Clinical Intervention Study Protocol

Optimization and Multi-Site Feasibility of Yoga for Chronic Pain in People in Treatment for Opioid Use Disorder

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TOOL REVISION HISTORY

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Version Number 1.1
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Summary of Revisions Made: Added personnel; updated planned enrollment numbers; clarified inclusion/ exclusion criteria; made other minor clarifications; added assessments of depression, anxiety, and prescribed medications; added a qualitative exit interview in Phase 1; clarified which staff will be blind to randomized assignment; defined unanticipated problems; updated plans for determination of final intervention components.

Version Number 1.2
Version Date: 6/25/20
Summary of Revisions Made: Modification to inclusion criteria regarding text messaging

Version Number 1.3
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Summary of Revisions Made: Provided an option for remote recruitment, classes, and assessments. Specified that we will give all participants a study cell phone. Modified inclusion criteria slightly because of remote recruitment, classes, and assessments. Changed the term "home practice" to "personal practice" to reflect terminology we have chosen to use in the study. Clarified several data analysis decisions.

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Changed amount for returned phone from $40 to $35.

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Corrected a typo: removed mention of urine toxicology in Table 4.

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PRÉCIS

Study Title

Optimization and Multi-Site Feasibility of Yoga for Chronic Pain in People in Treatment for Opioid Use Disorder

Objectives

Our project will have two phases. Specific aims for each phase are:

Phase 1 – MOST Preparation Phase:

1. To conduct a pilot trial at two new OAT clinic sites, enrolling n=10 at both sites, for a total n=20.
2. Establish clinical trial procedures and document feasibility at both sites prior to conducting a fully powered optimization trial.
3. Demonstrate our ability to a) recruit participants; b) train yoga teachers to fidelity; c) randomize participants to intervention components and correctly administer components; d) run classes; and e) collect follow-up assessments.

Phase 2 – MOST Optimization Phase:

1. To conduct a 2x2x2x2 factorial experiment that will allow us to evaluate the impact of each of the 4 intervention components on yoga dosage received. We plan to enroll a total n=192. All participants will receive the core yoga intervention, with random assignment to the additional four intervention components.
2. Use results from Phase 2 to choose an efficient combination of intervention components that, together with standard yoga classes, maximizes yoga dosage.
3. Examine mechanisms by which components are hypothesized to work.

The primary objective for this project is to develop an efficient combination of intervention components that, together with standard yoga classes, maximizes yoga dosage. We will also be able to examine mechanisms by which components are hypothesized to work.

Design and Outcomes

In Phase 1, we will conduct a pilot trial of our standard yoga intervention and four intervention components to demonstrate feasibility. Participants will be patients engaged in opioid agonist therapy (OAT) with chronic pain.

In Phase 2, we will conduct a factorial RCT to evaluate the impact of each of the 4 intervention components on yoga dosage received. Participants will be patients engaged in opioid agonist therapy (OAT) with chronic pain.

Interventions and Duration

Yoga classes. Participants will be asked to attend one class (approximately 45-60 mins long) per week for 12 weeks. Classes will be either in person or over a secure video-based platform, such as Zoom. Participants in Phase 1 will participate for 3 months (12 weeks of intervention, 3 month follow up interview at end of treatment). Participants in Phase 2 will participate for 12 months (12 weeks of intervention, 9 months of follow up).

Component 1: Participants will be randomized to receive or not receive personal practice videos featuring study yoga teachers.

Component 2: Participants will be randomized to receive or not receive initial and 1-month 1:1 sessions with a yoga teacher. Sessions will either be in person or over a secure video-based platform.

Component 3: Participants will be randomized to receive or not receive text messages cuing personal practice.

Component 4: Participants will be randomized to receive or not receive monetary incentives for class attendance.

Sample Size and Population

The proposed project will include up to 20 participants in a pilot trial (Phase 1), and 192 participants in a factorial randomized controlled trial (Phase 2). Participants will be individuals engaged in OAT with chronic pain aged 18 or over, regardless of gender.

1. STUDY OBJECTIVES

1.1 Primary Objective

Our project will have two phases. Specific aims for each phase are:

Phase 1 – MOST Preparation Phase:

1. To conduct a pilot trial at two new OAT clinic sites, enrolling n=10 at both sites, for a total n=20.
2. Establish clinical trial procedures and document feasibility at both sites prior to conducting a fully powered optimization trial.
3. Demonstrate our ability to a) recruit participants; b) train yoga teachers to fidelity; c) randomize participants to intervention components and correctly administer components; d) run classes; and e) collect follow-up assessments.

Phase 2 – MOST Optimization Phase:

4. To conduct a factorial experiment that will allow us to evaluate the impact of each of the 4 intervention components on yoga dosage received. We will enroll a total n=192. All participants will receive the core yoga intervention, with random assignment to the four intervention components outlined above.
5. Use results from Phase 2 to choose an efficient combination of intervention components that, together with standard yoga classes, maximizes yoga dosage.
6. Examine mechanisms by which components are hypothesized to work.

2. BACKGROUND AND RATIONALE

2.1 Chronic pain in people receiving OAT

Chronic pain is a significant problem for at least half of all persons receiving opioid agonist therapy (OAT) for opioid use disorder – i.e., buprenorphine/ naloxone (BUP) or methadone maintenance treatment (MMT). In OAT patients, chronic pain is associated with disability, psychiatric disorders, physical problems, and increased misuse of opioids or other illicit drugs. Behavioral interventions, such as CBT, mindfulness-based interventions, or yoga may be useful adjunctive interventions for decreasing pain-related disability. Hatha yoga may be a useful adjunctive approach for decreasing pain-related disability and pain severity, and preventing opioid misuse during OAT. There is evidence supporting its efficacy in other chronic pain populations, and yoga may target cravings and other risk factors for opioid relapse. It is essential that a future efficacy trial employ an intervention that is efficient, economical and scalable, but that allows (and encourages) participants to receive a "dosage" of yoga sufficient to adequately test the hypothesis that yoga is effective, i.e., reduces pain interference, and improves other pain and substance use outcomes.

2.2 Study Rationale

Yoga is an ancient Indian system of philosophy and practice [1]. Most U.S. practitioners practice *hatha* yoga, which includes physical postures (*āsanas*), breath control (*prāṇāyāma*), and meditative practices. (In this proposal, when we refer to yoga, we are referring to hatha yoga). A meta-analysis of yoga across chronic pain conditions (including back pain, headache, rheumatoid arthritis, n = 16 studies) reported that yoga had a moderate-large effect on pain[2]. Yoga also had a moderate-large impact on pain-related disability and a moderate impact on depressed mood (SMD = -0.65) [2].

There are various plausible mechanisms by which yoga may have an impact on individuals with chronic pain. First, yoga may promote mindfulness in everyday life. Mindfulness practices may help people with chronic pain experience the sensory component of pain with less negative affect, leading to better quality of life and less pain-related interference. Second, yoga may decrease pain catastrophizing [3, 4], in which patients develop a disproportionate interpretation of chronic pain as calamitous and threatening, leading to avoidance of physical and other activities [5]. Amongst OAT patients, pain catastrophizing is associated with increased risk for opioid misuse [6, 7], increased craving [8], and more pain-related disability [9]. Engaging in yoga may help people who have feared exercise to start engaging in gentle physical activity again. Third, yoga may have a direct impact on mood symptoms that often co-occur with pain such as depression or anxiety [10-12] which are common in people with opioid use disorder [13, 14] and are associated with increased risk for opioid or other substance misuse [15-17]. Finally, hatha yoga may serve to increase overall physical activity. Yoga may improve core and other muscle strength as well as endurance [18].

Yoga is increasingly popular and available, with the percent of US adults practicing yoga increasing from 8.9% in 2012 [19] to 14.3% in 2017 [20]. Yoga is increasingly being offered at addiction treatment centers [21, 22]. Yoga can also be adjunctive to other pain and substance use treatment. Yoga classes may also be structured in such a way to allow for rolling rather than cohort enrollment, thus increasing access.

Although yoga has been recommended as a complementary treatment [23], there are few studies of yoga for people with substance use disorders [24], including a few feasibility studies [25, 26]. The only study of which we are aware that hatha yoga for OAT patients with chronic pain is our pilot project. In brief, we assessed feasibility and acceptability of a 12-week manualized yoga program (vs. a 12-week health education program) in OAT patients with chronic pain. Our pilot study was largely successful, showing excellent feasibility for recruitment, instructor fidelity, and participant retention in follow-up assessments. Our primary challenge was in class attendance, a common problem with behavioral interventions for OAT patients [27-29].

3. STUDY DESIGN

In Phase 1, we will enroll 10 participants at each recruitment site (n=20). The purpose of Phase 1 (MOST Preparation Phase) is to allow us to establish and refine procedures at these new sites and document aspects of feasibility, including our ability to a) recruit participants; b) train yoga teachers to fidelity; c) randomize participants to intervention components and correctly administer these components; d) run classes; and e) collect follow-up assessments. Enrollment period for this phase will last approximately 4 months.

In Phase 2, we will conduct a fully powered optimization trial. We will enroll 192 participants, planning to role approximately equal numbers of participants in both sites. In both phases, all participants will receive the core yoga intervention (12 weeks of weekly manualized yoga classes), with random assignment to the 4 key intervention components. Participants will be patients enrolled in methadone or buprenorphine/naloxone treatment with chronic pain. Enrollment period for this phase will last approximately 2 years.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all of the relevant inclusion criteria to participate in the study.

Inclusion Criteria – Phase 1 and 2

1) Enrolled in MMT or BUP treatment for > 3 months

2) Plan to continue treatment for next 6 months

3) Chronic pain, defined as pain for at least half the days over the previous three months, a mean score of 4 or higher on the BPI Pain Interference Scale (with reference to chronic pain), and pain severity of 4 or higher on a Visual Analog Scale (0-10) indicating "worst pain in the last week." Pain severity score will also refer to the areas of their body in which they have chronic pain.

4) Aged $\geq$ 18

5) Proficiency in English sufficient to engage in informed consent in English, understand classes taught in English, and read short sentences

6) Available at least one of the times study classes are offered.

4.2 Exclusion Criteria

All participants meeting any of the exclusion criteria at baseline will be excluded from study participation.

Exclusion Criteria – Phase 1 and 2

1) Currently taking yoga classes or practicing yoga at home once per week or more often.
2) Medical conditions that would make participation in yoga unsafe or not possible, including active malignancy treatment, fracture, recent joint surgery, use of assistive ambulatory devices other than a cane. . (In cases where this is unclear, site PI will make final determination based on available evidence.)
3) Severe or progressive neurologic deficits. (In cases where this is unclear, site PI will make final determination based on available evidence.)
4) Other severe disabling chronic medical and/or psychiatric comorbidities deemed by the site PI on a case-by-case basis to prevent safe or adequate participation in the study (e.g., cognitive impairment that prevents a participant from understanding assessments; history of disruptive behavior in medical settings; severe disabling heart failure or lung disease)
5) Surgery requiring overnight hospitalization planned in the next 3 months
6) Pregnancy
7) Plan to move out of the area within 6 months.

8) Homeless, defined as any time in the past month sleeping in a shelter or on the street.

4.3 Study Enrollment Procedures

Recruitment and Screening

Recruitment will be in collaboration with opioid agonist therapy (OAT) clinics. The investigators will educate OAT providers about the study at regular clinic meetings. With assistance from clinic staff and using electronic health records, research staff will identify potentially eligible individuals. Research staff will call these participants, send them a letter, and/ or approach them at an appointment to tell them about the study if they are interested. We will also use passive recruitment methods, e.g., posting fliers in clinic spaces. Interested participants will undergo a brief (5-10 minutes) telephone or in-person screen to confirm inclusion/exclusion criteria. For those appearing to meet study criteria, the RA will explain the research study, and if the patient is interested, schedule a time to conduct informed consent, verify inclusion criteria, and administer baseline assessments. The research team will review recruitment (and retention) rates weekly.

Informed Consent Procedures

Research assistants will perform this process. Participants appearing to meet study criteria will be scheduled for a more comprehensive baseline assessment. This assessment may be either over the telephone or in person. If it is over the telephone, we will send a written version of the informed consent document to the participant ahead of time. With the participant's permission, this may be sent via email or US mail. During the baseline assessment, research staff will carefully explain all aspects of the study, then potential risks and benefits, and the expected duration and time commitment of their participation. If the patient verbally consents, the patient will be presented with a written explanation, will be given the opportunity to ask questions. Documentation of informed consent may occur via one of several methods: a) a written informed consent document; b) a REDCap document with an electronic signature; c) audiorecording of informed consent. The final option is necessary because a) participants may not be able to attend an in-person visit at the clinic due to COVID restrictions; and b) some participants may not have the technology needed to access REDCap.

A member of the research staff will also sign the consent form (either on paper or electronically). After informed consent is obtained, participants will then be evaluated using the baseline diagnostic and assessment measures to confirm eligibility. Consent forms will be stored in a secure location at Butler Hospital (for patients recruited at CODAC) or Boston Medical Center, or be located in REDCap. Participants will be given a copy of the consent form to keep.

Enrollment and Randomization

Enrollment procedures are identical for Phase 1 and Phase 2.

Randomization will occur after participants are deemed eligible. To be eligible after consent participants must: 1) have completed the baseline assessments and passed inclusion criteria, and 2) confirmed their interest.

All participants receive the standard yoga intervention, and are randomized to receive or not receive four intervention components. Each participant will be randomized to one of 16 study groups. Participants are considered "enrolled" after randomization.

Once enrolled, a participant will receive a) a study cell phone with a data plan; b) a yoga mat and two blocks; and c) a booklet describing basic yoga practices and ways to more safely engage in yoga. The study cell phone will be used for assessment phone calls, study classes via a secure video-based platform, and to administer some study intervention components. Once a participant receives the phone, a study staff member will call them to give the participant any guidance that they need regarding how to use the phone for study-related activities. During the course of the study, participants will not be restricted from using the phone for other activities. Participants will be asked to return the phone at the end of study participation.

Documentation of Reasons for Ineligibility

All participants who express interest in the study will be tracked in a separate database along with the status of their participation. Any participant who is screened for any aspect of the study including Phase 1 or Phase 2 (even if only one inclusion criterion is assessed before the participant is determined not eligible) will have a study record documenting which inclusion criteria were assessed and the outcome of that assessment (i.e., as part of a study log).

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Standard Yoga classes are administered to a group of participants. All participants will receive the standard yoga class intervention. Participants will be invited to attend one yoga class per week. Classes may be offered at multiple timeslots. Classes will take place at the clinic/facility where they receive OAT or via a secure video-based platform such as Zoom; they are planned to be 60 minutes long. Registered yoga teachers will deliver the intervention. Potential risks include loss of privacy or breach of confidentiality, increased distress or physical pain due to procedures, ineffective intervention (i.e., lack of improvement in physical pain symptoms), and mild physical injury.

Components of Yoga Intervention are delivered to participant individually based on randomization assignment. Components include: 1) Personal practice videos featuring study yoga teachers, 2) 1:1 session with yoga teacher at baseline and 1 month (in-person or via a secure video-based platform), 3) Text messages cuing personal practice, 4) Monetary incentives for class attendance. Potential risks include loss of privacy or breach of confidentiality, increased distress or physical pain due to procedures, ineffective intervention (i.e., lack of improvement in physical pain symptoms), and mild physical injury.

COVID-related adjustments. Due to COVID restrictions, we may not be able to offer

classes or 1:1 sessions with yoga teachers in-person. Thus, we will offer classes and meetings via a secure video-based platform on study-provided cell phones. Whether interventions are via a secure video-based platform or in person may fluctuate during Phase 1 of the study. Prior to the start of Phase 2, we will decide on the best modality to provide interventions for Phase 2, and then stay with that modality throughout the duration of Phase 2, barring unforeseen circumstances.

5.2 Handling of Study Interventions

Yoga Intervention

Yoga classes. All participants will receive the manualized hatha yoga program. Participants will be asked to attend one 60-minute class per week for 12 weeks in person or via a secure video-based platform. Each class will consist of: greeting and discussion of personal practice; centering and breath awareness; pranayama (breathing practices); warm up movements; an asana sequence; a seated meditation; and discussion of personal practice. Classes will acknowledge the validity of participants' pain and gently challenge them to try a new way of coping with it; emphasize breathing in every part of the class; and run the class at a slow pace. Class size will range between 1 and 12 participants.

Yoga Personal practice. Personal practice will be essential for increasing yoga "dosage." When participants first start class, we will give them a yoga mat to take home, a curated list of YouTube videos, and written instructions for personal practices that can be used to manage pain and cope with urges to misuse opioids and other substances. In each class, the yoga instructor will review specific practices and recommend that participants try those practices at home. The practices will always be ones that carry with it minimal risk of injury, and instructors will go over safe practice in class. Participants may continue in the study regardless of whether they practice at home.

Intervention Component 1: Personal practice Videos Featuring Study Yoga Teachers. As part of the standardized yoga intervention, all participants will receive a curated list of YouTube videos for yoga personal practice. However, participants randomized to receive component 1 will also receive study-specific videos of varying lengths featuring study teachers and only yoga practices taught in class. Participants will be randomized to either receive or not receive study-specific videos.

Intervention Component 2: Initial and 1-Month 1:1 Session with Yoga Teacher. Participants randomized to receive this component will receive two 1:1 sessions with the yoga teacher, with one session occurring prior to the first group class, and one after 1 month. Sessions will be in person or via a secure video-based platform. The yoga teacher will address the individual's specific physical concerns and provide individualized advice about a) listening to one's own body; and b) what to do if one is unsure about the physical sensations associated with a specific practice. Participants will be randomized to either receive or not receive 1:1 sessions.

Intervention Component 3: Text messages cuing personal practice. Text messages may be useful to cue participants to engage in yoga personal practice. Immediately post-

randomization, for applicable participants, we will ask participants to choose from a list of text messages the ones they expect would be most helpful to receive during the study. Participants may also choose to receive messages via email instead of text, and time of day they would like to receive them. We will send messages every day or every other day, per participant choice. They may choose to change their choices once per month. Participants will be randomized to either receive or not receive regular text messages cuing personal practice.

Intervention Component 4: Monetary incentives for class attendance. Transportation and other costs such as childcare associated with attendance may be a significant barrier for some participants. Financial incentives can increase session attendance for physical activity interventions. Participants randomized to this component will receive $15 for each yoga class attended. Participants will be randomized to either receive or not receive monetary incentives for class attendance.

Yoga Instructors. The Yoga Alliance is a professional organization which sets standards for yoga teacher training. Teachers will be Registered Yoga Teachers (RYTs) at the Yoga Alliance. Teachers will have study-specific training on research methods, OAT, chronic pain, adverse events, and the yoga manual They will meet approximately monthly for supervision. There will be at least 2 trained yoga teachers at each site. Yoga supervisors will also review audio recordings or video recordings of classes to assess instructor adherence.

Yoga instructor Manual Fidelity. All classes will be audio recorded or video recorded. We have developed a fidelity measure that assesses: a) practices used; and b) style in order to evaluate whether yoga teachers can reliably deliver the manualized program. We will conduct adherence ratings of 20% of classes on an ongoing basis, and review results with teachers.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Once a participant is enrolled in the study, participants will not be excluded for any concomitant intervention. For example, if a participant begins outside yoga classes or starts a pain management regimen while they are in the study, we will record that information, but not require that they discontinue study interventions. If a participant changes their dose of OAT, type of OAT, or stops taking OAT, we will record that information, but not require that they discontinue study participation.

5.3.2 Required Interventions

None

5.3.3 Prohibited Interventions

None

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Table 1: Assessment schedule for Phase 1 and Phase 2

Assessment	Type of Assessment	Screening: (Up to 30 days before BL1)	Baseline Visit 1	After initial class	Weekly M1, M2, M3	M1 visit	M2 visit	M3 visit	M6 visit (Phase 2 only)	M12 visit (Phase 2 only)
Inclusion/Exclusion	Interview, pre-randomize.	X	X							
Informed Consent Form	Pre-randomize.		X							
Enrollment and Randomization	Interview		X							
Credibility Expectancy Questionnaire (CEQ)	Self-report			X						
Homework Questionnaire	Self-report				X				X	X
Injuries due to yoga	Self-report				X					
Systematic Assessment for Treatment Emergent Events (SAFTEE)	Interview							X		
Chart Review	Chart Review		X		X				X	X
Other Adverse Events	Interview		X		X	X	X	X	X	X
SUD, psychiatric, sleep, and pain medications (modified TRAQ)	Interview		X					X	X	X
Tampa Scale of Kinesiophobia (TSK)	Self-report		X			X	X	X		
Self-efficacy for exercise	Self-report		X			X	X	X		
Logistic Factors	Self-report		X			X	X	X		
Behavioral Regulation in Exercise Questionnaire (BREQ-2), modified for yoga	Self-report		X			X	X	X		

Assessment	Type of Assessment	Screening: (Up to 30 days before BL1)	Baseline Visit 1	After initial class	Weekly M1, M2, M3	M1 visit	M2 visit	M3 visit	M6 visit (Phase 2 only)	M12 visit (Phase 2 only)
Brief Pain Inventory (BPI)*	Self-report		X			X	X	X	X	X
Numerical Rating Scale (NRS), Pain Severity	Self-report		X			X	X	X	X	X
WHO Quality of Life, Brief Version (WHOQOL-BREF)	Self-report		X					X	X	X
PROMIS Depression Scale	Self-report		X					X	X	X
PROMIS Anxiety Scale	Self-report		X					X	X	X
Addiction Severity Index (ASI)	Interview		X			X	X	X	X	X
Penn Craving Scale	Self-report		X			X	X	X	X	X
Demographics	Self-report, blind DB		X							
Review of Medical Comorbidities	Self-Report		X							
Qualitative Exit Interview (Phase 1 only)	Interview							X		
Payment			**$10**			**$20**	**$20**	**$30** (assmt) **+ $35** (return of study cell phone)	**$30**	**$40**

* When calculating the BPI- Pain Interference Scale, we will not include the "work" item, as we anticipate that this item does not apply to a large proportion of our sample.

6.2 Description of Evaluations

Assessments will be administered by research assistants (RAs) trained in procedures to ensure confidentiality and proper management of research data.

Assessments will be administered via interview (on the phone or in-person). We will provide participants with a document with response options to look at while they are responding to assessment questions.

We will track type of interview (on the phone or in-person) for each assessment.

6.2.1 Screening Evaluation

Consenting Procedure

All phases will have a) agreement from individual to conduct brief eligibility screening and b) informed consent individual at the first visit.

For information about agreement to screening, please see section 4.3 Study Enrollment Procedures.

Screening

For Phases 1 and 2, because all inclusion criteria are verified or re-verified at BL the screen may be conducted as many as 30 days prior to BL.

6.2.2 Baseline – Phase 1 and Phase 2

Consenting Procedure

Informed consent will be obtained at the baseline appointment.

Please see section 4.3 for more information about the consent procedures.

Documents will be stored in a locked file cabinet, or will be located in REDCap.

In-Person Screening

After informed consent/assent is complete, RAs will administer the following to ascertain inclusion criteria during BL1:

- BPI –Pain Interference
- NRS– Average and worst pain in the past week
- Review of Medical Comorbidities

If participants meet all eligibility criteria, we will then conduct the remainder of the BL assessments.

For participants who do not meet eligibility criteria, we will inform the individual without

stating specific reason for exclusion. We will provide referrals to the community upon request.

Baseline Assessments – Phases 2 and 3

Remaining Baseline1 assessments include:

- TRAQ
- TSK
- Self-Efficacy for exercise
- Logistic Factors (from Cardiac Rehabilitation Barriers Scale)
- BREQ-2
- WHOQOL-BREF
- PROMIS® Depression Scale
- PROMIS® Anxiety Scale
- ASI
- Penn Craving Scale
- Demographics

Randomization

Allowable window between BL1 and randomization is 14 days. Participants are considered enrolled after randomization. The participant is invited to begin the study intervention within 1 week of randomization.

Payment

Payment to participants for completion of this visit is $10.

6.2.3 Blinding

Follow-up assessments will be conducted by research staff who are blind to which arm participants were randomized. See table on next page.

Personnel	Role	Site	Blind?	Description of activities/ reason for status
Uebelacker, Lisa	MPI	Butler	Yes	
Abrantes, Ana	Co-I	Butler	No	Will serve as an Investigator who is not blind, and available to consult with project manager or other staff about a) SAE reports that may relate to randomization; b) other randomization-related activities or problems
Caviness, Celeste	Project manager	Butler	No	Will supervise randomization, conduct unblinded data audits at both sites, and prepare unblinded reports
Herman, Debra	Project manager	Butler	No	Will supervise randomization, conduct unblinded data audits at both sites, and prepare unblinded reports
Anderson, Bradley	Study statistician	Butler	Yes	
Audet, Daniel	Data manager	Butler	Yes	Will work with Dr. Anderson to provide blinded reports; will serve as back-up to blind RA at CODAC
TBN	Research assistant	Butler	Yes	Will assist with recruitment (pre-randomization) and conduct follow-up assessments at CODAC
TBN	Research assistant	Butler	No	Will recruit participants and facilitate randomized intervention components at CODAC
TBN	Consultant --Lead yoga instructor	Butler	No	Will provide supervision to yoga instructors re: 1:1 visits
Guastaferro, Kate	Consultant – MOST expert	Butler	Yes	
TBN	Yoga instructors (n=3)	Butler	No	Providing 1:1 visits
Stein, Michael	MPI	BU	Yes	
Taylor, Lynn	Site PI	CODAC	Yes	
Sprecht-Walsh, Sophie	Site coordinator	CODAC	No	Will serve as back-up to non-blind RA at CODAC
Bordeau, Alisha	CFO/ research administration	CODAC	Yes	
Tremont, Geoffrey	Co-I	RIH	No	Will provide supervision to yoga instructors re: 1:1 visits
Saper, Robert	Site PI	BMC	Yes	Oversee all recruitment, eligibility, consent, intervention, and data collection activities at BMC
D'Afflitti, Joanna	Co-I	BMC	Yes	Primary role in recruitment and consultation regarding any issues related to OAT treatment and eligibility
Lorin, LucyHoward, Jessica	Project manager	BMC	Yes	Subcontracts, invoices, oversee research staff
TBN	Research assistant	BMC	Yes	Will assist with recruitment (pre-randomization) and conduct follow-up assessments

TBN	Research assistant	BMC	No	Will recruit participants and facilitate randomized intervention components
Garcia Drago, Victoria	Yoga instructor	BMC	No	Providing 1:1 visits

6.2.4 Follow-up Visits

For the purposes of targeting dates for an assessment, we will consider each month = 28 days (4 weeks exactly). For all follow-up assessments, research staff will make every effort to conduct the assessment within one week before or one week after the exact due date of the assessment. However, because all data can be analyzed with modern statistical methods regardless of whether it was collected inside that window, RAs will still collect data if possible even if it is later than that two-week window. We will record optimum date for the assessment (e.g., Enrollment + 84 days for M3 assessment) as well as the actual date of the assessment. Note that we will attempt to conduct follow-up visits in person, but if that is not possible, we will collect data via telephone and a REDCap link, or via telephone only (if participant does not have access to a computer/ smartphone, e.g., pre-randomization, or at M6 or M12 follow-up).

Phase 1 and Phase 2 Visits:

- Weekly for 12 weeks
  - Study classes/groups
  - Homework Questionnaire
  - Injuries due to yoga
  - CEQ (after initial class only)
  - Any other AEs reported to RAs

- Month 1
  - Any other AEs reported to RAs
  - TSK
  - Self-efficacy for exercise
  - Logistic Factors
  - BREQ-2
  - BPI
  - NRS
  - ASI
  - Penn Craving Scale
  - Payment: $20

- Month 2
  - Any other AEs reported to RAs
  - TSK
  - Self-efficacy for exercise
  - Logistic Factors
  - BREQ-2
  - BPI
  - NRS
  - ASI

- Penn Craving Scale
- Payment: $20

- Month 3 (Final evaluation for Phase 1)
  - Any other AEs reported to RAs
  - TRAQ
  - TSK
  - Self-efficacy for exercise
  - Logistic Factors
  - BREQ-2
  - BPI
  - NRS
  - WHOQOL-BREF
  - PROMIS® Depression Scale
  - PROMIS® Anxiety Scale
  - ASI
  - Penn Craving Scale
  - SAFTEE
  - Chart Review
  - Qualitative Exit Interview (Phase 1 only)
  - Payment: $30

Phase 2 Visits Only:

- Month 6
  - Homework questionnaire
  - Any other AEs reported to RAs
  - TRAQ
  - BPI
  - NRS
  - WHOQOL-BREF
  - PROMIS® Depression Scale
  - PROMIS® Anxiety Scale
  - ASI
  - Penn Craving Scale
  - Chart Review
  - Payment: $30
  -
- Month 12 (Final evaluation for Phase 2)
  - Homework questionnaire
  - Any other AEs reported to RAs
  - TRAQ
  - BPI
  - NRS
  - WHOQOL-BREF
  - PROMIS® Depression Scale
  - PROMIS® Anxiety Scale
  - ASI
  - Penn Craving Scale

- Chart Review
- Payment: $40

6.2.5 Completion/Final Evaluation

Even if participants drop out of study treatment, we will attempt to collect data at all assessment points if participants agree to it.

7. SAFETY ASSESSMENTS

For yoga, the only expected adverse event is:

- Physical injury (mild). This includes mild aches or pain during or shortly after yoga classes.

Risks of study participation include:

- Perception of coercion
- Loss of privacy or breach of confidentiality
- Increased distress due to intervention or assessment procedures
- Physical injury

Risks and measures to reduce those risks are detailed below.

Perception of coercion to participate in the study. The risk of potential coercion will be minimized by following standard procedures for obtaining informed consent. All patients will be instructed that their decision as to whether to participate in the study will not influence their current or future standing with Butler Hospital, CODAC, or BMC. They will also be informed of their right to withdraw from the study at any time.

Confidentiality and loss of privacy. Breach of confidentiality is highly unlikely because all data are identified only by numeric code and are stored in locked file cabinets or secure databases. A master list of names and numbers is kept in a separate database and is used to facilitate the collection of follow-up data. Only research staff at the relevant sites will have access to the master list linking names and code numbers. All staff are or will be fully trained in relevant ethical principles and procedures, particularly around confidentiality and protection of human subjects. All assessment and treatment procedures will be closely supervised by the project's professional staff. All recordings will be erased upon completion of data analysis. The investigative team will strictly adhere to the guidelines for research outlined by the Butler Hospital's Institutional Review Board (IRB), Rhode Island State law, and the DHHS Federal Policy for the Protections of Human Subjects (45 CFR, Part 46).

All data collected will be entered into an electronic database which is stored on a secure server (REDCap) that is backed up on a daily basis. Patient identifying information will be stored in a separate database and will be password protected and stored on a secure server. All paper files will be kept in a locked filing cabinet. Audio recordings will be stored on a secure server or kept in a locked filing cabinet. No subject will be identified in any report of the project.

REDCap is a secure, web-based application developed by Vanderbilt University for building and managing surveys and databases. It is primarily designed to support online or offline data capture for research studies, quality improvement, and operations. REDCap provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records),

real-time data entry validation, and an automated export mechanism to common statistical packages.

Care New England's instance of REDCap is hosted within the Care New England data center in Warwick, RI. This REDCap instance is role-based and is fully integrated with CNE's Active Directory structure. It enjoys 24/7/365 enterprise-level support and security inherit to CNE's HIPAA-compliant data center. Network transmissions (data entry, survey submission, and web browsing) to and from REDCap are protected via TLS 1.2 encryption. REDCap's data is stored on encrypted servers within CNE's data center.

The REDCap Consortium is composed of thousands of active institutional partners in over one hundred countries who utilize and support REDCap. REDCap was developed specifically around HIPAA-Security guidelines, and more information about the consortium and system security can be found at http://www.projectredcap.org/.

Due to the nature of text messaging technology and email, there is a small, but potential, privacy risk when communicating through text messages or email messages. Text or email message communications are not encrypted and therefore this information can be read if intercepted while in transit. Although we have a strict patient confidentiality policy there is a possibility for the text messaging or email communications to be intercepted or accessed without the participant's authorization. This will be made clear in the informed consent process, and we will remind participants not to send sensitive information by text or email. It is important to note that we will only be conveying general information by text messaging or email. No confidential or sensitive personal information will be sent by text message at any time. Email messages may include links to REDCap. Text messages will be sent from a dedicated password-protected study cell phone; email will be sent from a carene.org account or an account at the site (e.g., BMC.org). The loss of privacy is a serious risk but we believe that it is highly unlikely as we have extensive experience taking measures appropriate to safeguarding confidential information.

For streaming video classes, we will choose a secure, HIPAA compliant video service such as Zoom. Classes will be monitored to ensure that people who should not be a part of the class do not enter electronically. We will ask participants to find as private a space as possible for their real-time yoga classes, and we will make sure all participants are aware of the possibility of a breach of privacy if another participant disclosestheir identity outside of the context of class. (This breach of privacy is possible in in-person classes as well). All participants will be asked to keep the names of other participants in their class confidential.

Protections against increased distress due to assessment or intervention procedures. The risks of possible distress due to the assessment and treatment procedures will be minimized by: a) using assessments and procedures which have been widely used in previous clinical and research studies; b) training yoga instructors in how to minimize and manage distress that may occur in class; and c) having study investigators with medical or psychology degrees available to counsel participants should they report experiencing distress.

Protections against risk of physical injury. The risk of physical injury will be minimized by: a) excluding participants with contraindicated medical conditions; and b) requiring all instructors to be certified yoga teachers with experience in directing people in how to achieve yoga postures without physical injury; and c) giving all participants a guidebook that explains safer ways to engage in yoga practices. Class content will be designed to accommodate the needs of yoga-naïve students who are not currently physically active. By presenting modifications of all postures, and by using props (e.g., chairs, blocks), the risk for injury will be minimal. We will

not use postures in this study that are most commonly associated with adverse events, such as headstands, shoulderstands, or handstands.

Potential Benefits

The direct benefits to participants include the possibility of enjoyment of yoga classes and decreased pain. By participating in the clinical research project, participants may benefit from the additional contact with research staff that they will receive. The participant will be contributing to scientific research on optimizing dosage of yoga to the greatest degree possible in an OAT population. Given this level of risk(s) to the patients and the likelihood that some will benefit and the even greater possibility of benefits to the larger population of individuals in OAT through scientific gain, the risk/benefits ratio seems favorable.

Risk-Benefit Ratio.

We believe that most serious risks (e.g., loss of confidentiality, major psychological distress due to study participation, or serious physical injury due to yoga participation) to subjects are very unlikely. We have attempted to minimize these risks (described above). While some risks may be more likely to occur (e.g., minor, transient psychological distress), these risks are much less serious. Therefore, the potential benefits of the proposed study seem to outweigh the potential risks of this study for the individual participants.

7.1 Specification of Safety Parameters

Table 2 Assessment and Management of Safety Issues

Safety Issue	How assessed	When Assessed in Phase 2/Phase 3	Relevant Research Staff Actions
Injuries due to yoga	Structured self-report	Weekly during first 3 months	Follow until resolution; may result in changes to yoga instructor manual
Other AEs	SAFTEE Participant report to research staff	M3 BL, M3, M6*, M12* Any point	If related to study participation, follow resolution; potential changes to procedures particularly if AE is also unexpected

*Phase 2 only

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

See Table 2

7.3 Adverse Events and Serious Adverse Events

Adverse Event (AE) definition: An adverse event (AE) is any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at

baseline, appears to worsen. Adverse events are to be recording regardless of their relationship to the study intervention.

Serious Adverse Event (SAE) definition: A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred; includes a suicide attempt or drug overdose)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Study staff will record all reportable events with start dates occurring any time after informed consent is obtained at least until the final day of study participation. Each time participants attend a yoga class, we will inquire about injuries due to yoga. For all participants in either the Phase 1 or 2, at Month 3 (end of intervention), study staff will administer the SAFTEE in order to inquire about the occurrence of AE/SAEs during the previous 3 months. This allows us to systematically assess number of adverse events, severity, and resulting impairment. Finally, any time a participant reports an adverse event to any staff member, a research assistant will contact the participant to ascertain information for recording of the adverse event. For adverse events ascertained by any of these three possible methods, the research assistant gets information on what happened, start and stop dates, severity, functional impact, interactions with healthcare professionals, perceived cause, and possible relation to study participation. With this information, Dr. Taylor or Dr. Saper, with input from Drs. Stein or Uebelacker, will code severity, causal relationship, and whether the event was expected. If necessary, staff will seek further information from the participant or other sources before coding. AEs will be coded on a weekly basis. Any potential SAE will be immediately reviewed by one of the MPIs or site PIs (or a qualified designee in their absence) and coded; this coding will subsequently be reviewed by the Safety Monitoring Committee (SMC).

7.4 Reporting Procedures

Reporting for Multi-Center Trials

The site PI must immediately report to the coordinating center MPIs any serious adverse event that is possibly study related within 48 hours of PI awareness of the event. Unrelated SAEs must be reported within 7 days.

The site PI must also report any unanticipated problems (see below) within 48 hours of PI awareness of the event. The Site PI must also report any protocol violations to the coordinating center PI within 7 days of PI awareness. Participating centers must also submit all reports to their local IRB in accordance with their institutional policies.

AE/SAE Reporting

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Safety Monitoring Committee (SMC), IRB, and NCCIH in accordance with requirements. We will use the Butler Hospital IRB-approved AE report form.

- Unexpected fatal or life-threatening SAEs related to the intervention will be reported to the IRB, NCCIH Program Officer, and SMC within 3 days of the investigator becoming aware of the event. Other serious and unexpected SAEs related to the intervention will be reported within 7 days. These timeframes follow guidance from NCCIH and are consistent to local IRB policies.

Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the SMC, IRB, and other oversight organizations in accordance with their requirements, and will be reported to NCCIH on an annual basis.

- Unrelated SAEs that are fatal or life threatening must be reported to the Butler Hospital IRB within 7 days of the investigator becoming aware of the event.
- Unrelated SAEs that are not fatal or life-threatening must be reported to the Butler Hospital IRB annually.

All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the SMC. The SMC Report will state that all AEs have been reviewed.

Unanticipated Problem Reporting

OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;

- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are not SAEs will be reported to the IRB, SMC, and NCCIH within 14 days of the MPIs becoming aware of the problem.
- See above for SAE reporting.

All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the MPIs.

7.5 Follow-up for Adverse Events

Any SAEs related study participation will be followed for outcome information until resolution or stabilization. Follow-up reports will be submitted to the IRB, SMC, or NCCIH as required in each specific instance.

7.6 Safety Monitoring

NCCIH requires that all Human Subjects research studies undergo independent monitoring, and NCCIH Program Officials will provide specific guidelines to the PI for the study.

8. INTERVENTION DISCONTINUATION

Participants will be discontinued from an intervention in the following circumstances:

- If a participant, their primary care provider, or their OAT provider does not believe it is in the best interest of the participant to continue. As soon as an MPI or site PI is informed of this, they will speak with the participant about discontinuation. There may be circumstances (e.g., worsening pain, an injury in yoga class) when the MPI reaches out to a primary care provider, OAT provider to actively inquire if they have concerns about the participant continuing to participate.
- If a participant chooses to discontinue attendance.
- If one of the MPIs or site PIs, in consultation with the relevant instructor, finds the participant to be so disruptive to the rest of the class that they have a repeated and substantive negative impact on the other participants.
- If a participant knowingly compromises the confidentiality of another class participant.

Participants will continue with subsequent assessments with their permission. Assessment schedule and assessments used will not change.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The overall goal of this balanced factorial optimization trial is to develop a yoga intervention package that is optimized for achieving maximal "dosage" of yoga received.

We will document feasibility and acceptability of a yoga program for chronic pain at two new recruitment sites and develop a yoga intervention optimized for maximizing the dose of yoga received. We will also examine mechanisms by which components may serve to increase yoga dosage received.

9.2 Sample Size and Randomization

In RCTs a conclusion is made regarding the effect of intervention based on rejecting the null hypothesis with Type I error < some predefined α. In contrast, in an optimization trial, a decision is made to include or exclude specific components in an intervention that will be tested in a future RCT. In this scenario, Type II error may be as pernicious as Type I error. Therefore, based on recommendations of Collins [30] this study will be powered with $\alpha/2 = .10$. Because intervention effects are uncorrelated (or nearly uncorrelated if the design is not perfectly balanced), the alpha will not be corrected for multiple comparisons and all effects have equal statistical power. Assuming approximately 17% attrition for our primary outcome of dosage, we estimated power for n= 158 (192-34). To estimate the minimum detectable effect size we assumed a small correlation (r = .15) between recruitment site and yoga attendance and used the FactorialPowerPlan [31] macro in R. The proposed design has sufficient power ($1 - \beta > .80$) to detect a standardized difference in means of .40 or larger. Power to detect a medium standardized effect (d = .50) is > .90.

9.2.1 Treatment Assignment Procedures

Eligible individuals who consent to participate will be randomly assigned to one of 16 study conditions (Table 3). Our study statistician who has no contact with study participants and will have no access to outcome data until database lock, will create randomization tables using Microsoft Excel and upload to our data collection system (REDCap) prior to the start of recruitment for Phase 1. Because this is a 16-cell design, we will not stratify by any variables at baseline. Block size is effectively 12 (i.e., number of participants per cell.)

Study staff will not have access to randomization tables. When a person is deemed eligible, study staff will verify the stratification variables in REDCap and then click the "RANDOMIZE" button.

For Phase 1, given there are few participants, we want to ensure that each site has an opportunity to pilot each intervention component and certain key combinations.

Table 3. Balanced Factorial Design Assessing Four Candidate Intervention Components						
	COMPONENT				Phase 1	Phase 2
Cell	1	2	3	4	n	n
1	No	No	No	No	1	12
2	No	No	No	Yes	1	12
3	No	No	Yes	No	1	12
4	No	No	Yes	Yes	1	12
5	No	Yes	No	No	1	12
6	No	Yes	No	Yes	1	12
7	No	Yes	Yes	No	1	12
8	No	Yes	Yes	Yes	2	12
9	Yes	No	No	No	1	12
10	Yes	No	No	Yes	1	12
11	Yes	No	Yes	No	1	12
12	Yes	No	Yes	Yes	2	12
13	Yes	Yes	No	No	1	12
14	Yes	Yes	No	Yes	1	12
15	Yes	Yes	Yes	No	2	12
16	Yes	Yes	Yes	Yes	2	12

9.3 Definition of Populations

All data analysis will use the intent to treat population and use all available data. There is no per protocol analysis planned.

9.4 Interim Analyses and Stopping Rules

9.4.1 Interim Analysis

There are no interim or futility analyses planned.

Data analysis of Phase 1 data will occur during and immediately after data collection in Phase 1.

Data analysis of Phase 2 data will occur after data collection in Phase 2.

9.4.2 Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

9.5 Outcomes

9.5.1 Primary/Proximal Outcome

Phase 1 is a pilot study to assess feasibility. The primary aims and outcome assessments are shown in Table 4 below.

Table 4. Targets for Phase 1 Pilot Study.		
Feasibility Area	Method of assessment	Target at each site
Recruit participants	Number recruited per month	Recruit 10 participants in 4 months.

Train yoga teachers to fidelity	Teacher fidelity scale	Each teacher demonstrates >80% fidelity on final 3 classes rated.
Randomize participants to intervention components and correctly administer these components	Randomization errors; receipt of incorrect intervention components	No errors/ incorrect components received in 2nd half of participants randomized.
Collect follow-up assessments	Percent of follow-up assessments collected (for M1, M2, and M3)	≥ 70% with sufficient data collected on dosage; ≥ 70% of other follow-up assessments collected, including chart reviews

The proximal outcome of Phase 2 is yoga dosage received. This will be calculated by adding total number of minutes per week in the study yoga class and total number of minutes per week in personal practice (or outside yoga classes). Research staff will take attendance at study yoga classes, and, in the event someone does not attend the entire yoga class, will record the number of minutes present in class. We will measure personal practice using the Weekly Personal practice Questionnaire.

9.5.2 Secondary/Distal Outcomes

Consistent with the U01 mechanism, our focus in this study is NOT on the distal outcomes; rather, it is on yoga dosage received. However, we will collect distal outcome data to demonstrate feasibility of data collection for future research. Distal outcomes include: Pain interference, Pain Severity, Quality of Life, Depression, Anxiety, Substance Use, Retention in OAT, and Opioid Craving. The primary outcome for a future efficacy study will be pain interference.

9.6 Data Analyses

Phase 1 Data Analysis: See Section 9.5.1

Phase 2 Data Analysis: We plan to assess 4 candidate intervention components for possible inclusion in an optimized intervention that will be evaluated in a future RCT. To do so, we will use a balanced factorial ANOVA illustrated in Table 2. Each component will have two conditions producing a $2^4 = 16$ cell design with 4 main effects, 6 possible 2-way interactions, 3 possible 3-way interactions, and 1 possible 4-way interaction. In a fully balanced design using effect coding (not dummy coding), all effects in the model are uncorrelated and the n for each condition for all effects is N/2 (i.e., 96 without attrition; 79 estimated with 17% attrition for this primary outcome). Note that specific cells are not compared against other specific cells.

We will use a general linear model with each candidate component coded using effect (1 vs -1) coding. Recruitment site, sex, age, and OAT type will be covariates. The pragmatic exigencies of field research will likely result in imperfect balance (e.g., individual cells may have slightly varying n). However, we anticipate only very small variations in cell sizes and thus estimated model coefficients will be nearly, but not perfectly, uncorrelated.

To augment traditional frequentist statistics and facilitate interpretation we will calculate the Bayes factor. Based on the observed data, a Bayes factor estimates the strength of evidence supporting one hypothesis (model) in favor of a competing hypothesis (model).[32]

We will track which classes each participant attends, and who teaches each class. As a sensitivity analysis, we will include not only site as a fixed effect, but also teacher. We will include a dummy variable for each teacher to represent whether or not the participant had exposure to that particular teacher (i.e., took at least one class with that teacher).

Determination of Final Intervention Components:

Goal: To determine which components will be included in the final, optimized intervention package.

Components:
All participants: attendance at 1 class (with 2 time choices) per week; materials for personal practice

1. Personal practice videos featuring study yoga teachers
2. Initial and 1-month 1:1 session with a yoga teacher
3. Text messages cuing personal practice
4. Monetary incentives for class attendance

Once data collection is complete, we will convene a meeting (or conference call) to make decisions about which intervention components should be included in the final intervention package. Participants in this meeting will include:

1. MPIs and co-Is and consultant Dr. Guastaferro;
2. Selected NCCIH staff (e.g., PO); and
3. Selected yoga instructors

At this meeting we will review all data collected.

Step 1: For each intervention component, we will first review the main and 2nd order interaction effects from the factorial experiment on the primary outcome of number of yoga minutes per week. We assume data will be missing at random. Missing data will be addressed using multiple imputation by chained equations.[33] Because the goal is intervention optimization, retention of components will not be based on a single criterion. We will initially choose to include all components for which there is a main or sympathetic interaction effect with a) an effect size (SMD) of 0.40 (estimated, based on preliminary data, to be 31 mins of yoga per week) or greater favoring the component; OR b) $p < .10$ favoring the component OR c) if the estimated Bayes factor provides substantial or stronger evidence preferring the intervention hypothesis to the hypothesis of no treatment effect. (See below for more information on Bayes factor).

Special cases:

1. Of monetary incentives for class attendance, we will look specifically at class attendance. If monetary incentives increase class attendance, and do not decrease overall minutes of practice, we will choose to include.
2. 3rd and 4th order interactions may be tricky to interpret. We will look at them, but place priority on main effects and 2nd order interactions in making decisions.
3. It is possible that 2nd order interactions may be antagonistic where the combination of two or more components is less effective than would be expected based on the main effects alone. At the same time, there may be significant positive main effects for both components. In this case, we will examine graphical depictions of results in order to determine whether to include both of the two components in question.

Step 2: All components that pass Step 1 will then be examined in light of their feasibility and acceptability. Data that bear on feasibility and acceptability include:

1. Participants' responses to qualitative interviews
2. Yoga instructors' experiences (field notes)
3. Feedback from administrators/ clinicians at sites [from field notes (clinicians) and structured interviews (key administrators)]
4. Adverse events determined to be related to a given component
5. Number of 1:1 sessions attended (relevant for the 1:1 session intervention component only); use of personal practice videos (relevant for the personal practice video component only). We note that even one 1:1 session, or a small amount of use of personal practice videos, could have an impact on pain interference or other relevant outcomes.
6. % of follow-up assessments completed (not expected to be different between groups; we would consider a difference of 15% in proportion of participants observed at M3 to be of concern, and would likely be a statistically significant difference)

In determining feasibility, each component that passed Step 1 will be determined to be:

1. Acceptable and feasible without any changes.
2. There are minor changes that we judge do not affect the core nature of the intervention that we can make to increase acceptability and feasibility to a higher level (e.g., 1:1 meetings were scheduled for 45 minutes but everyone agrees that 30 minutes was adequate and even preferable).
3. Not acceptable/ feasible.

Step 3. All components that passed Step 1 and Step 2 will be included in the final optimized intervention. We will make minor changes to components if indicated in Step 2.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Most data will be collected and entered directly into REDCap. Data collected on paper CRF will be double-entered into REDCap. There will also be a database that we will use for tracking participants.

Any data, forms, reports, audio recordings, and other records that leave either recruitment site will be identified only by a participant identification number (Study ID, SID) to maintain confidentiality. All paper records will be kept in a locked file cabinet. All data collected will be entered into an electronic database which is stored on a secure server (REDCap) that is backed up on a daily basis. Participant identifying information will be stored in a separate REDCap database. Care New England's instance of REDCap has been deemed HIPAA compliant by CNE Information Technology.

10.2 Data Management

All data will be collected via REDCap. Paper CRFs, when collected, will be double-entered into REDCap. The Data Manager, Mr. Audet will oversee the REDCap database. Any discrepancies will be resolved by the Project Manager in consultation with the MPIs as needed.

Please see also “Data Handling and Record Keeping” in the DSMP.

10.3 Quality Assurance

10.3.1 Training

All research personnel, including yoga instructors will have formal training in research with human subjects (e.g., CITI training, NIH Human Subjects training). Drs. Stein, Uebelacker, Saper, Taylor, Caviness, and Herman, and Ms. Howard will provide training to and supervise research assistants. Research assistants will also have training in Good Clinical Practice. Drs. Uebelacker and Tremont will provide training and supervision to yoga instructors.

10.3.2 Quality Control Committee

Drs. Uebelacker, Stein, Saper, Taylor, Herman, and Caviness will be responsible for quality control of this study. They review recruitment and retention reports, and AE reports, on weekly basis.

10.3.3 Metrics

Protocol Deviations

During weekly study meetings, protocol deviations will be discussed with the MPIs, including plans for corrective action. Drs. Caviness or Herman (at CODAC) or Ms. Howard (at BMC) will also be alerted to deviations as they occur and will alert the MPIs for any deviation requiring immediate action. Protocol deviations will be logged on the protocol deviation tracking sheet and filed in the regulatory binder.

All assessment time points have a window of time for completion. However, typically due to circumstances outside of the control of the research staff, assessments occasionally occur outside of that window. Assessments that occur outside of the recommended window for completion will be considered to be protocol deviations, and will be logged as such.

Protocol deviations will be reported to NCCIH once per year, in the annual review. The SMC will also receive a list of protocol deviations in their interim or annual reports. Per Butler Hospital IRB policy, “major protocol deviations/violations, defined as those which increase risk to participants” will be reported promptly to the IRB and no more than 10 working days after the investigator is aware of the event. Minor protocol deviations do not need to be reported.

10.3.5 Monitoring

Dr. Caviness or Herman will conduct protocol and data quality monitoring twice a year at each study site using the Quality Management review checklists. During Phase 1, all participant and other study records will be reviewed. During Phase 2, a random sample of 10-20% of participant and study records will be reviewed at each monitoring time point.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent documents and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. The consent form should be separate from the protocol document.

11.2 Informed Consent Forms

Informed consent will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record.

11.3 Participant Confidentiality

Any data, forms, reports, audio recordings, and other records that leave the site will be identified only by a participant identification number (Study ID, SID) to maintain confidentiality. All paper records will be kept in a locked file cabinet. All data collected will be entered into an electronic database which is stored on a secure server (REDCap) that is backed up on a daily basis. Participant identifying information will be stored in a separate database and will be password protected and stored on a secure server. Care New England's instance of REDCap has been deemed HIPAA compliant by CNE Information Technology.

Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NCCIH, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

There will be a Safety Monitoring Committee.

13. PUBLICATION OF RESEARCH FINDINGS

Drs. Stein and Uebelacker will be responsible for oversight and approval of any publications or presentations that arise from this research.

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15. SUPPLEMENTS/APPENDICES

None