The research assistant who will conduct outcome assessments will be blinded to group assignment. No one will be allowed access to randomization assignment until all baseline measures have been completed.

5.0 **Study Procedures**

- Following informed consent and once a participant has been screened and meets inclusion criteria per the screening interview, a baseline assessment will be performed. The baseline assessment includes collection of sociodemographic data, substance use, psychiatric treatment utilization history, and assessments of PTSD (CAPS) and PTSD symptoms (self-reported PTSD symptoms, anger, sleep, anxiety, depression), and related outcomes (pain, well-being, quality of life, interoceptive awareness, and self-regulation). Substance use will be measured with 2 items. Alcohol use disorders will be assessed with the Alcohol Use Disorders Identification Test Consumption (AUDIT-C), which is commonly used in primary care settings, including VA primary care[66] and corresponds reasonably well with the full AUDIT[90]. It can be scored continuously from 0 to 12, with higher scores representing riskier drinking, or categorically, with cutpoints of 3 for women and 4 for men having good sensitivity and specificity for hazardous drinking. Other substance use will be measured with the 10-item Drug Abuse Screening Test (DAST)[91] which has shown to have good test-retest reliability, validity, and sensitivity, and specificity in detecting problem substance use[69].

See **Table 1** below for the administration schedule for all measures and time estimates for the assessment batteries.

Table 1. Outcome Assessment Protocol: Measures and Schedule of Administration								
Domain	**Measure**	**Items**	**Time (min)**	**Schedule**				
				Screen	**BL**	**8 wk FU**	**4 Mo FU**	**7 Mo FU**
Demographics and Covariates	Screening Interview – Eligibility	22	10	X				
	Demographic/Covariate Form (BL/FU) AUDIT-C alcohol use DAST – drug use	21/12)	(7/3)		X	X	X	X
Overall PTSD Symptoms	CAPS – Clinician Interview	30	45	X			X	X
	PCL – Self Report	20	6		X	X	X	X
PTSD-Specific Symptoms	PROMIS Anger Short Form	5	2		X	X	X	X
	MOS – Sleep	12	3		X	X	X	X
PTSD-Related Outcomes	BDI – Depression	21	7		X	X	X	X
	STAI – Anxiety (state only)	20	5		X	X	X	X
	BPI – Pain	11	3		X	X	X	X
	SF-20 – Well-being/quality of life	20	6		X	X	X	X
Other Related Outcomes	MAIA - Interoceptive Awareness and /Self Regulation SCS-SF-Self compassion NGSES – self-efficacy Mental Illness Stigma FACIT-SP - spirituality	32 12 8 6 12	10 3 3 2 3		X X X X X	X X X X X	X X X X X	X X X X X
Treatment Factors	PPQ – Treatment Credibility	5	2		X			
	CSQ-8 – Client Satisfaction	9	3				X	
	Program Evaluation Questionnaire	10	8				X	
Total Time				***55 Min***	***67 Min***	***61 Min***	***117 Min***	***106 Min***

Primary Outcome Measures. The primary outcome measures include the total score from the Clinician Administered PTSD Scale (CAPS) [65] and the total score from the PTSD Checklist (PCL).[66] The CAPS is considered the "gold standard" diagnostic tool for PTSD assessment by the National Center for PTSD and has been extensively used and validated in clinical trials.[68,69] The CAPS is a semi-structured clinician interview that measures PTSD diagnostic status and symptom severity consistent with the Diagnostic and Statistical Manual of Mental Disorders (5th ed.).[67] The CAPS yields both continuous and dichotomous scores for current PTSD symptoms. PTSD self-reported symptom severity will be assessed with the PTSD Checklist, a 20-item self-report measure of the DSM-5 symptoms of PTSD used as a measure of change in PTSD symptoms as a function of treatment. The PCL has demonstrated sensitivity and specificity >70%.[66, 69, 70] The DSM-5 versions of these measures are not yet normed but should be available for use in this study.

PTSD-Specific Symptoms: The Medical Outcomes Study 12-item Sleep Scale (MOS) will assess **sleep quality** (sleep disturbance, adequacy of sleep, and sleep quantity) and has demonstrated good psychometric properties.[74] **Anger** will be assessed by the PROMIS Item Bank v. 1.1 – Emotional Distress - Anger - Short Form 5a PROMIS stands for the NIH Patient Reported Outcome Measurement Information System which provides questions to produce numeric values which indicate patients' state of wellbeing or suffering as well as their ability or lack of ability to function that have been psychometrically validated..

PTSD-Related Symptoms/Outcomes: Depression will be measured by the Beck Depression Inventory (BDI), a 21-item self-report measure,[71] and **anxiety** will be measured by the Spielberger State-Trait Anxiety Inventory (STAI), consisting of a 20-item scale: State Anxiety.[72] These measures have well-established reliability and validity and have been widely used in PTSD treatment research. **Pain** will be assessed using the Brief Pain Inventory (BPI), an 11-item, multidimensional pain measurement tool with demonstrated reliability in patients with arthritis as well as other pain conditions.[75, 76] The BPI rates the intensity of pain as well as the interference of pain with mood, physical activity, work, social activity, relations with others, sleep, and enjoyment of life. **Physical and Psychological Well-Being/Quality of Life** will be measured by the Medical Outcomes Study Short Form Questionnaire (SF-20), which assesses physical and mental functioning/well-being in 8 domains and gives reliable, valid and responsive summary scores.[77] The SF-20 is a widely used self-report instrument that assesses perception of overall health status and the impact of physical limitations, emotional problems and pain on work, social activities and everyday tasks during the preceding 4 weeks. The SF-20 will be used to evaluate potential changes in perceived physical and psychological well-being and QOL that may be associated with the study intervention.

- **Potential Mediators/Moderators: Interoceptive Awareness and Emotional Awareness/Self-Regulation** will be assessed by the Multidimensional Assessment of Interoceptive Awareness (MAIA), a 32-item measure designed to assess interoceptive body awareness, includes eight subscales: noticing, not-distracting, not-worrying, attention regulation, emotional awareness, self-regulation, body listening and trusting. Psychometric properties are acceptable for the intended use in an exploratory analysis.[80] We will use the total score for interoceptive awareness and the self-regulation subscale total as an indicator of emotional regulation. The Self-Compassion Scale-short form (SCS-SF) is a 12-item scale used to measure the degree to which individuals display self-kindness against self-judgment, common humanity, isolation, mindfulness and over-identification. The short scale has a near perfect correlation with the long scale when examining total scores. Questions are rated on a Likert scale from 1 (almost never) to 5 (almost always) with subscales scores computed by calculating the mean of subscale item responses. The New General Self-Efficacy Scale will be used to measure the general self-efficacy of participants. It is an 8 item, 5-point scale consisting of *strongly disagree* (1) to *strongly agree* (5)[96]. The sum of this unidimensional[96] measure indicates the level of general self-efficacy, defined as "one's belief in one's overall competence to effect requisite performances across a wide variety of achievement situations,"[97] (p.75) with higher scores indicating greater levels of general self-efficacy. Internal consistency of the test responses range from .85-.90[98], while the stability coefficients of $r = 62$[96]. Mental Illness Stigma asks respondents about personal and perceived societal attitudes towards mental illness, including 3 questions used in a CDC random survey of 202,065 adults in the U.S[93] and 3 questions developed in focus groups of depressed patients[94] and completed by more than 78,000 depressed individuals responding to an Internet survey[95]. The FACIT-SP (Functional Assessment of Chronic Illness Therapy – Spirituality) is a 12-item scale designed to measure spiritual well-being independent of religious beliefs. It has been adapted for use with non-medical populations and comprises two subscales; meaning and peace and faith[99] The FACIT-Sp is a part of the larger FACIT battery[100] that assesses quality of life associated with chronic illness and has been found to be valid and reliable ($\alpha = .81$-$.88$)[99].

Treatment Factors will be assessed by three measures. The Pre-Program Questionnaire (PPQ)[81] is an adaptation of Borkovec and Nau's format[82] and is a frequently used measure of treatment credibility. The questionnaire asks subjects to rate how confident they are in the program, how logical the program seems,

how successful they think it will be, how helpful the program leaders will be, and whether they would recommend the program to a friend, on a 10-point Likert-type scale. Treatment Satisfaction will be measured by the Client Satisfaction Questionnaire (CSQ-8), an 8-item scale that uses a 4-point likert scale to indicate participants' appraisal of their satisfaction with the intervention.[83] The CSQ-8 has excellent internal consistency, with a coefficient alpha of .87-.93, and evidence for the construct and concurrent validity of this measure has been reported as well.[84] A one-hour Program Evaluation Focus Group will be conducted with 15 randomly selected HYP participants to gather detailed information about participants' experience of the intervention to guide improvement of its structure and content. These participants will receive $15 for completing the interview. Dr. Sternke, a sociologist experienced in qualitative methods, will train a member of the study staff to conduct the interviews, which will be audio recorded and transcribed. Dr. Sternke will explore the data in order to understand participants' perceptions of the program, particularly in relation to PTSD, using Grounded Theory, an emergent constant comparative method.[89] The secondary analysis (Situational Analysis), will map all major features of participants' characteristics, perceptions, material elements and settings, in order to understand the relations and differences among them. All other participants will complete a brief program evaluation questionnaire with open-ended questions to ascertain likes and dislikes as well as suggestions for improvement of HYP or WLP. Treatment Engagement will be assessed by examining totals of treatment sessions attended and home practice completed.

Study questionnaires, rating scales, and other assessments will be completed by study participants through an on-line survey or paper questionnaires (when the participant is unable to use the on-line survey and to capture home practice), assisted if needed by trained study staff blinded to condition. When on-line surveys are used to capture data, participants will be provided with a survey link and a code which will allow them to access the survey. The survey link will be sent to the participant in an email from Outlook on the VA network. The access code will be provided to the participant separately by another method, such as a hard-copy presented in-person, verbally over the phone, or a STREEM text. Data will be entered from paper self-report questionnaires or interviews conducted by trained study staff (e.g. CAPS). Within the REDCap database, algorithms will be created to check for inappropriate or missed data entry. Computer algorithms will automatically score questionnaires within the same database. These data will be backed up daily onto a password protected, secured server at the IU School of Medicine. Participant social security numbers, names, addresses and other personally identifiable information will be restricted to authorized personnel to protect confidentiality and will be stored in a separate password protected Microsoft Access Database on the RVAMC secured server. We have experience in setting up data integrity protocols and data back-up to minimize the risk for lost or inaccurate data. Participant personally identifiable information will be restricted to authorized personnel to protect confidentiality. We have experience using this strategy successfully in previous research, accurately completing assessments, protecting patient privacy and minimizing the risk for lost or inaccurate data. For our current PTSD study, audits revealed very low rates of data entry error (0.00079 or 0.079%) and missing data (average of 0.00083 or 0.083%). We have used similar length or longer batteries of measures in several previous or current trials without over-burdening patients. Self-report assessments will be completed via on-line surveys (REDCap) and interviews will be conducted in-person as we have found that rapport is more easily established face-to-face. If multiple attempts have failed for on-line surveys and/or in-person interviews, we have employed two strategies to capture outcome assessments: (1) conduct assessments by phone; and (2) mail questionnaires with postage paid, self-addressed envelope to our office. At times in past studies, participants have needed assistance to cover the cost of driving to the RVAMC for an assessment, especially if they live more than 30 minutes away. In these situations, the Project Coordinator may authorize a $10 gas card to defray the round trip cost of travelling to a scheduled study visit for assessment purposes. We have previously arranged taxi cab rides to and from our VA. To maintain participant confidentiality, our study staff will adhere to careful interview and data collection procedures. First, participants will be told that their responses will remain confidential and that every effort will be made to fulfill that assurance. Second, the interviews will be conducted in an appropriate setting (i.e., private interview room). Third, any completed paper surveys will be stored in a secure location in our locked RVAMC office in a locked file cabinet. The screening and assessment interviews and study databases (using Microsoft Access) will be designed by trained study staff under the direction of Dr Davis or the Project Manager.

Once baseline assessments are completed, the participant will be randomly assigned to the Holistic Yoga Program (HYP) or Wellness Lifestyle Program (WLP). The Holistic Yoga Program (HYP) arm will involve a standardized 16-week, yoga intervention consisting of: 1) a program orientation session conducted by a yoga instructor; 2) once weekly in-person group yoga class (postures, breathing practices, deep muscle contraction practices, relaxation practices) taught by a yoga instructor registered with Yoga Alliance at a minimum of the 200 hour level; 3) audio recordings of guided yoga postures, breathing, and relaxation practices for home-use; 3) a handbook to reinforce concepts taught during in-person session. Patients randomized to the Wellness Lifestyle Program (WLP) arm will participate in a standardized 16-week intervention that will consist of: 1) a program orientation conducted by a trained member of the study staff; 2) once weekly in-person group wellness classes (didactics and discussion of wellness topics and low intensity physical activity consisting of walking taught by a clinical psychologist with experience in trauma with consultation available from an experienced athletic trainer; 3) a handbook to reinforce wellness concepts and physical activity instructions taught during in-person session and to assist with home practice. After completing the program, participants will be asked to complete the same assessments as baseline with the addition of 2 program evaluation questionnaires. To minimize the potential for ascertainment bias, follow-up assessments (8 weeks, 4 months, 7 months) will be conducted by on-line survey and the interviews by a trained research assistant who will be blinded to treatment assignment. Participants will receive $25 for completing the 8-week assessments, $35 for completing the 16-week assessments and $45 for completing the 7-month follow-up assessment. Those who fail screening will be given $15.

We will conduct both interventions on a continuous schedule so that interested participants may begin the intervention immediately without having to wait for an entire cohort to be recruited. The Holistic Yoga Program (HYP) and Wellness Lifestyle Program (WLP), will both provide one 90-minute session each week for 16 weeks. The first session for each participant will consist of an orientation session with a trained member of the study staff. Group sessions will average 7-8 participants with the upper limit of 15 participants.. We may offer an additional 16-week session in years 2-4 if needed to recruit adequate numbers of participants to accommodate participants who are unable to attend the ongoing class day/time. Sessions will be held in a large multipurpose room at the RVAMC or the National Guard Armory at Stout Field or a classroom at the Regenstrief Institute on W. 10th Street (a block from RVAMC). Attendance will be recorded to assess adherence. If a participant is assigned to an intervention class that meets at a location offsite and paid parking is required, study staff will provide a parking voucher to the participant at the end of each class attended in order to cover the cost of parking.

6.0 **Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others**

Adverse events that are expected and do not pose additional risk to participants will be reported at the time of continuing review. Adverse events that pose risk to participants and unanticipated problems will be reported to the IRB within 5 business days of becoming aware of the event. The event will be reported using the “Prompt Reporting Form for VA Research” and will be submitted both to the IU IRB and the Indy VA Research Compliance and logged by the Project Coordinator.

7.0 **Study Withdrawal/Discontinuation**

A participant may withdraw from the study at any time by notifying the PI, Dr. Louanne Davis, of their request in writing. Additionally, participants may be urged to withdraw for clinical reasons, such as severe suicidal thoughts. Their participation may also be terminated at the discretion of the PI if they violate any rules or regulations of the Roudebush VA Medical Center.

8.0 **Statistical Considerations**

RELIEVE will involve a 2-arm, parallel group, RCT. Since participants cannot be blinded to treatment assignment, observed outcomes (if positive) could be affected by expectation bias. To account for this potential bias, we will assess treatment expectations at baseline and account for them in our analyses. We will

randomize at the patient level rather than the provider level for two reasons (1) randomization at patient level saves sample size; and (2) patients from the same provider in the two arms will be adjusted for "provider effect." Contamination will also be low because there is relatively minimal involvement required of VA providers in RELIEVE. In addition, randomization will be stratified by veteran and non-veteran status and gender (4 strata) to avoid potential imbalance of these factors between the two arms. Dr. Daggy, PhD (statistician) will create a randomization scheme in REDCap for each of the four strata to randomize patients in blocks of 4 assignments within each of 4 stratum.

Sample size. Our sample size is calculated based on estimated differences of intervention effects between two arms on the primary outcome: CAPS total score at 4 months, or treatment end. The CAPS total score is a continuous measure (0-136) and reflects a combined score reflecting symptom frequency and symptom severity. A recently published yoga pilot study for patients with PTSD[9] found a pre-treatment CAPS score of 77.33 (standard deviation = 28.6). Post-treatment scores were reduced by 34% (CAPS = 51.1, SD = 27.6, effect size = 0.9) from the yoga intervention. We powered on a medium effect size of 0.55 which requires a larger sample size than 0.9. We recognize the correlation of outcomes from subjects within the same yoga class may reduce the effective sample size compared to the same sample with independent observations. This possible "clustering effect" has implications for power. Randomization will occur at the individual not cluster or clinic level. Also, we expect that the intra-cluster correlation (ICC) will be near zero because groups will have a mixture of participants from the various recruitment sites: therefore, there is no reason to believe that participants within groups would be more correlated on the outcomes than participants from different groups. We have no preliminary data to estimate the intra-cluster correlation (ICC) for participants within the same group. However, based on similarly designed published studies, we expect the ICC to be relatively small and balanced across the two treatment arms since the cluster sizes will be similar. We will assume an ICC of 0.05 for both groups. We will also assume a 20% difference between treatment groups. The absolute score difference at 4 months is estimated to be approximately 15.4 points (61.6, 80% of 77). Assuming a common standard deviation of 28 and using a two-sample t-test, we will need 60 evaluable subjects in each arm to detect such a difference (Cohen's d = 0.55) with >85% power and 5% Type I error rate. With approximately 8 subjects per treatment group/class session or cluster, the design effect is 1+ (8-1) ×0.05=1.35. Therefore, we will inflate our sample size by 35% to accommodate the potential clustering effects. We then need 81 evaluable subjects in each arm. With an assumed 30% attrition, we will then need (81*2)/0.70 = 232 subjects (116 in each arm).

Data analysis: Baseline characteristics of the RELIEVE sample. To evaluate representativeness, we will compare enrollees and those who decline enrollment on baseline characteristics (socio-demographic variables, psychiatric comorbidity, and current and prior PTSD treatments). Any differences will be considered when interpreting results of subsequent analyses. We will also examine differences in baseline characteristics between patients who remain in the study and those who dropout. The linear mixed modeling approach (see next section) will ensure that all available data are used for subjects who have missing data. The models will also incorporate dropout status to adjust for follow-up missing data pattern. All participants will have baseline data. The possible missing data patterns will be (1) missing 4 month, not 7 month, (2) missing 7 month, not 4 month, (3) missing both 4 and 7 months, and (4) complete data.

Main analysis of the primary outcome. Our main analysis will use the ANCOVA (analysis of covariance) approach to linear mixed modeling of repeated measures in which the baseline measure of the relevant outcome scores (i.e., CAPS or PCL) is adjusted as a covariate in the model.[85] The model for CAPS will be adjusted for baseline CAPS score. The model for PCL, a continuous measure with a possible range of 17-85, will be adjusted for baseline PCL score. The CAPS and PCL are measured at every time point (baseline, 8 weeks, 4 months, 7 months) except the CAPS is not administered at 6 weeks in order to reduce participant burden, since the CAPS and PCL are highly correlated. We plan an intent-to-treat analysis with the primary endpoint at 4 months and evaluation of "early" response at 8 weeks and "sustained" response at 7 months (3 months post-intervention). The models will simultaneously incorporate three post-baseline measures (8 weeks ([PCL only], 4 months, and 7 months) of the relevant response variable. The main predictors will be group (treatment arm), time (categorical with indicator variables to avoid restrictive assumption of linearity over time), and their interaction. A random intercept will be used to adjust for the potential clustering effect for patients in

a specific yoga group. And a subject-specific random intercept (nested within the group effect) will accommodate the correlation among repeated measurements from the same patient. Aim 1 will involve testing intervention effects by using the appropriate contrast from the model to test the difference in CAPS score and PCL score between the two treatment arms at 8 weeks (early response), 4 months (the primary end point which occurs immediately post intervention), and 7 months (sustained effect of intervention). Descriptive statistics including adjusted means, SD, and effect sizes (differences between two arms on adjusted means divided by pooled SD) will be reported for outcomes at each time point. Variables that are either known, or shown with our data, to be significantly correlated to the outcomes, will be considered as covariates, irrespective of their degree of baseline imbalance between randomized groups (e.g., combat vs. con-combat PTSD, baseline credibility score, and mTBI).

Secondary analysis of primary outcome. For the CAPS and PCL total scores, we will also report a clinically relevant descriptive statistic in which we define the patients with more than 30% reduction from baseline as "responders." We will then compare the probability of responders between treatment arms using a generalized linear mixed model with a logit link. The responding status of each patient at 8 weeks (for PCL only), 4 months and 7 months will be used as the outcome variables. Main predictors are group (treatment arm), time (8 weeks for PCL only, 4 months and 7 months) and their interaction. A significant coefficient of group indicates a significant odds ratio of being a responder between the two arms.

Analysis of secondary outcomes. Since RELIEVE is not specifically powered for secondary outcomes, these results should be interpreted cautiously unless they are highly significant ($p < .001$). PTSD-specific symptoms (anger, sleep) and PTSD-related symptoms/outcomes (well-being/QOL, depression, anxiety, pain) will be analyzed using the linear mixed modeling approach described above for the primary outcome. The secondary outcomes will be PTSD-specific symptoms including: anger (STAXI score), sleep (MOS score) and PTSD-related symptoms/outcomes: depression (BDI score), anxiety (STAI score), well-being/QOL (SF-12), and pain (BPI). Since there will be a number of secondary outcomes, we will adjust for multiple-comparisons by using the false discovery rate (FDR) [86] method to control the overall false positive rate at 0.05. Exploratory analyses of potential mediators/moderators: interoceptive awareness and self-regulation. Moderation effects will be assessed by testing two-way interactions between intervention group membership and demographic and baseline scales including treatment credibility, interoceptive awareness, self-regulation and type of trauma (combat vs non-combat related), mTBI. Mediation effects will be analyzed using the MPLUS structural equation modeling (SEM) software to test the direct, indirect, and total effects of paths in a multilevel SEM model that includes potential mediators measured at various study points (see table of measures) including client satisfaction, interoceptive awareness and self-regulation. Adherence to the interventions and home practice will also be assessed for its dose-response effects on the primary and secondary outcomes.

Missing data.[87] Based on our prior studies, we anticipate a possible dropout rate of 30%, which is reflected in the sample size calculation. We will first run a logistic model with missing status as the response variable, intervention arm, patients' demographic characteristics as covariates, to check whether the missing status depends on the intervention group assignment and patient characteristics. Second, our linear mixed effects model can accommodate missing-at-random (or MAR which is assumed in many trials) where no bias will be introduced by ignoring the missing-data mechanism. If drop-outs are Missing Not At Random (MNAR), meaning the likelihood of drop-out depends on an un-observed outcome, and the missing data mechanism is ignored, potential bias can be introduced. We will run sensitivity analyses using linear mixed models with the "multiple imputation" method and 100 generated data sets to compare results with the standard linear mixed effects modeling without imputation to assess the robustness of the inference.

9.0 Privacy/Confidentiality Issues

Participants names will not appear on any of the data collected, including video or audio recordings. All of their answers will be matched with a code number only. The key to this code number will be stored in a password protected computer file, separate from other data. All VA sensitive research information and any copies thereof will be used, stored, and remain within the VA. Only de-identified data will be stored in the IU REDCap

database. Only staff working on this project and designees or members of the IU Institutional Review Board will be able to see records relating to this study.

10.0 **Follow-up and Record Retention**

This study will last for approximately 1 year. Research records, including audio and video, will be maintained by the investigator in accordance with the VHA Records Control Schedule.

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