Program to Overcome Pelvic Pain Study (POPPY)

(a.k.a. A Feasibility Trial of a Group Based Yoga Intervention for Chronic Pelvic Pain in Women)

Protocol Number: 1.0

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Principal Investigator: Alison J. Huang

Institution: University of California San Francisco

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CONFIDENTIALITY STATEMENT

Acceptance of this confidential document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

This trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, and 21 CFR Part 56).

Investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of this clinical trial will have completed Human Subjects Protection and ICH GCP Training.

The trial protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval before any participant is enrolled in the study. Any amendment to the protocol will undergo review and approval by the IRB before the changes are implemented to the study.

All changes to the consent form(s) will also be approved by the IRB before implementation. At that time, a determination will be made regarding whether a new consent needs to be obtained from participants who previously provided consent using an earlier approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator: Alison Huang

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

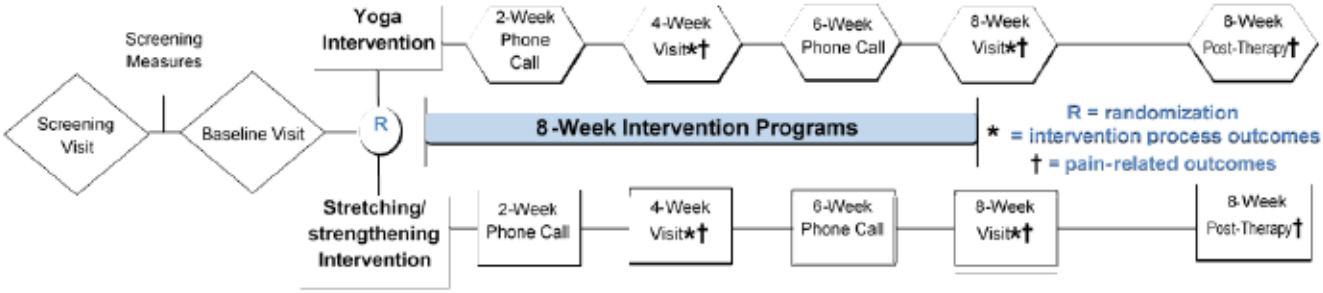
Title:	Program to Overcome Pelvic Pain Study (POPPY) (a.k.a. A Feasibility Trial of a Group Based Yoga Intervention for Chronic Pelvic Pain in Women)
Grant Number:	R34AT010356
Study Description:	Pilot, randomized, parallel-group trial of a group-based therapeutic yoga program versus non-specific muscle stretching/strengthening program for women with chronic pelvic pain.
Objectives*:	To evaluate the feasibility of procedures for a future full-scale rigorous efficacy trial of a group-based therapeutic yoga intervention for women with chronic pelvic pain.
Endpoints*:	Outcomes of this feasibility trial include: a) rates of participant randomization, retention, and adherence to study interventions; b) participant self-efficacy and observed competence in performing study-specific intervention techniques by the end of the intervention program; and c) completeness and quality of data obtained from pain-related outcome measures.
Study Population:	Women aged 18 years and older from the general San Francisco Bay Area who report pelvic pain for at least 6 months, are not participating in other organized activities involving yoga or muscle conditioning exercises, are willing to temporarily forgo using other clinical treatments for pelvic pain, and meet minimum mobility and other clinical eligibility criteria.
Description of Study Sites	Study personnel are based at two study locations (San Francisco, CA, and Oakland, CA) affiliated with the University of California San Francisco and one study location (Redwood City, CA) affiliated with Stanford University.
Description of Study Interventions:	Participants are randomly assigned to take part in either an 8-week group-based yoga intervention consisting of twice-weekly group class instruction and at least once-weekly home practice of alignment-based yoga techniques, or an 8-week group-based physical conditioning intervention consisting of time-equivalent group class instruction and home practice of non-specific muscle stretching and strengthening exercises. For both study arms, the majority of intervention classes will use a Zoom-based videoconference platform designed to maximize participant convenience and safety.

Study Duration: Total study duration is estimated at 20 months from the start of enrollment to the completion of data collection activities.

Participant Duration: Estimated time spent by participants in the study is 18-20 weeks, including 2-4 weeks for completion of screening activities, 8 weeks for participation in study interventions, and 8 weeks of post-intervention follow-up.

1.2 SCHEMA

The following diagram summarizes the structure of assessments in this clinical trial:



1.3 SCHEDULE OF ACTIVITIES

Overview of Major Measures and Procedures at Study Visits							
	Screening Visit	Baseline Visit	2-Week Phone Call	4-Week Visit	6-Week Phone Call	8-Week Visit	8 Weeks Post-intervention
Informed consent (and HIPAA waiver if needed)	X						
Demographic, medical, and reproductive/sexual history	X						
Pelvic pain and pain-related history	X						
Self-reported physical function and activity	X						
Assessment of internet access and computer/device proficiency							
Review of prescription and OTC medications	X			X		X	X
Assessment of use of co-interventions	X			X		X	X
Trauma history and PTSD symptom measures		X*					
Alcohol, tobacco, and substance use forms		X*					
Daily pain log return and blinded data abstraction		X*		X		X	X
Pain-related impact questionnaires		X*		X		X	X
Anxiety, depression, and sleep measures		X*		X		X	X
Pain-related cognitions and self-efficacy measures		X*		X		X	X
General physical examination measures		X					
Urinalysis and urine pregnancy testing		X					
Optional pelvic floor tenderness and tonicity assessment		X†					
Physical performance assessment		X		X		X	
Review of eligibility and randomization		X					
Yoga/stretching self-efficacy questionnaires		X*		X		X	X
Competency evaluation by yoga/PT consultant				X		X	
Adverse events and safety assessment			X	X	X	X	X
Assessment of satisfaction with interventions						X	

*To be completed by participants between the Screening and Baseline Visits and returned at the Baseline Visit

†Optional assessment that may be performed at an alternate time agreed upon by the participant and assessor

2 INTRODUCTION

2.1 STUDY RATIONALE

One in ten U.S. women suffer from chronic pelvic pain, a syndrome that can lead to depression, social isolation, physical inactivity, sexual dysfunction, and dependence on or abuse of pain medications. Unfortunately, current clinical treatment strategies for chronic pelvic pain, including pain medications and invasive procedures, have limitations that decrease their efficacy, safety, and accessibility for many women suffering from pelvic pain in the community.

Yoga is a complementary set of physical and mental practices with the potential to improve multiple contributors to chronic pelvic pain and pain-related disability. When practiced in a way that emphasizes careful anatomic alignment, mindful awareness of bodily structures, and deep breathing during the practice of yoga postures, yoga can help women with chronic pelvic pain to identify and relax the muscles of the pelvic floor, manage their co-morbid depression and anxiety, and help them overcome their fear-avoidance of physical activity.

To explore the potential benefits of yoga for this indication, the investigative team previously collaborated with a panel of expert yoga consultants to develop a group-based therapeutic yoga program for female chronic pelvic pain, consisting of twice-weekly group classes supplemented by home yoga practice.[1] After pilot-testing this program in a small sample of women, we are now evaluating the feasibility of conducting a future rigorous, multisite, randomized trial of the efficacy and tolerability of a refined version of this yoga intervention in women with chronic pelvic pain. In contrast to our prior research that required women to travel twice a week to attend yoga classes in person, this follow-up pilot study now explores a refined version of the yoga intervention that is taught through interactive, on-line, videoconference-based classes.

Specifically, this pilot trial is designed to assess the feasibility of: a) recruiting, randomizing, and retaining women with chronic pelvic pain from multiple northern California locations into a randomized trial of 8-week yoga intervention versus a non-specific muscle stretching and strengthening intervention, b) teaching women to practice study-specific intervention techniques through a combination of group classes and home practice, and c) collecting high-quality data from multiple pain-related outcome measures. If successful, this pilot trial will prepare the investigative team to launch a future, full-scale trial to provide rigorous evidence of the efficacy and safety of yoga as a community-based management strategy for chronic pelvic pain in women.

2.2 BACKGROUND

Chronic pelvic pain is a common, debilitating, and costly syndrome that goes untreated in many women. Approximately one in ten women suffer from continuous or intermittent pain in the pelvis or lower abdomen that interferes with their day-to-day activities, emotions, and relationships.[2,3] Among women in the community, chronic pelvic pain is associated with depression, social isolation, sexual dysfunction, physical inactivity, and

dependence on and abuse of opioids and other controlled substance medications.[4,5] Nevertheless, over half of women with chronic pelvic pain report receiving no treatments that are effective in alleviating their pain.[6-9]

Due to the multifactorial etiology of pelvic pain, treatment strategies directed at a single organ-specific process may not be effective. While many women with pelvic pain are diagnosed with gynecologic, urologic, or colorectal disorders, no specific organ-specific process is detected in up to half of women who undergo clinical evaluation for their pain.[4,10] More importantly, even when a visceral organ abnormality is identified, women tend to report persistence of pain after treatment for visceral disease,[11,12] indicating that other mechanisms are continuing to perpetuate pain in the absence of visceral stimulus. Further, many women with pelvic pain also exhibit signs of more than one organ-specific disorder,[13,14] suggesting that pain originating with trauma or inflammation in one visceral organ can generalize to other organs.[15,16] As a result, there is a need for treatment strategies that are effective in improving pelvic pain regardless of initial identifiable visceral contributors.

Even with visceral organ involvement, many women with chronic pelvic pain exhibit pelvic floor dysfunction, suggesting that treatment directed at the pelvic floor may be beneficial for this condition. In clinical studies, many women with chronic pelvic pain demonstrate pelvic floor hypertonicity, characterized by increased pelvic floor tone, decreased relaxation capacity, and lowered tenderness threshold.[17-20] Among women with visceral organ dysfunction, visceral pain can cause the pelvic floor to reflexively guard, tighten, and develop trigger points, such that the tight pelvic floor can become a secondary source of pain exacerbating underlying visceral processes. Pelvic floor dysfunction can also be a primary cause of pelvic pain in women with myofascial disorders involving the muscles or fascia of the pelvic floor, in which increased muscle tone provides the initial stimulus for pain.[20] As a result, guidelines from multiple national or international organizations recommend treatment of pelvic floor dysfunction in chronic pelvic pain, even if other visceral contributors may be present.[21-23]

Women with chronic pelvic pain also need help overcoming the cycle of pain-related anxiety leading to avoidance of activities associated with pain, inappropriate compensatory behaviors, and subsequent deconditioning. Due to fear and anxiety about their pelvic pain, women may develop problematic behavioral responses such as avoidance of physical activities, which can accelerate physical deconditioning and pain-related disability.[24,25] Women may also adopt poor posture and guarding behaviors that are initially intended to avoid pain, but can lead to overuse of compensatory muscle groups, further sensitizing other musculoskeletal areas to contribute to pain. Emotional reactions to pelvic pain may also lead to negative cognitive responses such as rumination on pain, magnification of perceived pain intensity, and pain catastrophizing that further decrease pain-related functioning and reinforce maladaptive behaviors.[26]

Existing treatments for pelvic pain are associated with problematic side effects or other limitations that decrease their effectiveness, tolerability, or accessibility. While a variety of medications are prescribed to women with pelvic pain,[27] many of these are associated with problematic side effects and diminishing benefits over time, as well as

risk of dependence or abuse.[28] For women wishing to avoid medications, physical therapy techniques such as myofascial release of pelvic floor trigger points and Thiele massage of the pelvic floor have been recommended;[29,30] however, this type of intensive, individualized physical therapy is costly, and access to trained pelvic floor therapists in the community is limited. Furthermore, while physical therapy may address important physical contributors to chronic pelvic pain, it is not designed to improve psychological factors that can exacerbate and perpetuate this syndrome.

Yoga can be used to increase women's awareness and control over their pelvic floor in order to improve pelvic pain associated with pelvic floor dysfunction. Hatha yoga, the branch of yoga that includes practice of physical yoga postures (a.k.a. asanas), has long been used by practitioners to improve overall muscle awareness and control.[31] When taught in a way that emphasizes mindful awareness of specific bodily structures during the practice of yoga postures, yoga can help women identify, stretch, and/or relax individual muscle groups, such as the muscles of the pelvic floor. As a result, a group yoga program that incorporates practice of yoga postures to promote awareness and relaxation of the pelvic floor has the potential to provide a more accessible alternative to one-on-one pelvic floor rehabilitation therapy.

Yogic breathing and restorative techniques can also alleviate anxiety, stress, and associated autonomic imbalance, as factors that increased perceived pain intensity or decrease pain-related functioning. Because women with chronic pelvic pain exhibit high rates of comorbid anxiety and perceived stress[24,32] as well as abnormalities in autonomic function associated with anxiety and depression disorders,[33-35] psychological interventions such as cognitive behavioral therapy have been explored and found to have preliminary benefits for some pelvic pain-related conditions.[24,36] However, similar to other forms of individual therapy, these strategies are limited by the need for intensive, one-on-one sessions with mental health specialists. In contrast, a group yoga program that promotes relaxation through restorative yoga techniques may provide a more generalizable strategy for women to decrease pain-related anxiety and stress[37-39] and improve autonomic function[40-43] outside of traditional healthcare settings.

Yoga may help women overcome the fear-avoidance cycle that causes them to progressively limit their activities and perpetuates their pain-related disability. A yoga intervention that features regular but gentle practice of yoga postures that involve stretching of the pelvic floor can provide a safe environment for women to overcome maladaptive behaviors arising from their pain, such as excessive avoidance of physical activities that are associated with pelvic pain. Regular yoga practice may also help women avoid progressive physical inactivity and deconditioning of other core muscle groups that can further accelerate pain-related disability.

Online or telehealth-based yoga training can increase the accessibility of yoga to women with chronic pelvic pain in the community. Although past approaches to teaching people to practice yoga for health or well-being have relied on repeated in-person classes or workshops, this type of in-person instruction requires participants to commute regularly to yoga studios to see their instructors. Unfortunately, many women with chronic pelvic pain do not live in close proximity to a yoga studio or in a community

with a high density of trained yoga instructors. Furthermore, individuals with chronic pain face special challenges in traveling or commuting outside of their homes, which creates a barrier to engaging in in-person yoga classes. In the post-COVID era, online platforms are increasingly being used to deliver yoga and other mind-body interventions, with the goal of promoting safety but also increasing availability. Online or telehealth yoga training offers a potentially efficient way to deliver yoga instruction to large numbers of women with pelvic pain in the community, provided that they have access to internet and to a computer or mobile electronic device. However, research is needed to assess whether online yoga interventions can be delivered in a way that is safe, effective in improving chronic pain, and accessible to women in the community.

3 OBJECTIVES AND ENDPOINTS

The objectives of this pilot feasibility trial are to:

1) Evaluate the feasibility of recruiting and retaining women with chronic pelvic pain in a randomized trial of an 8-week therapeutic yoga program versus non-specific muscle stretching/strengthening program.
2) Examine the success of this yoga program in teaching women to perform program-specific yoga postures and techniques, based on both their own self-efficacy and independent evaluation.
3) Examine rates of data completion/missingness, quality, and distribution from pain-related outcome measures to assess the viability of administering measures in a future full-scale trial.

To address objective 1, we will examine rates of randomization, retention, and adherence in the overall participant sample as well as within each recruitment wave and intervention arm. Specifically, we will examine the ratio of screenees to randomized women, rates of retention versus drop-out, and adherence to group intervention classes and home intervention practice.

To address objective 2, we will examine data collected from participants in the yoga intervention group to evaluate: 1) the percentage of participants who indicate they are at least “moderately” or at least “very” confident that they can perform all core postures emphasized in the program after receiving intervention instruction, and 2) the percentage of participants who are rated by the expert consultant as being at least “moderately” or at least “very” successful in performing all postures after intervention instruction.

To address objective 3, we will examine rates of completion/missingness and distribution of data from pain-related outcome measures (i.e., daily pain logs, pain interference and impact questionnaires, anxiety and depression symptom measures, sleep quality measures, and pain-related cognitions/self-efficacy measures).

4 STUDY DESIGN

4.1 OVERALL DESIGN

The Program to Overcome Pelvic Pain studY (POPPY) study is a pilot, multisite, single-blinded, parallel-group, randomized trial of a group-based therapeutic yoga intervention versus non-specific muscle stretching and strengthening control intervention in women with chronic pelvic pain. Approximately 36 women age 18 or older who report pelvic pain of at least moderate severity for at least 6 months and who meet other eligibility criteria will be recruited from northern California and screened through a combination of telephone, video, and clinic assessments. Eligible women will be randomly allocated by a computer algorithm to take part in either an 8-week therapeutic yoga program consisting of twice-weekly group classes supplemented by home practice of study-specific yoga techniques, or a physical conditioning program involving a time-equivalent schedule of group classes and home practice of non-specific muscle stretching and strengthening exercises. Participants will undergo assessments of self-efficacy and observed competence in performing study-specific intervention techniques (i.e., yoga postures or stretching/strengthening exercises) after 4 weeks and 8 weeks of intervention training. They will also complete pain-related outcome measures (including multiple questionnaires) after 4 weeks and 8 weeks of intervention training, as well as 8 weeks after the end of the intervention programs.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This feasibility trial is designed to test, refine, and evaluate procedures for a future multicenter randomized controlled trial that will evaluate the efficacy and tolerability of a group-based therapeutic yoga intervention to manage chronic pelvic pain in women. Correspondingly, the investigators have incorporated most if not all procedures expected to be included in a future, full-scale, multisite trial of this intervention in the anticipated target population.

Similar to the anticipated future full-scale trial, participants will be randomly assigned in equal ratios to either the experimental yoga practice intervention or a time-equivalent physical conditioning control intervention. The latter includes time-equivalent group instruction in and practice of non-specific muscle stretching and strengthening exercises, to promote retention and adherence among participants in the control arm and minimize reporting bias arising from participants' differential expectations of treatment success.

In a potential future efficacy trial, this same study design will allow the study team to distinguish the specific effects of yoga above and beyond non-specific physical activity-based interventions, thus providing insight into the unique benefits of yoga for chronic pelvic pain.

4.3 JUSTIFICATION FOR INTERVENTION

The study yoga intervention will consist of twice-weekly group yoga classes led by a trained instructor for 8 weeks, supplemented by at least weekly home yoga practice

outside of class. This frequency of instruction will provide intensive exposure to study-specific intervention techniques to guide participants who may be naïve to yoga at the start of the study. Instruction will also ensure that participants are introduced to all study-specific yoga techniques in the first 4 weeks of the program and then develop greater confidence in performing these techniques during the second 4 weeks. Class instruction will be supplemented by at least weekly home practice to reinforce skills acquired during classes and help participants establish a habit of home practice.

In the physical conditioning control group, participants will receive the same intensity and duration of group class instruction as women assigned to the yoga intervention, as well as the same encouragement to practice their assigned intervention at home at least weekly. This will help promote equipoise in participant expectations and study contact across both intervention groups.

For this pilot study, group class instruction in both study arms will be delivered using an online video conference platform (Zoom), which will allow participants to receive instruction from the comfort and safety of their own homes or any other private location in which they have the necessary access to the internet. In these live interactive video-conference classes, participants will be able to see, hear, and engage with their instructor and with each other in real-time, to promote a sense of community and mutual support among women seeking to overcome the shared problem of pelvic pain. The target class size will be 6 participants, which will be large enough to promote meaningful interaction and a sense of connection between participants, but small enough to allow instructors to properly observe and tailor instruction to participants by videoconference.

In this pilot study, all women who participate in at least one intervention session (including the orientation session) will be considered to have been exposed to the intervention and will be included in analyses of study retention. Women who participate in at least one intervention session and complete the 8-week study follow-up visit at the end of the intervention program will be included in analyses of adherence to study intervention classes and home practice sessions.

4.4 END-OF-STUDY DEFINITION

In this trial, participants will be considered to have completed the intervention phase of the study if they have been randomized, have attended at least one intervention session, and have completed the 8-week follow-up visit. Participants will be considered to have completed the post-intervention portion of the study if they additionally complete the 8-week post-intervention visit. The end of the overall study is defined as completion of the 8-week post-intervention assessment as shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

The target population for this study is ambulatory adult women who have chronic pelvic pain that is unlikely to be caused by an easily reversible etiology, are temporarily willing to forgo engaging in other clinical therapies for pelvic pain, are not already engaged in

organized yoga (or muscle stretching/strengthening) activities, have no major contraindications to practicing yoga or stretching/strengthening exercises, meet minimum mobility requirements, and are willing and able to complete study visits, intervention classes, and other required study procedures.

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1) Women aged 18 years or older who report chronic or recurrent pelvic pain for at least 6 months
2) Report a pain intensity score of at least 4 out of 10 (at its worst) on a screening 7-day pain log
3) Report prior clinical evaluation of pain by a healthcare professional including at least a superficial pelvic exam
4) Willing to refrain from initiating new clinical treatments that may affect their pain during the study period

5.2 EXCLUSION CRITERIA

Candidates will be excluded from participation in this study if they meet any of the following criteria:

1) Report pelvic pain occurring exclusively with menses or exclusively during sexual intercourse (note that women with at least some pain between menses or intercourse are still eligible)
2) Participation in organized yoga classes or muscle strengthening programs (e.g., Pilates) in the past month, or prior yoga therapy specifically directed a pelvic pain
3) Currently pregnant (by self-report or screening test), pregnant within the past 6 months, or planning pregnancy during the study period
4) Diagnosed with an alternate, reversible cause of pain that is unlikely to respond to yoga and requires another treatment modality (e.g., current pelvic infection or a gynecologic dermatosis)
5) Initiation, dose escalation, or weaning of pharmacologic agents that may affect pelvic pain severity in the past 1 month (e.g., pain medications, antidepressants, anticonvulsants)—note that women on stable doses will be eligible
6) Surgery to the genital or pelvic structures within 3 months, or prior cancer or irradiation to these structures
7) Use of formal psychological therapies specifically for pelvic pain (e.g., systematic desensitization, sex therapy, cognitive therapy, relaxation therapy) within 1 month of screening
8) Use of formal behavioral therapies for pelvic or genital pain (e.g., pelvic floor rehabilitation or biofeedback performed by a certified healthcare practitioner) within 1 month of screening

9) Unable to walk up a flight of stairs or at least 2 blocks on level ground (i.e., functional capacity < 4 METs), or unable to get up from a supine to a standing position without assistance
10) Participation in another interventional study that might interfere with or confound study procedures
11) Known conflict with multiple available study intervention class times, or lacking technical requirements to complete intervention classes by video
12) Inability to sign an informed consent or fill out questionnaires or complete study interviews in English

5.3 LIFESTYLE CONSIDERATIONS

During this study (both the main intervention phase and the 8-week post-intervention follow-up period), participants are asked to avoid:

- Engaging in formal yoga or physical conditioning activities outside of the study (including non-study yoga, physical therapy, or exercise classes involving muscle strengthening exercises)
- Starting, stopping, or changing the dosage of medications that could affect the severity of their pain (including opioid, neuropathic, or other pain medications, as well as psychoactive medications)
- Initiating other clinical therapies for pelvic pain—including other formal behavioral, mindfulness, or invasive or surgical interventions)

However, participants do not need to refrain from other lifestyle measures that they believe helpful for managing their pain, including dietary strategies or primarily aerobic exercise.

5.4 SCREEN FAILURES

For this study, screen failures are defined as participants who initially consent to participate in the study but are not subsequently assigned to one of the two study intervention arms. From an operational perspective, this refers to participants who provide written consent at the Screening Visit but do not go on to be randomized to the therapeutic yoga or physical conditioning intervention groups. Participants may be screen failures because they do not meet eligibility criteria or because they decline or fail to complete baseline assessments necessary for randomization.

Individuals who do not initially meet criteria for participation in this trial because they meet one or more exclusion criteria that can change or be addressed before enrollment may be rescreened before being considered to be screen failures. Examples include rescreening of an individual who has undergone successful treatment of a urinary tract infection that previously resulted in detection of hematuria on a screening urinalysis test, or an individual who completes a washout period after initiation or discontinuation of a medication that initially interfered with eligibility.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment for this study will be spearheaded in successive waves in order to assemble cohorts of approximately 12 women (6 for each intervention arm) in each wave who meet all eligibility criteria and are available for site-specific group intervention classes. For each recruitment wave, the study team anticipates a multi-month period of recruitment and screening before study intervention programs begin. Recruitment waves will be initiated approximately twice a year and will be timed so that intervention dates do not fall during major holiday periods that may interfere with attendance or adherence. The study team will complete one wave before beginning another, to ensure that the investigators can evaluate the success of recruitment and retention strategies from one wave before initiating another. At least three recruitment waves are expected to meet the study goal of randomizing 36 participants.

The study team will pursue a multi-pronged participant recruitment strategy that has been used successfully in prior pilot studies of yoga as well as other clinical trials focused on genitourinary or pelvic symptoms and/or complementary behavioral interventions in women in northern California. Recruitment will be based at three main study locations (San Francisco, CA; Oakland, CA; and Redwood City, CA) that are collectively affiliated with the two academic study sites (San Francisco and Oakland affiliated with UCSF, and Redwood City affiliated with Stanford). Specific recruitment strategies that may initially be employed (but also studied and iteratively refined or eliminated) in this study include:

- Commercial mass mailing service to send recruitment letters to households located in the zip codes surrounding the study locations that have been identified as having female household members in the target age range.
- UCSF Participant Recruitment Service to identify female patients in the target age range who have recently received care in clinics or hospitals affiliated with UCSF Health.
- San Francisco Bay Area newspapers such as The San Francisco Chronicle, The East Bay Times, or Palo Alto Weekly.
- On-line and social network recruitment such as on-line support groups for individuals with chronic pain in the San Francisco Bay Area.
- UCSF Women's Health Clinical Research Center database of former participants and/or screenees who have agreed to be contacted about future women's health research opportunities, using an IRB-approved process.
- Clinic Notice Boards and Electronic Displays at UCSF Medical Center, including notice boards in the waiting rooms of women's health or primary care clinics at UCSF.

Candidates responding to recruitment advertisements will initially be screened by telephone, and those that appear potentially eligible will be invited to take part in a Screening Visit to complete additional screening measures. Screening procedures will be completed at the Baseline Visit, at which time final eligibility for randomization will be determined (see section 8.1, Non-Safety Assessments).

Given the racial/ethnic diversity of the San Francisco Bay area, at least 25% of women randomized are expected to belong to racial/ethnic minority groups. The study team will

track enrollment of participants from racial/ethnic minority groups in each wave, to guide strategies for recruiting a diverse population of women in a future full-scale trial. This will allow the study team to determine whether some recruitment strategies (e.g., online or social network recruitment, clinic-based recruitment) or study locations are more or less successful in promoting participation by women from minority backgrounds.

The investigators anticipate that most women volunteering to participate in this study will be motivated by the opportunity to obtain free yoga or physical conditioning instruction tailored to their pelvic pain as well as free materials (yoga or exercise mats and props) to facilitate their practice of yoga or physical conditioning exercises at home. Participants will also be reimbursed up to $125 in gift cards over the course of the study, starting with the Baseline Visit and ending with the 8 Week Post-Intervention Visit. This remuneration is designed to compensate participants appropriately for their time and trouble of completing study measures without constituting undue financial influence.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTIONS

6.1.1 STUDY INTERVENTIONS DESCRIPTION

Yoga practice intervention:

The study yoga intervention is designed to provide instruction and practice in selected yoga postures and techniques chosen by an expert panel for their potential to improve pelvic pain in women as well as promote safety and tolerability in this population. The program focuses on a form of Hatha or "physical" yoga based on the teachings of B.Y. Iyengar, which is known for its potential therapeutic applications, has been employed successfully in other therapeutic studies of yoga for different clinical indications,[44-50] and differs from other Hatha yoga styles (power yoga, Bikram yoga) in ways that are likely to maximize both efficacy and safety in this study.

Particular features of this alignment-based yoga program that make it appropriate for women with pelvic pain include 1) emphasis on precise anatomical alignment during the practice of postures to maximize awareness of specific body structures, including the pelvic floor; 2) incorporation of yoga props (i.e., blocks, straps, bolsters) to accommodate those with lower strength or flexibility and minimize the risk of injury; and 3) inclusion of restorative yoga techniques and breathing exercises that may promote relaxation and improve autonomic function and response.

The yoga program, which was pilot-tested and refined after our study team's previous, pilot, single-arm, 6-week trial,[1] is designed to maximize women's awareness of and control over the pelvic floor, improve comorbid anxiety and perceived stress, and address maladaptive compensatory postural or physical behaviors, while still being feasible for ambulatory women of a wide range of ages. While tailored to women with chronic pelvic pain, the program is grounded in postures common to Hatha yoga at large, making it appropriate for future dissemination through yoga studios, women's

health centers, or other community health organizations, in the event it is eventually found to be effective and well-tolerated.

The program will focus on a set of 16 postures that are widely used in Hatha yoga practice, are potentially generalizable to yoga instruction across the country, and can be safely adapted for women of all ages, including those with decreased flexibility or mobility: Supta Baddha Konasana (reclining bounded angle pose), Viparita Karani (legs up the wall pose), Salamba Setu Banhasana (supported bridge pose), Supta Padagusthasana I (reclining hand to big toe pose), Supta Padagusthasana 2, Supta Padagusthasana 3, Ardha Ananda Balasana (half happy baby pose), Anjaneyasana variation 1 (Lunge with circular movement), Anjaneyasana variation 2 (lunge on a chair), Prasarita Padottanasana (wide-legged standing forward bend pose), Adho Mukha Svanasana (downward dog), Utkata Konasana (goddess), Malasana (squat pose), Salabhasana (locust pose), Savasana (corpse pose), leg lifts, and Bhravajasana (seated twist pose). Instruction will emphasize the practice of postures in ways likely to foster awareness of the pelvic floor, in addition to promoting deep breathing and mindfulness relaxation.

Physical conditioning intervention:

The study team has developed a low-impact, non-specific muscle stretching and strengthening program (i.e., physical conditioning program) to provide a rigorous time-and-attention control for the yoga program. These exercises avoid engaging the pelvic floor or core lower extremity muscles or promoting mindful relaxation. However, they control for the time and attention spent on group classes and home practice, are designed to be sufficiently engaging promote participant retention and adherence over 8 weeks, and provide an ethical alternative to the yoga intervention in that they may offer other general health benefits.

The stretching/strengthening exercises have been adapted from control exercises used in prior NIH-funded studies of yoga (also involving Sarah Pawlowsky, DPT, expert consultant on this proposal[51,52]), including a pilot trial of a different yoga program for urinary incontinence in older women (see section C.2). The study team's previous experience suggests that these exercises can be performed safely by women across a range of ages and flexibility levels, although this new study will allow specific field-testing in women with chronic pelvic pain.

After a brief overview, the physical conditioning control program will focus on a core set of stretching and strengthening exercises, the majority of which are performed sitting in a chair. Seated stretching exercises include stretches for levator scapulae, upper trapezius, shoulder horizontal adduction, triceps, and hamstrings. Stretching exercises that incorporate a stretching strap include pectoral stretch with strap and gastrocnemius stretch with strap. One stretching exercise for the quadriceps is performed in the standing position.

Seated strengthening exercises with a resistance band include biceps, lateral raises, triceps, shoulder external rotation, shoulder internal rotation, fibularis, posterior tibialis,

quadriceps, hamstrings, and rows. Seated lower trapezius squeezes are performed without a resistance band. Two exercises will be performed on an exercise mat on the floor using a resistance band: shoulder horizontal abduction and shoulder diagonals. Three strengthening exercises will be performed in standing: wall push-ups, standing calf raises, and a squat through a limited range.

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6.1.2 ADMINISTRATION AND/OR DOSING

Yoga practice intervention:

Instruction in the therapeutic yoga intervention will be delivered through 90-minute group classes occurring twice weekly for 8 weeks, involving a trained instructor and approximately 6 students (a.k.a. participants). The twice-weekly frequency of class instruction will allow for intensive exposure to study-specific intervention techniques to guide participants in learning to practice these techniques even if they are naïve to yoga at the start of the study.

For this pilot study, group class instruction will be delivered using the on-line video conference platform (Zoom) approved by the participating institutions. In these live Zoom-based classes, participants will be able to see, hear, and interact with their instructor and with each other in real time, and instructors will also be able to observe participants' practice of intervention techniques and provide real-time instruction through the video interface. Participants will receive mats and necessary props (i.e., yoga blocks, straps, and bolsters) to practice intervention techniques from home as they would in a public studio. In light of the video-conference format of instruction, the target class size will be 6 participants, to avoid technical challenges associated with instructors needing to observe and tailor instruction to a larger number of participants by video.

At the start of group instruction, participants in each yoga class series will attend a 90-minute orientation led by a yoga instructor who has completed in-depth study-specific training. This orientation will include an overview of the general principles of alignment-based yoga, an introduction to the structures of the pelvis, spine, and lower extremity, and a preview of the yoga props to be used. After this orientation, women will attend 90-minute group classes twice weekly for 8 weeks, led by the same instructor. During these classes, the instructor will guide women in practicing yoga postures, calling attention to ways in which they can improve pelvic floor function, and guiding women in adapting postures to overcome physical limitations.

Following a study-specific guide that includes week-by-week introduction and reinforcement of postures and techniques, instructors will gradually introduce postures as classes progress. Participants will be introduced to all yoga postures and techniques in the first 4 weeks of the program and then develop greater confidence and skill in performing these postures and techniques to manage their pelvic pain during the remainder of the 8-week yoga program.

Group class instruction will be supplemented by home practice, in which participants will be asked to practice study yoga techniques for a minimum of one additional hour per week to reinforce skills acquired during intervention classes. Women will be given a detailed written manual that includes pictures and descriptions of each posture, along with instructions for practicing postures in ways that are likely to promote improvement in pelvic pain and alleviate comorbid anxiety/stress, as well as modifying postures to accommodate limitations in mobility or flexibility. After the 8-week intervention, women will be encouraged to continue practicing yoga at home for two or more hours a week.

Physical conditioning intervention:

The format, intensity, and duration of class instruction and home practice for women assigned to the physical conditioning control intervention will be the same as for women assigned to the yoga intervention, to promote equipoise in participant expectations and study contact across both intervention groups.

Similar to the yoga intervention, the stretching/strengthening intervention will begin with a group orientation led by a physical therapist/trainer and an assistant, who will provide an overview of the program. This will be followed by 90-minute twice-weekly group classes, each with an expected class size of approximately 6 participants, led by the same therapist/trainer who has received study-specific training from the study's expert physical therapist consultant, and using the Zoom video-conference platform. Classes will be designed to make women familiar with all exercises by 4 weeks and fully comfortable with exercises by 8 weeks.

In addition to attending group Zoom-based classes, women will be asked to perform stretching/strengthening exercises at home at least one additional hour per week during the 8-week intervention period and record the dates and times of practice in a home log similar to the yoga home practice log. Women will receive a manual with pictures and descriptions of each exercise to guide home practice, as well as a set of stretch bands, straps, and a mat to use at home. Similar to the yoga group, women in the control group will be encouraged to continue home exercises after the end of the intervention for two or more hours per week.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Yoga class instructors will be required to have at least 4 years of experience teaching yoga to adults in the community and have completed at least 4 hours of dedicated, study-specific training with one or more of the study yoga expert consultants (i.e., Leslie Howard). Expert consultants will also lead twice-monthly conference calls during each class series to help instructors troubleshoot issues that arise in instruction and promote adherence to the protocol. Additionally, an expert yoga consultant will observe at least one class in each series to ensure that postures are being taught according to the intervention protocol, evaluate students' success in learning yoga, and ensure fidelity across instructors.

Similarly, instructors leading the physical conditioning classes will be physical therapists licensed by the Physical Therapy Board of California or physical trainers certified by a national organization such as the National Academy of Sports Medicine, the American College of Sports Medicine, or the National Strength and Conditioning Association. Instructors will have at least 2 years of experience working with adults in the community, and will have completed at least 2 hours of in-person training with a study expert physical therapy consultant (e.g., Sarah Pawlowsky, DPT). During each class series, the expert consultant will lead twice-monthly conference calls with instructors to promote standardization of instruction and fidelity to the protocol. She will also observe at least one class in each series to provide direct quality monitoring, assess participants' success in learning study program exercises, and promote fidelity across instructors.

6.3 RANDOMIZATION AND BLINDING

Eligible women will be randomized in a 1:1 ratio to the therapeutic yoga or physical conditioning interventions, with stratification by study site. The randomization scheme will be generated by a computer algorithm using randomly permuted blocks of sizes of 2 and 4. To avoid manipulation of randomization, a statistician/analyst who is not otherwise involved in the study will prepare the randomization scheme.

When a participant is found to be eligible and willing to be randomized at the Baseline Visit, the coordinator will confirm appropriateness for randomization on the randomization assignment form in the Medrio electronic data capture system. The system will provide a randomization number corresponding to the participant's intervention assignment, consistent with the randomization scheme. Sequential randomization numbers will provide a check on the validity of randomization, and the system will be configured to prevent reversal or manipulation of randomization.

Although there is no effective way to completely blind participants in this trial to their intervention assignment, study procedures will preserve the blinding of investigators and staff involved in abstracting or analyzing outcomes. Only study personnel who are directly responsible for randomizing participants, administering interventions, or promoting adherence to interventions will be aware of intervention assignment. All personnel involved in abstracting, assessing, or analyzing pain-related outcomes will remain blinded until all participants have completed the final visit, trial data are edited and cleaned, and the dataset is locked.

The Medrio electronic data capture system will be programmed to hide information about intervention assignment from study investigators or staff who are required to remain blinded. Only study personnel who are required to remain unblinded will be given user rights in the Medrio system that allow them to view the intervention assignments for individual participants.

To minimize differential expectations of success between groups, participants will be told that they are participating in a study of two types of low-impact physical activity programs and that the investigators do not know which intervention is more effective for the management of chronic pelvic pain (which is true). While awareness of group

assignment can affect participants' use of co-interventions, women will be asked to refrain from starting, stopping, or changing dosage/frequency of other clinical treatments for pelvic pain during the study. Information about co-interventions will be collected at follow-up visits to facilitate the assessment of differential use of co-interventions.

6.4 STUDY INTERVENTION ADHERENCE

Adherence to group intervention sessions will be assessed by attendance logs kept by intervention instructors, who will forward completed logs on at least a weekly basis to clinical research coordinators based at their study site. Class attendance log data will be used to determine overall participant adherence to group intervention sessions in each intervention arm and across each study site.

Adherence to home intervention practice will be assessed by home practice logs that participants will be instructed to complete at home and return weekly. Home practice logs will record the dates of practice, the amount of time practiced on those dates, and the specific postures (for the yoga practice intervention) or muscle stretching/strengthening exercises (for the physical conditioning intervention) practiced at home during each practice session.

Adherence to study follow-up visits and telephone calls will be recorded by clinical research coordinators and documented in the study Medrio database, which will track the timing of completion of visits and whether they are completed within or outside of recommended time windows.

6.5 CONCOMITANT THERAPY

Participants may use concomitant pharmacologic treatments for pelvic pain during this study, provided that they remain on stable dosages of these medications. This includes using stable dosages of prescribed or over-the-counter analgesics. However, participants will be instructed to avoid initiating, dose-escalating, dose de-escalating, or weaning off of analgesic medications during the study. Further, participants will be asked to avoid initiating, dose-escalating, dose de-escalating, or weaning off medications that may affect their mood, such as antidepressants or anxiolytics.

Participants may engage in other forms of informal aerobic exercise such as jogging, swimming, or hiking. However, they will be instructed to avoid engaging in outside organized yoga or physical conditioning activities during the study, such as attending outside yoga or physical conditioning classes or workshops. Participants will also be asked to avoid using formal psychological therapies (e.g., systematic desensitization, sex therapy, cognitive therapy, relaxation therapy), mindfulness (e.g., formal meditation or mindfulness training sessions) or behavioral therapies (e.g., pelvic floor rehabilitation or biofeedback performed by certified healthcare practitioners) directed at pelvic pain during the study, although they may engage in psychological or behavioral interventions directed at other physical or mental health problems.

Participants will also be asked to avoid undergoing invasive procedures for their pelvic pain during the study. This includes surgical resection or invasive treatment of endometriosis, pelvic scar tissue, vulvar/vestibular tissue, or uterine myomas or polyps as potential contributors to chronic pelvic pain.

The recommendation to avoid using concomitant therapies will apply to both the main 8-week intervention phase of the study and the post-intervention follow-up period. However, only the former will constitute a protocol deviation; use of the above concomitant therapies during the post-intervention follow-up period will not be classified as a protocol deviation (see section 10.1.10, Protocol Deviations).

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTIONS

Participants may discontinue participation in study interventions at any time, although the investigative team will strive to minimize early discontinuation except when necessary for participant safety. Investigators may also discontinue a participant's involvement in study interventions for the following reasons:

- Continued participation would not be in the best interest of the participant or might require an additional treatment that would confound interpretation of the study data
- Disruptive behavior by a study participant that interferes with the conduct of study intervention classes
- New development or discovery of a study exclusion criterion that precludes further study participation

When a participant discontinues her participation in study yoga or physical conditioning classes or home practice but does not withdraw from the overall study, attempts will be made to complete remaining study procedures as indicated by the study protocol. At the time of intervention discontinuation, the study team will document:

- The reason(s) for discontinuing participation in study interventions,
- Whether the participant is expected to continue study follow-up assessments

If the reasons for discontinuation of study interventions is an Adverse Event (AE) or Serious Adverse Event (SAE), or unanticipated problem, study staff will collect information about the AE/SAE or unanticipated problem and document that this is the cause of study intervention participation (see sections 8.3 and 8.4).

7.2 PARTICIPANT WITHDRAWAL FROM THE STUDY

Participants may also withdraw from participation in the overall study at any time upon request, although the investigative team will strive to minimize participant withdrawal from the overall study except for safety reasons. The study investigators may also discontinue a participant's involvement in the study for the following reasons:

- Lost-to-follow up, or inability to contact the participant (see **Section 7.3, Lost to Follow-Up**)
- Occurrence of any event or medical condition or situation that indicates that continued collection of follow-up study data would not be in the best interest of the participant or would confound interpretation of the study data
- Disruptive behavior by a study participant that interferes with the conduct of future study visits
- New development or discovery of a study exclusion criterion that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on study forms at the time of early discontinuation. Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced by other participants if these are identified early enough to allow their participation in study intervention programs. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw or are discontinued from the study will not be replaced.

If the reason for a participant's withdrawal from the study is an Adverse Event (AE), Serious Adverse Event (SAE), or unanticipated problem, study staff will collect information about the AE/SAE or unanticipated problem and document that this is the cause of participant withdrawal (see sections 8.3 and 8.4).

7.3 LOST TO FOLLOW-UP

An enrolled participant will be considered lost to follow-up if she misses two consecutive study visits after randomization and is unresponsive to study contact or is no longer participating in study activities. The following actions will be taken if a participant misses a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit (within recommended time windows if possible), counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and/or e-mail messages). These contact attempts will be documented in the participant's medical record or study file.
- If the participant continues to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 NON-SAFETY ASSESSMENTS

This trial involves the following procedures required for: 1) Screening/Baseline Evaluations; 2) Randomization and Blinding, 3) Therapeutic Interventions, and 4) Follow-Up Evaluations below:

1. SCREENING/BASELINE EVALUATIONS

Preliminary eligibility will be determined by research coordinators through a Screening Telephone Interview followed by a video-based Screening Visit. The final review of eligibility will take place after a clinic-based Baseline Visit, after which candidates will be eligible for randomization.

All screening evaluations will be conducted by clinical coordinators affiliated with UCSF or Stanford University. Clinic visits will take place in outpatient facilities of UCSF in the city of San Francisco, rented research facilities in Oakland, CA affiliated with UCSF, or outpatient facilities of Stanford University. All screening procedures must be completed within a 2-month period; if screening cannot be completed within this period, initial procedures will be repeated to ensure that eligibility has not changed before randomization.

Telephone Screening Interview

- Women who call in response to recruitment advertisements will be provided with a brief overview of the study goals and procedures by a clinical coordinator over the telephone.
- If interested, candidates will complete a brief telephone survey to assess preliminary eligibility (including age, gender, duration/severity of pelvic pain, current and past pelvic pain treatment, prior yoga or stretching/strengthening practice, exclusionary conditions and medications, and availability for upcoming group intervention classes).

Screening (Video) Visit

- Before or at this visit, a coordinator will explain the requirements of the study while referring to an IRB approved informed consent form, and candidates will provide informed consent if they are interested in proceeding with the study.
- Candidates will complete questionnaires about their demographic, medical, pain-related, and urologic/gynecologic history for eligibility assessment.
- Over-the-counter and prescription medications will be reviewed to assess for recent initiation, escalation, or weaning of medications that would be exclusionary.
- Candidates will provide information about their recent use of computers and mobile electronic devices and confirm their access to devices and the internet.
- Potentially eligible women will provide information about their overall physical function and history of physical activity.

- Potentially eligible women will be instructed on completing 7-day diaries to document baseline pain severity and sexual activity before the Baseline Visit.
- Potentially eligible women will also be asked to complete questionnaires about substance use, trauma history, pain-related functioning, sexual functioning, anxiety and depression symptoms, sleep quality, and pain cognitions/self-efficacy and return them by the Baseline Visit.

Baseline Clinic Visit

- Candidates will return with their completed 7-day diaries and questionnaires, and results will be reviewed by a clinical coordinator for eligibility (particularly regarding the pain logs).
- A clean catch urine sample will be collected to assess for possible urinary tract infection or hematuria and rule out pregnancy (for women of reproductive potential).
- Height and weight measurements will also be obtained for characterization of the study sample.
- Physical performance, including balance testing, lower extremity strength, and aerobic endurance will be assessed by a coordinator.
- Participants will be invited to undergo optional pelvic floor tenderness evaluations by a clinician investigator or consultant experienced in gynecologic evaluation.
- If the Baseline Clinic Visit takes place within 2 weeks of the start of the next intervention orientation session, eligible participants will be randomized to one of the two interventions at this visit (see below).

3. FOLLOW-UP EVALUATIONS

Follow-up evaluations after the start of the study intervention programs will consist of a 2-week telephone call, 4-week video visit, 6-week telephone call, 8-week video visit, and 8-week post-intervention video visit:

2-Week Telephone Call

- Two weeks after the start of the intervention programs, coordinators will call women to assess adverse events, address any concerns, and reinforce adherence to group classes and home practice of yoga or stretching/strengthening exercises.

4-Week (Video) Visit

- Four weeks after the start of the intervention programs, women will have a follow-up video visit, by which time they will be asked to complete follow-up pain diaries for data abstraction by blinded analysts.
- Adverse events will be assessed using standardized procedures and forms.

- Home practice logs will be reviewed, and yoga/stretching self-efficacy questionnaire measures will be re-administered.
- Women will re-self-administer questionnaires about pain-related outcomes including pain-related functioning, sexual functioning, anxiety and depression symptoms, sleep, and pain-related cognitions/self-efficacy.
- Women will undergo repeat assessment of physical performance.
- Current use of prescription and over-the-counter medications and use of co-interventions will be re-reviewed and recorded.

6-Week Telephone Call

- Six weeks after the start of the intervention programs, coordinators will call women to assess adverse events, address any concerns, and reinforce adherence to group classes and home practice of yoga or stretching/strengthening exercises.

8-Week (Video) Visit

- Eight weeks after the start of the intervention programs, women will return for another video visit, bringing their third set of pain diaries for data abstraction by blinded analysts.
- Adverse events will be assessed using standardized procedures and forms.
- Home practice logs will be reviewed, and yoga/stretching self-efficacy questionnaire measures will be re-administered.
- Women will return self-administered questionnaires about pain-related outcomes that they completed for the 4-week visit.
- Women will undergo repeat assessment of physical performance.
- Current use of prescription and over-the-counter medications and use of co-interventions will be re-reviewed and recorded.
- Women will be encouraged continue practicing yoga or stretching/strengthening exercises for at least two hours per week and record this practice in their home practice logs.

8 Week Post-Intervention (Video) Visit

- Eight weeks after completion of the intervention programs, participants will return for another video visit, returning their fourth set of pain diaries for data abstraction by a blinded analyst.
- Adverse events will be reassessed using standardized procedures and forms.
- Home practice logs will be collected and reviewed, and yoga/stretching self-efficacy questionnaire measures will be re-administered.

- Women will return the same self-administered questionnaires about pain-related outcomes as they completed for the 8-week visit.
- Current use of prescription and over-the-counter medications and use of co-interventions will be re-reviewed and recorded.
- A closeout satisfaction questionnaire will be administered that includes assessment of satisfaction with and barriers to intervention practice.

8.2 RISK/BENEFIT ASSESSMENT

8.2.1 KNOWN POTENTIAL RISKS

Study interventions and procedures may pose the following risks to participants:

a) Yoga Intervention: Possible risks associated with group yoga instruction and home yoga practice include muscle soreness and muscle/ligament strain, or other musculoskeletal injury sustained by participants while trying to practice yoga poses.

b) Stretching/Strengthening Control Intervention: Similar to the yoga intervention, possible risks associated with the stretching/strengthening control intervention include muscle soreness and muscle/ligament strain, or musculoskeletal injury sustained by participants while trying to learn or practice the stretching exercises.

c) Questionnaires and Diaries: Although the information participants provide on data collection forms and diaries is confidential, some participants may feel embarrassed at having to answer questions, especially those related to sexual function, anxiety, or depression. There will be slight inconvenience in time and effort to complete diaries and questionnaires.

d) Physical Exam Measurements: There are no direct risks associated with undergoing measurement of height and weight, although participants may experience this as inconvenient or unpleasant.

e) Pelvic Floor Assessment: Digital pelvic examination and assessment of pelvic floor muscle tenderness and hypertonicity may be associated with discomfort or soreness in the perineal or vaginal area, emotional reaction to being touched in the genital area, feeling of fullness or pressure in the rectum, or urge to urinate during or following the exam.

f) Urinalysis and Urine Pregnancy Testing: There are no direct risks associated with collection of the clean-catch urine sample, although some participants may experience this as inconvenient or unpleasant.

8.2.2 KNOWN POTENTIAL BENEFITS

Potential benefits of the yoga program: Participants in the yoga intervention group will receive free instruction in alignment-based yoga techniques through the 8-week yoga program, as well as a limited set of yoga props that they can use to practice study yoga techniques at home. Regardless of the yoga intervention's effects on their pelvic pain or pain-related functioning, participants may find that regular practice of these yoga

techniques is associated with improvement in their general health and well-being. Prior studies of Hatha yoga interventions have reported that participants experience improvement in anxiety or depression symptoms, sleep quality, physical function, and/or overall quality of life, although those studies may have focused on different populations or involved alternate yoga techniques.

Potential benefits of the stretching/strengthening program: Participants in the physical conditioning intervention group will receive free instruction in performing general muscle stretching/strengthening exercises through the 8-week yoga program, as well as a limited set of props that they can use to practice exercises at home. Regardless of the control intervention's effects on their pelvic pain or pain-related functioning, participants may find that regular practice of these exercises is associated with improvement in their general health and well-being. Prior studies of physical conditioning programs have reported that participants experience improvement in anxiety or depression symptoms, sleep quality, physical function, and/or overall quality of life, although those studies may have focused on different populations or involved alternate physical conditioning techniques.

Potential benefits of discussing pelvic pain in a study context: Indirectly, participants in both intervention groups may find it comforting to discuss their pelvic pain, associated anxiety or depression symptoms, and other pelvic symptoms with study personnel, intervention instructors, or other participants in their intervention classes. They may feel empowered by their participation in a group intervention program that acknowledges the impact of pelvic pain on their day-to-day lives. They may benefit from informally sharing their strategies for coping with their pain with other afflicted women.

Potential benefits of other study measurements: Study measurements performed as a part of this study may also reveal incidental abnormalities in participants' blood pressure, heart rate, or mood that will be shared with participants. This may prompt participants to seek further evaluation or treatment through their regular source of health care, which may in turn lead to improvements in their health.

8.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Although participation in this study is associated with risks, these risks can be minimized through the following protective measures:

Yoga Intervention: The instructors leading the group yoga classes will be trained yoga teachers who have experience in teaching adults from a wide range of ages to learn and practice yoga safely, and who will undergo specific, in-person training by the study's yoga expert consultants. The study intervention protocol is designed to avoid precipitating pelvic floor strain and incorporates yoga props such as blocks and blankets to help participants perform yoga postures in such a way that will minimize the likelihood of muscle strain or musculoskeletal injury. The yoga instruction manuals are designed to include explicit tips on modifying or adapting postures to accommodate problems with mobility, flexibility, or balance.

Stretching/Strengthening Intervention: Instruction for the control intervention classes will be provided by trained physical therapists or personal trainers who are experienced in teaching patients of all ages to perform physical exercises safely, and who have completed in-person training with the study expert physical therapy consultant. Stretching and strengthening exercises have been selected to be appropriate for women who may have flexibility or mobility limitations in addition to pelvic pain.

Questionnaires and Diaries: Any paper-based questionnaires or diaries collected in this research will be stored in a locked file cabinet in a locked room in research facilities, and data obtained from diaries and questionnaires will be stored on password-secured servers. All study staff will be fully trained in good clinical practice and HIPAA procedures, and the importance of participant confidentiality will be emphasized.

Physical Examination Measures: Study coordinators who are responsible for obtaining general physical exam measures will have prior experience with performing physical exam measurements in women of all ages (through the investigators' other clinical studies), and/or will receive study-specific training to ensure that they perform measurements in a manner that is sensitive and minimizes discomfort to participants.

Pelvic Floor Assessment: Assessment of pelvic floor tenderness and hypertonicity will be performed by investigators experienced with performing gynecologic and pelvic exams (e.g., Tami Rowen, Alison Huang, Leslee Subak) with experience performing pelvic exams for clinical care in a manner that is sensitive and minimizes discomfort to participants. Even if they agree to undergo this assessment, participants will be informed that they can ask to stop the exam for any reason. Women with a history of pelvic/sexual trauma or extreme pain with the pelvic exam can decline this measurement but still take part in other study procedures.

Urinalysis and Pregnancy Testing: Study coordinators who are responsible for performing urine testing will be trained to instruct participants on providing urine samples in a manner that is sensitive and minimizes embarrassment.

Because the potential risks to participants are modest and can be managed through the above protective measures, the study team believes the benefits of the knowledge to be gained from the study, as well as the indirect potential benefits to women from study participation, outweigh the potential risks.

8.3 SAFETY ASSESSMENTS

Clinical coordinators will proactively monitor participant safety by asking participants about negative changes in health at scheduled follow-up visits and telephone calls starting with the 2-Week Telephone Call. Negative changes in health reported by participants will be recorded as adverse events on standardized forms as appropriate.

Coordinators will not prompt participants to provide information about specific types of adverse events, but instead will encourage participants to volunteer information by asking the standardized, open-ended question, "Have there been any changes in your health since your last visit?" Any negative changes in health reported in response to this question will then be recorded on standardized forms.

Participants will also be given telephone numbers at the Screening Clinic Visit to call study staff before the scheduled 2-week telephone call or between scheduled study visits or calls to report negative changes in their health. If reported, these changes will be recorded on standardized adverse event forms.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS

For this study, an adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research. In general, medical conditions or diseases present before starting study interventions should only be considered adverse events if they worsen after starting the interventions.

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS

For study purposes, a serious adverse event (SAE) is any AE that results in death, is life-threatening, or places the participant at immediate risk of death from the event as it occurred; requires or prolongs hospitalization, causes persistent or significant disability or incapacity, or results in congenital anomalies or birth defects. Additionally, any other important medical event may be considered an SAE if it is judged by the investigators to jeopardize the safety of a participant or to require medical or surgical intervention to prevent one of the above outcomes listed in this SAE definition.

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 SEVERITY OF EVENT

Using the Common Terminology Criteria for Adverse Events (CTCAE) system, all adverse events detected in this study will be graded in severity using the 5-point CTCAE scale. According to this scale, AEs are considered grade 1 if they represent only mild symptoms or asymptomatic laboratory findings; grade 2 if they cause moderate symptoms that interfere with instrumental activities of daily living (shopping, transportation, household tasks); grade 3 if they are serious or disabling events or result in hospitalization or prolongation of hospitalization without being directly life-threatening; grade 4 if they are life-threatening events in which the participant is at risk of death at the time of the event if immediate intervention is not undertaken; or grade 5 if they are

fatal adverse events. By definition, a “serious adverse event” is an adverse event that is CTCAE severity grade 3 or higher.

8.4.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs will also be categorized according to the likelihood that they are related to the therapeutic study interventions. Specifically, AEs will be labeled as unrelated, unlikely related, possibly related, probably related, or definitely related, based on the opinion of the Site PI:

- *Unrelated*: the time course between administration of the study intervention and occurrence or worsening of the AE rules out a causal relationship, and/or another cause is confirmed and no indication of involvement of the study intervention in the occurrence or worsening of the AE exists.

- *Unlikely related*: the time course between administration of the study intervention and occurrence or worsening of the AE makes a causal relationship unlikely, and/or; the known effects of the study intervention provide no indication of involvement in the AE and another cause adequately explaining the AE is known, and/or; a plausible causal chain may be deduced from the known effects of the study intervention, but another cause is much more probable, and/or; another cause is confirmed and involvement of the study intervention in the AE is unlikely.

- *Possibly related*: a plausible causal chain may be deduced from the nature of the study intervention, but another cause just as likely to be involved is also known, or; although the nature of the intervention does not create a strong expectation of involvement in the AE, involvement of the intervention is still possible, and no other cause gives adequate explanation.

- *Probably related*: The nature of intervention indicates that it probably caused the AE, and/or; the course of the AE after stopping study intervention improved and, if applicable, worsened after re-challenge, and/or; a specific test suggests the involvement of the study intervention, although another cause cannot be ruled out.

- *Definitely related*: The biological properties of the study intervention are known to cause the AE, and/or; the AE improves after stopping study intervention and, if applicable, worsens after re-challenge, and/or; a specific test indicates the involvement of the study intervention, and no indication of other causes exists.

8.4.3.3 EXPECTEDNESS

Adverse events will be assessed as to whether they were expected to occur or unexpected (i.e., not anticipated based on current knowledge found in the protocol or known information about the study intervention). Categories are:

1) *Unexpected – the* nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, or product brochure; or

2) *Expected* – the event is known to be associated with the intervention or condition under study.

8.4.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

New AEs or SAEs will be considered reportable any time after the Baseline Clinic Visit (which is the first scheduled visit involving in-person assessments) until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

Clinical coordinators at each site will proactively assess for adverse events by asking participants about negative changes they have experienced in their health at scheduled follow-up study visits and telephone assessments starting with the 2-Week Telephone Call. Coordinators will not prompt participants to provide information about specific types of adverse events, but instead will encourage participants to volunteer information by asking a standardized, open-ended question, “Have there been any changes in your health since your last visit?” Any negative changes in health reported in response to this question will then be recorded on standardized forms.

Participants will also be given telephone numbers at baseline to call study staff before the scheduled 2-week telephone call or between scheduled study visits or calls to report negative changes in their health. If reported, these changes will be recorded on standardized adverse event forms.

Medical or psychiatric conditions that are present at the time that participants are screened will be considered to reflect participants’ baseline status and will not be reported as adverse events. However, if the study participant’s condition deteriorates at any time during the study, this deterioration will be recorded as an AE even if it is related to a pre-existing condition.

Adverse events will be characterized by clinical coordinators at each clinical site in collaboration with the Site Principal Investigator (Site PI) or other investigators if appropriate. The clinical coordinator in conjunction with the Site PI will document events on standardized adverse event forms. The Site PI will review information about individual AEs collected by clinical coordinators twice monthly to guide determinations about the relationship to study interventions, expectedness, and severity.

Adverse event forms will indicate the severity of the event, the likelihood of relationship to study interventions, and the expectedness of the event. Adverse event forms will also note the date of onset of the adverse event, record whether the event has resolved or is continuing at the time of assessment, record the date of resolution, and note any important study actions taken in response to the event. For SAEs, standardized SAE forms will also record the nature of the event, the outcome of the event to date, whether

the event resolved or continues, and any medications or other treatments provided in response to the SAE.

Any detected AEs and SAEs will be followed until resolved or considered stable. At each scheduled follow-up contact after the initial discovery of an AE or SAE, clinical coordinators will assess whether the AE or SAE is continuing or has resolved, and will update information about event status on the AE or SAE form, as appropriate.

For SAEs, coordinators will also make more active attempts to communicate with the participant in between scheduled study visits (with the participant's permission) to monitor the resolution of SAEs.

8.4.5 ADVERSE EVENT REPORTING

Non-serious adverse events detected 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 semi-annual AE summary which will be provided to the DSM and the NCCIH. The DSM Report will confirm that all AEs have been reviewed.

Non-serious adverse events will not automatically be reported to the UCSF IRB, but the Principal Investigator may report or consult the UCSF IRB for input on the handling of non-serious AEs if they may still pose a substantial risk of harm to a participant or are potentially associated with study interventions or procedures.

8.4.6 SERIOUS ADVERSE EVENT REPORTING

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent DSM/MSO, IRB, and NCCIH in accordance with requirements:

- Unexpected fatal or life-threatening SAEs related to the intervention will be reported to the NCCIH Program Officer and Independent DSM/MSO within 3 days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 7 days.

- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent DSM/MSO, IRB, and other oversight organizations in accordance with their requirements and will be reported to NCCIH on a semi-annual basis.

8.4.7 REPORTING EVENTS TO PARTICIPANTS

The investigative team may inform participants about other individual or aggregate level AEs or SAEs detected in the course of the study if these events have important implications for the risks associated with study participation. The decision to inform participants about other AEs or SAEs will be made by the investigative team with input from the IRB, the DSM, and other regulatory bodies as necessary.

If information about AEs or SAEs is shared with participants who were not directly involved in the events, then the study team will share information in such a way as to protect the confidentiality and privacy of the individuals involved.

8.4.8 EVENTS OF SPECIAL INTEREST

For this study, special procedures have been developed to monitor and follow-up participants' scores on selected questionnaires assessing depression or anxiety symptoms or on questionnaires assessing Post-Traumatic Stress Disorder (PTSD) symptoms. Scores will be reviewed on an ongoing basis to identify participants with elevated scores that may indicate increased risk of at least moderate depression or anxiety or PTSD.

Procedures for reviewing and notifying participants about potentially concerning scores on these measures are described in detail in the Data & Safety Monitoring Plan (DSMP). For score elevations indicating moderately increased risk of depression or anxiety, the study team will arrange for the participant to receive a standardized letter indicating the score and the normal score range, along with a recommendation that participants seek further evaluation or treatment from a health care provider and a list of mental health resources in the area. For score elevations indicating severely increased risk of depression or anxiety or indicating clinically significant PTSD symptoms, a study clinician will additionally attempt to contact the participant by telephone.

8.4.9 REPORTING OF PREGNANCY

Screening procedures have been designed to exclude women who are pregnant or planning to become pregnant during the study period. If a participant becomes pregnant after enrollment in the study, this event will be reported to the DSMs, IRB, and NCCIH in the same time frames and using the same procedures as a serious and unexpected SAE, even if pregnancy is not accompanied by other conditions of an SAE.

Any participant discovered to be pregnant after study enrollment will discontinue participation in the study interventions, but will be permitted to continue contributing follow-up data. If permitted by the participant, study staff will continue to follow the participant until the resolution of the pregnancy.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS

This study uses the Office for Human Research Protections (OHRP) definition of an unanticipated problem as any incident, experience, or outcome that meets all of the following criteria:

1) is unexpected, in terms of nature, severity, or frequency, given the research procedures described in the protocol and the characteristics of the study population;
2) is related or possibly related to participation in the research; and

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

8.5.2 UNANTICIPATED PROBLEMS REPORTING

Incidents or events that meet the OHRP criteria for unanticipated problems will prompt the study team to submit an unanticipated problem report to the IRB, which will include:

- 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 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 serious adverse events will be reported to the IRB, Independent DSM/MSO, and NCCIH within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, Independent DSM/MSO, and NCCIH within 14 days of the investigator becoming aware of the problem.
- 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 investigator.

8.5.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The investigative team may inform participants about other individual or aggregate level unanticipated problems if these problems have important implications for the risks associated with study participation. The decision to inform participants about unanticipated problems will be made by the investigative team with input from the IRB, the DSM, and other regulatory bodies as necessary.

If information about unanticipated problems is shared with participants who were not directly involved in the problems, then the study team will share information in such a way as to protect the confidentiality and privacy of the individuals involved.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This pilot randomized trial is designed to field-test procedures and assess the feasibility of conducting a future full-scale clinical trial. As a result, the investigators have not established any formal hypotheses about intervention efficacy or safety as part of this study. However, the study team has set benchmarks for assessing the feasibility of:

- Aim 1: Recruiting, randomizing, and retaining participants, as well as maintaining adherence to the study interventions;
- Aim 2: Successfully teaching participants to practice study-specific intervention techniques
- Aim 3: Obtaining complete and high-quality data from pain-related outcome measures.

Assessment of these benchmarks will guide future refinement of trial procedures and help the investigators assess the feasibility of eventually launching a larger-scale trial designed to collect rigorous evidence of the efficacy and safety of the yoga intervention in the target population.

9.2 SAMPLE SIZE DETERMINATION

In this pilot randomized trial is designed to assess the feasibility of and field-test procedures for a future full-scale randomized efficacy trial, a sample size of 36 participants has been selected based on consideration of the study goals as well as the time and budget constraints of the R34 funding mechanism. This pilot sample size allows for group intervention classes with an average size of 6 participants per class to be assembled for each intervention group at each of the three proposed study locations, consistent with expectations for a possible future full-scale randomized trial.

In the overall sample of 36 women, margins of sampling error (MSEs; i.e., half-widths of 95% CIs) for continuous and binary feasibility measures will be greater than 0.30 SDs and up to 15 percentage points, respectively, with the latter depending on the true proportion. Within arms, corresponding MSEs will be greater than 0.45 SDs and 20 percentage points. Given the substantial MSEs, the investigative team will take into account uncertainty about parameter estimates when drawing study conclusions.

9.3 POPULATIONS FOR ANALYSES

Selection of participants for inclusion in analyses will depend on the endpoints involved. Specifically:

- Analyses addressing the feasibility of recruitment will focus on the total number of women responding to recruitment advertisements, as well as the smaller subset of women who provide informed consent at the Screening Visit.
- Analyses addressing the feasibility of retention in the 8-week intervention period will focus on participants who are randomized to an intervention group, even if these participants do not go on to complete recommended intervention sessions.

Analyses of the feasibility of retention in the post-intervention follow-up phase will focus on participants who complete the 8-week intervention programs.

- Analyses addressing adherence to study intervention classes and home practice will focus on the subpopulation of participants who complete their 8-week intervention programs. In the case of adherence to post-intervention practice, analyses will focus on the subpopulation of participants who complete the additional post-intervention follow-up period.
- Analyses addressing the feasibility of teaching participants to practice intervention techniques will focus on participants who: 1) are randomized to one of the two intervention programs, and 2) do not withdraw early from their assigned 8-week intervention program. Participants will be included in analyses even if they miss one or more intervention classes or do not complete home intervention practice.
- Analyses addressing completeness of pain measure outcomes data will focus on participants who are randomized to an intervention group and who complete: a) the 8-week intervention portion of the study (for assessment of completeness of 8-week pain outcomes data), and b) the 8-week post-intervention follow-up visit (for assessment of 8-week post-intervention follow-up pain outcomes data).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

For descriptive statistics, categorical variables will be presented as frequency counts and percentages. Continuous variables will be presented as means and standard deviations. If on visual inspection of q-q plots, distributions deviate significantly from normality continuous variables will also present median and interquartile range.

Where needed, inferential statistics will be generated using Chi-square tests, Fisher's exact tests, or t-tests as appropriate. If outcome variable distributions deviate significantly from normality then comparisons will be made using the Mann-Whitney U test .

9.4.2 MAIN ANALYSES TO ADDRESS AIM 1

Analyses to assess the feasibility of participant recruitment, retention, and adherence to interventions will use data obtained from study visit and randomization logs, intervention class attendance logs, and home intervention practice logs, primarily during the baseline and 8-week intervention period.

Feasibility of recruitment will be assessed by examining the proportion of participants who attend a Screening Visit who go on to be randomized ("Percentage of screenees who are eventually randomized").

Feasibility of participant retention during the intervention phase of the research will be assessed by examining the proportion of randomized participants in each intervention

arm who drop out before the 8-week visit ("Percentage of randomized participants who drop out by 8 weeks, by intervention arm").

Feasibility of promoting participant adherence to group intervention classes will be assessed by examining the percentage of non-dropout participants in each intervention arm who complete at least 75% of recommended group classes during the 8-week intervention period ("Percentage of non-drop-outs completing at least 75% of intervention classes over 8 weeks, by intervention arm").

Feasibility of promoting adherence to home intervention practice will be assessed by examining the percentage of non-dropout participants in each arm who complete at least 75% of recommended home practice hours during the 8-week intervention period ("Percentage of non-drop-outs completing at least 75% of home intervention practice over 8 weeks, by intervention arm").

For these aim 1 outcomes, the investigative team has set benchmarks of randomizing at least 50% of women who undergo screening visits. Participant drop-out rates of <15%, 15-25%, and >25% will be interpreted as indicating optimal, acceptable, and inadequate retention, respectively. Among non-dropouts, completion of >85%, 75-85%, and <75% of group classes and home practice hours will be considered to indicate optimal, acceptable, and inadequate adherence, respectively.

Although the main analyses to assess the feasibility of recruitment, retention, and adherence will rely on descriptive statistics, the investigative team may generate 95% confidence intervals (CIs) to explore the precision of these performance estimates if this is deemed useful to guide planning for a future randomized trial.

9.4.3 MAIN ANALYSES TO ADDRESS AIM 2

Analyses to assess the feasibility of teaching participants to practice their assigned interventions will focus on data obtained from a) participant questionnaires assessing their confidence in performing yoga or physical conditioning techniques according to protocol (i.e., self-efficacy in performing postures/exercises), and b) expert consultants' observations of participants' competence in performing these techniques (i.e., observed competence in performing postures/exercises). Participants will rate their self-confidence in performing each posture/exercise on a 5-point Likert scale (5-extremely, 4-very, 3-moderately, 2-somewhat, and 1-not at all confident). Expert consultants will observe and rate participants' success in performing each posture/exercise on a 5-point Likert scale (5-extremely, 4-very, 3-moderately, 2-somewhat, and 1-not at all confident).

Using data from the 8-week yoga posture self-efficacy questionnaires, the investigators will examine the percentage of participants completing the yoga intervention program who demonstrate at least moderate self-efficacy in performing postures, based on an average posture self-confidence/self-efficacy rating of 3 or higher ("Percentage of participants with at least moderate self-efficacy in performing yoga postures at 8 weeks").

Using data from expert yoga consultants' 8-week evaluations of participants, the investigators will examine the percentage of participants completing the yoga intervention program who are rated by the study yoga expert consultant as being at least "moderately" successful in performing core yoga postures at 8 weeks, based on an average observed posture competency rating of 3 or higher ("Percentage of participants rated as being at least moderately competent in performing yoga postures at 8 weeks").

For equipoise, similar analyses will be conducted for the physical conditioning group. Analyses will examine the percentage of participants completing the physical conditioning intervention program who indicate that they are at least "moderately" confident that they can perform core exercises at 8 weeks ("Percentage of participants with at least moderate self-efficacy in performing physical conditioning exercises at 8 weeks"), as well as the percentage of participants who are rated by the physical therapy expert consultant as being at least "moderately" successful in performing core exercises at 8 weeks ("Percentage of participants rated as being at least moderately competent at performing physical conditioning exercises at 8 weeks").

The investigators anticipate that over 75% of participants who complete the 8-week intervention programs will be at least "moderately" confident in performing postures or exercises by 8 weeks. Additionally, investigators expect that over 75% of participants completing intervention programs will be rated by an expert consultant as being at least "moderately" successful in performing study-specific postures or exercises by 8 weeks.

Although the primary analyses to assess the feasibility of teaching participants to perform study-specific intervention techniques will rely on descriptive statistics, the investigative team may generate 95% CIs to explore the precision of these estimates if this is deemed useful to guide planning for a future randomized trial.

9.4.4 MAIN ANALYSES TO ADDRESS AIM 3

Analyses to assess the completeness, quality, and distribution of data from pain-related outcome measures will focus on participants' pain severity/intensity, interference, and impact measures after 8 weeks of intervention training.

Among participants completing the 8-week intervention programs, the investigative team will examine the percentage who complete 7-day pain severity/intensity measures 8 weeks, either within or outside of recommended time windows ("Percentage of expected pain logs returned at 8 weeks"). The investigators will also examine the percentage of participants who complete pain interference questionnaires at 8 weeks ("Percentage of expected pain interference questionnaires returned at 8 weeks") and pelvic pain impact measures at 8 weeks ("Percentage of expected pelvic pain impact measures returned at 8 weeks").

The investigative team anticipates that over 90% of pain severity/intensity, interference, and impact measures anticipated at 8 weeks will be completed and returned. Additionally, the investigators anticipate that over 75% of these measures will be completed and returned within recommended time windows.

If rates of return of the above outcome measures at 8 weeks are adequate, the investigators will also examine the mean (and/or median) and standard deviation (and/or interquartile range) of change in pain severity/intensity, interference, and impact scores over 8 weeks. This may guide future efforts to identify well-behaved and relatively precise pain-related outcome measures for use as primary and secondary efficacy outcomes in a future full-scale efficacy trial.

Analyses will focus on the combined sample of participants reaching the 8-week timepoint, although further analyses may be performed to explore differences between intervention arms if the completeness or quality of outcomes data at 8 weeks is lower than expected. Additionally, investigators may generate 95% CIs to explore the precision of estimates if deemed useful to guide future trial planning.

9.4.5 PRIMARY COMPOSITE FEASIBILITY OUTCOME

Although each of the above feasibility analyses will be important in planning for a future full-scale efficacy trial, the investigative team has also designated a single composite feasibility outcome that incorporates multiple of the above outcomes. This is the cumulative number of participants from all three planned intervention waves who:

a) are randomized to one of the two intervention groups (yoga or physical conditioning),

b) do not drop out of the study before the end of their assigned 8-week intervention program,

c) attend at least 75% of their recommended group intervention classes over 8 weeks,

d) report at least moderate self-efficacy (on average) in performing intervention techniques, and

e) provide 7-day pain severity/intensity, impact, and interference data at 8 weeks.

The investigative team has set a benchmark of enrolling and following at least 24 women (or two-thirds of the randomization target of 36 women) who meet all of the above criteria by the end of three planned intervention waves of this feasibility trial. If this benchmark is not met, the study team will re-consider the advisability of proceeding with a full-scale trial that uses the same approach to recruitment and retention, delivering the study interventions, and collecting pain outcomes data.

9.4.6 ADDITIONAL ANALYSES

A) Additional analyses to assess the feasibility of recruitment, retention, and adherence:

Additional analyses will examine the number of initial inquiries, screening visits, and randomized participants generated by different types of recruitment methods in order to guide refinement of recruitment strategies. To assess the effects of study eligibility criteria on the feasibility of recruitment, the investigative team will tabulate the major reasons why screenees are found to be ineligible in the screening phase of the study.

To assess the feasibility of participant retention during the post-intervention phase of the study, the investigative team will examine the proportion of participants completing each intervention program who subsequently drop out of the study or are lost to follow-up by the 8-week post-intervention visit.

To examine the feasibility of promoting continued adherence to intervention practice after the end of the intervention programs, investigators will examine the proportion of participants completing the post-intervention follow-up phase of the study who also complete at least 75% of recommended home practice hours during this 8 week post-intervention period.

If participant retention is poor, the investigative team may conduct additional exploratory pooled logistic regression analyses to try to identify participant characteristics associated with drop-out by 8 weeks or 8 weeks post-intervention. Similarly, if adherence to group intervention classes or home practice is lower than expected, the investigative team may explore simple linear, logistic, and/or proportional odds models, depending on the distribution of the adherence measure, to explore associations of participant characteristics with poor adherence.

B) Additional analyses to examine the feasibility of teaching women to perform intervention-specific techniques:

Additional descriptive statistics may examine participants' self-efficacy and observed competence in performing intervention techniques during the mid-point of intervention programs (4 weeks). Within the yoga arm, investigators may examine participants' average self-efficacy in perform yoga postures at 4 weeks. Investigators may also examine average posture competency ratings based on the study yoga expert consultant's observations at 4 weeks. Similar analyses may be conducted for the physical conditioning group.

Within the yoga intervention arm, additional analyses may be conducted to examine participants' self-efficacy and observed competence in performing each individual yoga posture, to identify specific components of the yoga program that may post special challenges for the target population. Within the physical conditioning intervention arm, similar additional analyses may be conducted to examine participant's self-efficacy and observed competence in performing each physical conditioning exercise. These analyses will focus on 8-week data, although additional exploratory analyses may examine participants' self-efficacy and observed competence in performing intervention techniques mid-way through the intervention programs at 4 weeks.

C) Additional analyses to examine the completeness/quality of follow-up outcomes data:

Additional analyses may be performed to assess the completeness and quality of data obtained from pain logs and pain-related outcome questionnaires at the 8-week post-intervention timepoint. This includes the percentage of completed 7-day pain severity/intensity, interference, and impact measures returned at the 8-week post-intervention timepoint.

Additional analyses may examine the percentage of other expected pain-related outcome measures that are returned at 8 weeks or 8-weeks post-intervention. These include pain self-efficacy or fear-avoidance questionnaires, anxiety and depression symptom questionnaires, and sleep disturbance questionnaires. For all of the above, analyses will focus on the combined available sample of participants at the relevant timepoint, although further exploratory group-specific analyses may also be performed.

The study team may also examine the distribution of data from all of the above pain-related outcome measures at baseline, 8 weeks, and 8 weeks post-intervention, and calculate their standard deviations (SDs) and within-subject and within-site intraclass correlations (ICCs). These exploratory analyses may alert the investigative team to the need for transformation and ceiling/floor effects as well as guide decisions about the inclusion of measures in a future full-scale trial.

In recognition of potentially important differences in data completion, quality, or distribution, the investigative team may also pursue a limited set of analyses stratified by clinical recruitment site (i.e., San Francisco, Oakland, and Palo Alto, each of which will be the focus of a different intervention wave). This may alert investigators to gross variation or clustering across sites which could complicate a future multisite trial.

9.4.7 SAFETY ANALYSES

No formal safety analyses such as between-group comparisons of adverse events will be performed as part of this feasibility trial. However, the investigative team will monitor the safety of participants using procedures outlined in Section 8.2, Safety Assessments, including standardized procedures for assessing, classifying, and reporting adverse events.

Aggregate information about adverse events in each intervention arm as well as the overall trial population, including adverse events resulting in early termination from study interventions or from the overall study, will be presented in tables or listings that will be reviewed internally by the investigative team on an ongoing basis as well as presented to the independent Data & Safety Monitor (DSM) / Medical Safety Officer (MSO) at scheduled semiannual DSM reviews. Aggregate information about adverse events will also be presented in external presentations, reports, or publications arising from this research.

9.4.8 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics of randomized participants in each intervention arm as well as the overall study population will be examined using descriptive statistics. As a minimum, this will include:

a) demographic characteristics such as age, race/ethnicity, and educational attainment
b) pelvic pain characteristics such as pain severity and duration, past use of treatments for pain, co-morbid pain conditions, and pain-related cognitions

c) sexual and reproductive history including sexual activity status, menstrual status, and history of pelvic surgery
d) depression and anxiety symptoms, and selected other quality of life variables relevant to pain
e) health-related habits including physical activity level, tobacco use, and alcohol use
f) physical examination variables including body mass index calculated from height and weight
g) interpersonal traumatic exposures and post-traumatic stress disorder (PTSD) symptoms

9.4.9 PLANNED INTERIM ANALYSES

The investigative team will examine interim data on feasibility outcomes described in sections 9.4.2 and 9.4.3 after completion of the first and second intervention waves, corresponding to completion of 8-week follow-up of 12 and 24 participants. The results of interim analyses may be used by the investigators to refine procedures for subsequent recruitment and intervention waves of this study. Consideration may also be given to stopping the trial early if interim analyses indicate that recruitment and retention are so poor that the ability to meet recruitment or retention thresholds appears seriously compromised.

Because this feasibility study is not designed to test any efficacy hypotheses, no interim analyses of intervention efficacy will be performed, and no halting guidelines have been developed based on early evidence of efficacy or inability to demonstrate efficacy.

As the study involves only low-risk behavioral interventions, no formal interim safety analyses are planned by the investigative team. However, consideration may be given to stopping the trial early if unexpected and clinically significant adverse effects occur in either intervention group that may endanger the safety of participants.

9.4.10 SUB-GROUP ANALYSES

No formal subgroup analyses of intervention effects are planned for this pilot trial that is not designed to test hypotheses about efficacy or safety.

9.4.11 TABULATION OF INDIVIDUAL PARTICIPANT DATA

No individual participant data will be listed by measure or timepoint, except for listings of Serious Adverse Events, if detected, that will be listed individually in data tables reviewed internally by the investigative team and by the study DSM.

9.4.12 EXPLORATORY ANALYSES

If participant drop-out or non-adherence is substantial, the investigative team will conduct exploratory pooled logistic regression analyses to try to identify participant

characteristics associated with drop-out by 4 or 8 weeks. Similarly, if adherence is less than expected, simple linear, logistic, and/or proportional odds models may be developed (depending on the distribution of the adherence measure) to explore associations of participant characteristics with poor adherence to group classes and home practice.

10 DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

The informed consent process for this trial is designed to comply with NIH Human Research Protection Program policies, applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56), and ICH Good Clinical Practice. Informed consent documents and procedures have been approved by the Institutional Review Board for this study before being administered to participants.

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS

Before providing consent, each participant will receive information about the potential risks and benefits of study participation. An IRB-approved consent form describing in detail the study procedures and associated risks will be given to the participant electronically or on paper. The participant will be asked to read and review the document or have the document read to her by the start of the Screening Visit.

Coordinators may also have the participant read and sign a HIPAA authorization form granting study staff permission to access protected health information if needed. Depending on the clinical site, the participant may be asked to sign a HIPAA authorization form at the same time as the study consent form; alternately, she may be asked to sign a HIPAA form at a later date if needed to gain access to outside medical records.

Pursuant to California Health & Safety Code 24172, each participant will also receive a copy of the Experimental Subject's Bill of Rights, a document designed to describe in lay language the rights of every person who is asked to be in a research study. Study staff will document the participant's receipt of this document in her study file.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Before obtaining written consent from participants, study staff will explain the study requirements and ask participants if they any questions or concerns. Participants will have the opportunity to discuss the potential risks and benefits of participation with study staff and with any surrogates and to think over their decision before providing consent. Study staff will emphasize the rights and welfare of participants by emphasizing that the quality of the participants' clinical care will not be adversely affected if they decline to participate. Once participants' questions or concerns about

the study have been addressed, they will be asked to sign the consent form and will be given a copy of the consent form for future reference.

For this study, documentation of informed consent may involve paper-based consent forms or an electronic DocuSign-based consent process approved by the study IRB. For paper-based consent, a copy of the signed consent form and HIPAA form will be stored in the participant's chart in locked research offices. For electronic DocuSign-based consents, study coordinators will download an electronic file and store them in a UCSF IT managed PHI folder.

The consent process will be documented in the clinical or research record. To complete the informed consent process at the end of study participation, study staff will inform the participant when her participation has come to an end and will document this in the study record.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Circumstances that may warrant termination or suspension of the study include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (i.e., major protocol violation)
- Determination of the futility of proceeding with the study.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and/or the funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

In the event of study suspension, the study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, IRB, DSM, or other relevant regulatory or oversight bodies (OHRP).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality will be held in trust by the investigators, study staff, and the sponsor(s) and their agents. Study data will be protected to ensure participant confidentiality both during and after the study.

To promote confidentiality, each participant will be assigned a unique numerical study identifier that will be used on study forms instead of names or other individually identifying information. The document linking study ID to participant identifiers (name, address, and contact names and addresses) will be maintained in a password-protected file stored on a secure server protected by firewalls. Only the clinical coordinators who

need regular access to participant identifiers to contact participants will have access to the password.

If study team members or collaborators communicate electronically about participants, they will use study IDs in place of participant identifiers where possible. If electronic communication involving identifiers is necessary, study team members will use HIPAA-compliant secure electronic forms of communication only.

Information that could identify individual participants will not be released without the written permission of the participant, except as necessary for monitoring by the IRB, NCCIH, the OHRP, or other government agencies responsible for protecting participant safety. A study monitor or other authorized representatives of the sponsor may request to inspect study documents and records required maintained by the investigative team. If so, the clinical study site will permit access to such records to facilitate monitoring of the quality of the conduct of the study or the safety of participants.

10.1.4 FUTURE USE OF STORED DATA

Data collected during the trial may be stored in a de-identified form after the conclusion of the study to facilitate future research. When the study is completed, access to study data will be overseen by the UCSF Women's Health Clinical Research Center, using a data request process (see section 10.1.11, Publication and Data Sharing Policy).

Informed consent forms for this study will indicate that de-identified data may be stored for future research. However, during the conduct of the study, an individual participant can choose to withdraw consent to have data stored for future research.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

The primary governing body of the study is the **POPPY** Steering Committee (SC), composed of the Principal Investigator (PI), Co-Investigators (Co-I), and statistician. The SC will direct all aspects of the study, including protocol design, development of the operations manual, and selection of data collection instruments. As recruitment and enrollment begin, the SC will monitor study progress and quality and resolve issues that arise during follow-up. Finally, the SC will review and approve proposals for ancillary studies, analyses, and reports or presentations.

Independent monitoring of study safety and quality will be provided by a Data and Safety Monitor (DSM)/Medical Safety Officer who is independent of the institution and investigators participating in the study and has no financial, scientific, or other conflict of interest with the trial. The DSM will have experience in general, urological, or gynecologic medicine, clinical trial methodology, and biostatistics necessary to provide appropriate oversight for the proposed research. The DSM will not participate in the study as an investigator or be involved in any way in the conduct of the study.

Principal Investigator	Medical Monitor or Independent Safety Monitor
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10.1.6 SAFETY OVERSIGHT

The POPPY investigators will oversee the safety of participants enrolled in this study, following the procedures outlined in the Data and Safety Monitoring Plan (DSMP) approved by the NCCIH and the institutional IRB. Additionally, ongoing safety monitoring will be provided by an independent Data and Safety Monitor (DSM)/Medical Safety Officer (MSO) approved by the NCCIH.

The DSM/MSO will review the study protocol and the DSMP prior to initiation of any participant recruitment activities. Following initiation of recruitment, the DSM/MSO will review data on participant safety and data quality at least semiannually. Following each review, the DSM/MSO will make recommendations about continued conduct of the study, potential modification of study procedures, or potential early termination of the study to the study PI as well as to the NCCIH Program Official.

10.1.7 CLINICAL MONITORING

Not applicable—this study does not involve clinical monitoring by an independent party. Self-monitoring activities are described in Section 10.1.8, Quality Assurance and Quality Control.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

All study staff will follow Standard Operating Procedures (SOPs) previously established by the UCSF Women's Health Clinical Research Center that address:

- Training and Good Clinical Practice of study personnel and delegation of authority for research studies
- Procedures and standard for obtaining and documenting informed consent from participants
- Source documentation, data quality, data security and storage, and data transfer for data collection measures
- Documentation, reporting, and (if appropriate) corrective action for protocol deviations detected in the course of research

Should independent monitoring become necessary, the PI will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring

and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The investigative team under the direction of the Principal Investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data collected and reported. All source documents will be completed in a clear and legible manner to ensure accurate interpretation of data. The investigators will maintain accurate data forms and source documentation as relevant, using procedures outlined in Standard Operating Procedures (SOPs) by the study team, and follow procedures ensuring the accuracy and completeness of electronically entered data.

Accurate and complete data collection at each of the clinical sites will initially be the responsibility of the site-specific study staff under the supervision of the Site PI or other site-specific investigators. Any source documents collected at a study site must be reviewed by clinical coordinators at the relevant clinical site under the supervision of the Site PI, who will take initial responsibility for ensuring that they are accurate and complete. Site-specific personnel will also have initial responsibility for entering data completely and accurately into the electronic database.

Study data will be electronically entered, managed, and edited by clinical coordinators or other study staff at each of the clinical sites using Medrio, a secure, web-based application that is designed for research data entry and management and is compliant with 21 CFR Part 11. The Medrio system will automatically generate queries for missing data or of-range values based on initial programming by analysts at the UCSF Data Coordinating Center.

The UCSF Data Coordinating Center under the supervision of the coordinating center PI (who is also the overall study PI) will provide a secondary layer of oversight for data accuracy and completeness by tracking data queries posted in the electronic data capture system, prompting site-specific study personnel to address data queries for missing or out-of-range data in a timely manner, and generating study-wide reports for reviews of missing data or data outliers.

Overall data completeness and quality will be periodically assessed by the UCSF Data Coordinating Center using measures such as the number of missing data forms and the number of outstanding data queries flagged within this system. The study PI will review these indicators of data completeness and quality at monthly study-wide meetings involving investigators and personnel at all clinical sites.

For data derived from measures that require abstraction by study staff (i.e., pain log diaries, sexual activity logs), electronically entered data will be verified against source forms by a staff member who was not originally involved in entering the data. Hard

copies of these logs will be retained as source documents for each participant consented/enrolled in the study.

10.1.9.2 STUDY RECORDS RETENTION

Paper-based study documents will be retained for a minimum of 3 years after the date of Federal Financial Report (FFR) submission. This includes any paper-based participant consent forms, study charts, diaries, questionnaires, or other source documents. After that time, the investigators may destroy records without seeking permission from the sponsor or any external bodies.

10.1.10 PROTOCOL DEVIATIONS

Exceptions or deviations from this protocol are expected to occur rarely and, where possible, will be approved in advance by the principal investigator. Protocol exceptions/deviations may arise on the part of a participant, investigators, or study site staffs, and fall into one of two categories:

a) exceptions necessary to protect the safety or well-being of a participant (in this case, the protocol exception should apply to that participant only)

b) deviations due to oversight or error on the part of study investigators, staff, or participants, subsequently detected by the investigators or study personnel

For each protocol exception/deviation, study staff will document the event on a Protocol Deviations Log (located in an electronic regulatory folder). Entries in the Protocol Deviations Log will include the participant ID, date of the deviation, date the deviation is recorded, description of the deviation, and action taken in response to the deviation, if any. The study PI will document approval for each deviation determined in advance, or acknowledge each deviation detected after the fact. Protocol deviations will also be reported to the independent DSM and the NCCIH Program Official; any protocol deviations that may have a major impact on participant safety or the integrity of the study will also be reported to the institutional IRB. For deviations due to oversight or error, corrective actions will be developed and implemented by the study leadership, and a description of the steps taken to prevent recurrence will be submitted to the NCCIH Program Official, the independent DSM, and (if relevant) the institutional IRB.

For this study, missed yoga or control intervention classes will not be considered a protocol deviation, and neither will participants' failure to complete recommended home practice sessions (although study staff will make every effort to promote participants' adherence to classes and home practice). However, a participant's use of prohibited or discouraged interventions during the main intervention phase of the study will be considered a protocol deviation. This includes outside instruction in yoga or physical conditioning exercise techniques, initiation of new pain medications, or initiation of other formal psychological or behavioral treatments for pelvic pain during the main intervention phase of the study. A participant's use of these interventions during the post-intervention follow-up period will not be considered a protocol deviation, although study staff will record this in the study record.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study is subject to the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. The trial is registered at ClinicalTrials.gov, and summary results information from this trial will be submitted to ClinicalTrials.gov for public posting after completion. This includes information about the number of participants starting and completing the study, study performance on relevant outcomes, and important adverse events experienced by study participants. Results information will be submitted not later than one year after the trial's primary completion date, which will be defined as completion of all data collection activities (i.e., completion of all study outcomes and safety monitoring data collection procedures).

This research is also subject to the NIH Public Access Policy, which requires scientists to submit peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. The investigators intend to submit the results of this trial for publication in a peer-reviewed medical journal after data collection is complete. Submission of a manuscript presenting the primary trial findings is planned not later than one year after the trials' primary completion date, defined as completion of all trial-specific data collection activities. The trial steering committee, composed of the principal and co-investigators, will develop a publication plan upon the conclusion of the trial, which will take into account the significance, novelty, and diversity of trial results at the time that data analyses are conducted.

The investigative team has also developed a data sharing plan consistent with recommendations of the International Committee of Medical Journal Editors (ICMJE), recognizing the benefits of responsible sharing of data generated by interventional trials. Starting no later than 6 months following publication of the main trial results (including on-line publication), the investigative team will make publicly available de-identified individual participant data that underlie the results reported in the publication. This will include data about the baseline characteristics of the participants and any primary or secondary trial outcomes presented in the publication. To gain access, data requestors will be asked to sign a data access agreement.

When the study is completed, access to study data will be available through a data request process overseen by the UCSF Women's Health Clinical Research Center. Data requestors seeking to use trial data to generate new publications or presentations will be asked to submit a publication/presentation proposal that will be reviewed by the members of the trial steering committee of principal and co-investigators. Publication/presentation proposals will be reviewed for overlap with existing proposals as well as methodological appropriateness.

10.1.12 CONFLICT OF INTEREST POLICY

The study leadership has established policies and procedures for study group members to disclose conflicts of interest and to manage all reported dualities of interest, in compliance with the Department of Health and Human Services (HHS) conflict of

interest regulations. Any persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be required to disclose any actual conflicts of interest. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of the trial.

10.2 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
CI	Confidence Interval
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSM	Data and Safety Monitor
FFR	Federal Financial Report
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NCCIH	National Center for Complementary and Integrative Health
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.1	4-2-2021	Description of the poses in the yoga program amended to acknowledge Savasana (corpse pose) and include Sanskrit names for all poses	For the weighted breathing exercises in the yoga program, participants are taught to assume Savasana pose.

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