Lessening Incontinence through Low-impact Activity (LILA)

(a.k.a. Yoga to Enhance Behavioral Self-Management of Urinary Incontinence in Women)

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PRÉCIS

Study Title

Lessening Incontinence through Low-impact Activity (LILA), a.k.a. Yoga to Enhance Behavioral Self-Management of Urinary Incontinence in Women

Objectives

To develop and test procedures for a future full-scale efficacy trial of a group-based yoga therapy intervention in middle-aged and older women with urinary incontinence.

Design

Pilot, randomized, parallel-group trial of a group-based yoga therapy program versus physical conditioning control program for treatment of urinary incontinence in ambulatory middle-aged and older women.

Sample Size and Population

Up to ninety women aged 50 years and older who document stress-, urgency-, or mixed-type incontinence occurring an average of once per day on a voiding diary, are not participating in other organized yoga activities, are not using other clinical treatments for incontinence, and meet minimum mobility and other eligibility criteria will be recruited from the general San Francisco Bay Area.

Interventions and Duration

Eligible women will be randomized in a 1:1 ratio to participate in either a 12-week yoga therapy program (N~45) or a time-equivalent physical conditioning exercise control program (N~45). Women randomized in the yoga therapy program will take part in twice weekly group yoga classes focusing on selected Iyengar-based yoga techniques as well as practice study-specific yoga techniques at home for at least one hour per week for a total of 12 weeks. Women randomized to the physical conditioning control group will take part in twice weekly group physical conditioning classes and practice physical conditioning exercises at least one hour per week at home for 12 weeks.

Outcomes and Measurements

To assess feasibility, rates of enrollment and retention will be carefully monitored, and adherence yoga or stretching practice will be assessed during the 12-week intervention as well as 12 weeks after the end of the intervention programs. To collect preliminary data on treatment efficacy for urinary incontinence, validated 3-day voiding diaries will be used to document changes in the frequency of incontinence over 12 weeks of treatment, as well as persistence of changes 12 weeks after the end of the intervention programs. To collect preliminary data on treatment efficacy for other symptom and quality-of-life outcomes, validated self-administered questionnaires will also be used to examine changes in other urinary tract symptoms, condition-specific quality of life, and anxiety and perceived stress over 12 weeks of treatment, as well as persistence of changes12 weeks after the end of the intervention programs.

1. STUDY OBJECTIVES

Aim 1: To examine the feasibility of recruiting and retaining ambulatory women aged 50 years and older into a randomized trial of a yoga therapy versus physical conditioning program for treatment of incontinence, and explore potential differences in retention and adherence by duration of treatment and follow-up.
Expected outcome 1: We expect to recruit and randomize 15 to 30 women in each 3-month enrollment wave to confirm our ability to assemble a class size of 8 to 15 women per group per wave in a future full-scale trial.
Expected outcome 2: We expect drop-out rates in both treatment groups to increase over time, but remain <20% after 12 weeks of treatment and <30% at 12 weeks of post-treatment follow-up.
Expected outcome 3: We expect adherence to decrease over time, but remain >75% at 12 weeks of treatment (for group classes and home practice) and >50% at 12 weeks post-treatment (for home practice only).

Aim 2: Explore whether a clinically meaningful reduction in incontinence frequency could be detected in a full-scale trial of yoga versus physical conditioning, and examine potential differences in treatment efficacy by duration of treatment and follow-up.
Expected outcome 1: We will collect data on the standard deviation, intra-class correlation, and between-group difference in change in incontinence frequency to guide sample size projections for a future full-scale trial powered to detect a 25% greater reduction in incontinence frequency associated with yoga therapy.
Expected outcome 2: We will examine time-related trends in treatment effects on incontinence frequency to guide expectations of treatment efficacy over 8 versus 12 weeks of treatment as well as persistence of treatment benefits after 12 weeks of post-treatment follow-up in a future full-scale trial.

Aim 3: Explore potential effects of yoga versus physical conditioning on other symptom and quality-of-life outcomes associated with incontinence and examine potential differences in treatment efficacy by duration of treatment and follow-up.
Expected outcome 1: We will collect data on standard deviations, intra-class correlations, and between-group differences for changes in anxiety, depression, and quality-of-life questionnaire scores to guide estimates of minimum detectable effects for these secondary outcomes in a future full-scale trial.
Expected outcome 2: We will examine time-related trends in treatment effects on these secondary outcomes to guide expectations of treatment efficacy over 8 versus 12 weeks as well as persistence of benefits after 12 weeks of post-treatment follow-up in a future full-scale trial.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition

Approximately one in four middle-aged and older women suffer from urinary incontinence, a condition associated with depression, social isolation, functional decline, falls and fractures, and admission to long-term care facilities.[1-8] In economic analyses, the annual estimated direct costs of incontinence among U.S. women exceed $20 billion, greater than that of breast, ovarian, cervical, and uterine cancers combined.[9]

Current first-line treatment for both stress- and urgency-type incontinence includes behavioral management strategies such as bladder re-training and pelvic floor exercises to increase bladder capacity, strengthen the muscles supporting the bladder neck, and suppress involuntary bladder contractions. Unfortunately, many patients who attempt to practice these techniques after routine teaching by general practitioners are not able to do so effectively.[10-13] Although the efficacy of these techniques can be improved by in-depth, one-on-one training and biofeedback with pelvic physical therapists or other specialized medical practitioners, this type of intensive pelvic floor rehabilitation therapy is costly, and access to trained pelvic physical therapists in the community is limited.[14,15]

Second-line treatment for urgency-type incontinence (i.e., leakage caused by a sudden urge to void) consists primarily of anticholinergic drugs that are modestly effective in reducing incontinence, but have multiple side effects such as dry mouth, stomach upset, constipation, and cognitive impairment. As a result, over half of patients who initiate anticholinergic therapy discontinue it within a year.[16-18] For stress-type incontinence (i.e., leakage with activities that increase abdominal pressure), surgery and other invasive procedures can be effective, but are inappropriate or poorly tolerated by many patients, especially older women who are at greatest risk of incontinence.[19] There is a need for alternate therapies that that are not only effective, but also more accessible and better tolerated.

2.2 Study Rationale

Yoga is a complementary behavioral intervention with the potential to improve incontinence through multiple mechanisms, while avoiding the shortcomings of existing therapies. When taught in a way that emphasizes mindful awareness of specific bodily structures, yoga can be used to help women control and strengthen their pelvic floor muscles through group instruction and home practice. As a result, a group-based yoga program that incorporates practice of specific yoga postures to promote awareness and engagement of the pelvic floor may provide a more accessible alternative to traditional, one-on-one pelvic floor rehabilitation therapy, provided that it can be taught in a standardized way that is appropriate for patients' clinical and safety needs.

Yoga can also alleviate anxiety, stress, and associated autonomic imbalance, as factors that contribute to incontinence and magnify its impact on quality of life. Clinical studies indicate that women with high self-reported levels anxiety or stress are at increased risk of developing incontinence, and that women with chronic incontinence experience worsening of their incontinence after exposure to stress-inciting events.[20-27] Although cognitive behavioral therapy, hypnotherapy, and other types of psychotherapy have been explored as potential treatments for incontinence,[28-31] these strategies are again limited by the need for intensive, one-on-one sessions with mental health specialists. In contrast, a group-based yoga program that promotes relaxation through deep breathing and other restorative techniques may provide a more generalizable, community-based strategy for women to decrease anxiety and stress[32-36] in order to improve both bladder control and quality of life.

To examine the feasibility of using yoga to treat incontinence in middle-aged and older women, our research team previously developed a group-based, Iyengar-style yoga therapy program consisting of twice weekly classes and once weekly home practice sessions. In a pilot trial involving 19 ambulatory middle-aged and older women with at least 7 episodes of urgency, stress, or mixed-type incontinence per week, women

randomized to this therapeutic yoga program experienced a 70% decrease in incontinence frequency over 6 weeks, versus 16% for the waitlist control (P=.05), without any increase in adverse events.[37]

We now plan to conduct an R34-scale pilot study to develop, test, and refine procedures for a more rigorous, full-scale efficacy trial of yoga for treatment of incontinence in middle-aged and older women. Information collected during this pilot trial will allow the research team to evaluate and strengthen procedures for recruiting, randomizing, and retaining participants for a future efficacy trial, as well as collect more preliminary data on the potential efficacy of the study interventions on clinical and quality-of-life outcomes.

3. STUDY DESIGN

The LILA study is a pilot randomized parallel-group trial of a group-based yoga therapy program versus physical conditioning control program for treatment of urinary incontinence in ambulatory middle-aged and older women. Women aged 50 years and older who document at least 3 episodes of stress-, urgency-, or mixed-type incontinence on a screening 3-day voiding diary, are not using other clinical treatments for incontinence, and meet minimum physical mobility requirements and other eligibility criteria will be recruited from the general San Francisco Bay Area by research coordinators based at the University of California San Francisco. Eligible women will be randomized in a 1:1 ratio to participate in either a 12-week yoga therapy program (N~45) focusing on selected Iyengar-based yoga techniques, or a time-equivalent physical conditioning exercise control program (N~45). Women randomized in the yoga therapy program will take part in twice weekly group yoga classes involving 8 to 15 other women as well as practice study-specific yoga techniques at home for at least one hour per week for a total of 12 weeks. Women randomized to the physical conditioning control group will take part in twice weekly group physical conditioning classes and practice physical conditioning exercises at least one hour per week at home for 12 weeks. During a 12-week post-treatment follow-up period, participants will also be encouraged to continue practicing yoga or stretching exercises for at least an hour per week.

To address aim 1, the study team will carefully track the progress of recruitment and randomization and monitor participants' adherence to group classes and home practice over 12 weeks of yoga or stretching training as well as 12 weeks after the end of the training programs. To address aim 2, validated voiding diaries will be used to document changes in the frequency of urinary incontinence over 12 weeks of yoga or stretching training as well as persistence of changes 12 weeks after the end of the training programs. To address aim 3, validated questionnaires will be used to examine changes in anxiety and perceived stress symptoms and condition-specific quality of life over 12 weeks of yoga or stretching training as well as persistence of changes 12 weeks after the end of the training programs.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

Eligibility criteria have designed to identify a population that is generalizable to most ambulatory middle-aged and older women with incontinence in the community who do not have a major contraindication to practicing yoga.

4.1 Inclusion Criteria

Candidates must meet all of the following criteria to participate in the study:

- Women aged 50 years or older who report urinary incontinence starting at least 3 months prior to screening
- Self-report at least 3 urinary incontinence episodes on a screening 3-day voiding diary (i.e., an average of at least one episode per day)
- Self-report urgency-predominant (i.e., at least half of incontinence episodes being urgency-type), stress-predominant (i.e., at least half of episodes being stress-type), or mixed-type (i.e., an equal number of stress- and urgency-type episodes) incontinence on the screening voiding diary
- Willing to refrain from initiating medical treatments that may affect their incontinence or voiding pattern during the study intervention period

4.2 Exclusion Criteria

Candidates meeting any of the following criteria at baseline will be excluded from participation:

- Participation in formal or organized yoga classes or instruction within the past 3 months; or any prior yoga therapy directed specifically at improving urinary incontinence or pelvic floor dysfunction
- Participation in at least weekly organized physical conditioning classes or instruction in the past 3 months involving muscle stretching and strengthening exercises (not including aerobic classes that do not emphasize stretching or strengthening).
- Currently pregnant (by self-report or screening urine pregnancy test), gave birth within the past 6 months, or planning pregnancy during the study period (approximately 2 to 6 months)
- Current urinary tract infection (screening dipstick urinalysis with leukocyte estrace, nitrites or blood) or a history or 3 or more urinary tract infections in the preceding year
- Report history of neurologic conditions such as stroke, multiple sclerosis, spinal cord injury, or Parkinson's disease, or a lumbosacral spine condition associated with neurological symptoms
- Unable to walk up a flight of stairs or at least 2 blocks on level ground without assistance (i.e., functional capacity < 4 METs)
- Unable to get up from a supine to a standing position in 10 seconds or less and without assistance
- Morbid obesity defined by a measured body mass index of >40 kg/m^2 at the screening evaluation.
- Report any history of prior anti-incontinence or urethral surgery (not including urethral dilation), pelvic cancer, or pelvic irradiation for any reason
- Report use of bladder botox, electrostimulation, bladder training, or pelvic floor exercise training (with certified practitioners) in the past 3 months
- Report other surgery to the pelvis (hysterectomy, oophorectomy, vaginal surgery, bladder surgery, colon surgery) within the past 3 months
- Report use of medications with the potential to affect incontinence (anticholinergic bladder medications, tricyclic antidepressants, selective norepinephrine reuptake inhibitors, mirabegron, loop diuretics) within the past month
- Report starting stopping, or changing the dose of a medication with the potential to affect anxiety or stress symptoms (i.e., selective serotonin reuptake inhibitors, anxiolytics/sedatives, antipsychotics) within the past 1 month, or plans to start, stop, or change to dose of such a medication during the study period

- Report use of medical devices (i.e. pessary) for incontinence within the previous month (participants may stop use of device and re-present for study)
- Report history of interstitial cystitis, fistula or hole in bladder or rectum, or birth defect leading to urine leakage
- Report symptomatic pelvic organ prolapse (assessed using a standardized question, ""Have your pelvic organs (uterus, bladder, or rectum) been dropping out of your vagina causing a feeling of bulging, pressure, or protrusion or a sensation like your "insides are coming out"?")
- Report history of vulvodynia, chronic pelvic pain, or pain when practicing pelvic floor exercises
- Report conditions that, in the judgment of the investigators, render potential participants unlikely to follow the protocol, including plans to move, substance abuse, significant psychiatric problems, or dementia
- Participation in another research study that involves investigational drugs or devices that could potentially confound the results of this study
- Unable to understand study procedures, complete study interviews, or and provide informed consent in English

4.3 Study Enrollment Procedures

Recruitment: Participants will be recruited from the greater San Francisco Bay area using a multi-component approach that has been employed successfully in past clinical trials led by the investigators. This includes community-based media efforts (newspaper and radio advertisements, notices posted in community and senior centers, mass community mailings), recruitment from a database of women who have given permission to be contacted for women's health research studies based at the University of California San Francisco, and posting of recruitment fliers in clinician offices (such as general internal medicine, geriatrics, gynecology, or alternative medicine).

Recruitment will be organized in waves to assemble successive cohorts of women who are confirmed to meet all eligibility criteria and who are available to attend upcoming group yoga or physical conditioning classes. Based on past experience, the investigators assume that three waves will be needed to recruit and randomize at 60 eligible participants, with up to three months of recruitment required per wave, and 15 to 20 eligible women randomized in each wave. This will allow for a minimum of ~8 women taking part in each class series in each intervention group.

Screening: Preliminary eligibility will be determined by research coordinators through a Screening Telephone Interview followed by an in-person Screening Clinic Visit. During the Screening Telephone Interview, coordinators will follow a standardized screening interview script to assess preliminary eligibility related to age, gender, incontinence history, and exclusionary conditions and medications and document reasons for ineligibility on the screening interview form (see section 6.2.3, Screening Procedures, for more detail). Candidates who appear preliminarily eligible at the end of the screening telephone interview will be scheduled to attend an in-person Screening Clinic Visit. After providing written informed consent at this visit, women will undergo more detailed assessment of incontinence symptoms, use of clinical incontinence therapies, exclusionary medical conditions, exclusionary medications, urine dipstick and pregnancy testing (for women of childbearing potential), and brief physical function assessment (see description of study procedures below), with reasons for eligibility or ineligibility documented on the screening clinic intake form.

At the end of the Screening Clinic Visit, women who appear eligible will be given a blank voiding diary and instructions for completing it at home over a 3-day period and returning it to study staff at a Baseline Clinic Visit. Those who are confirmed to have stress-predominant, urgency-predominant, or mixed urgency-stress incontinence occurring at least 3 times over the 3-day diary period and meet all other inclusion/exclusion criteria at the Baseline Clinic Visit will be considered eligible for randomization to one of the two intervention groups.

Randomization: During each recruitment/randomization wave, eligible women will be randomized in a 1:1 ratio to one of the two intervention groups. Randomization will be stratified by clinical type of incontinence (i.e., stress, urgency, or mixed), to ensure adequacy of randomization within these three types. Randomization will be implemented by computer algorithm using randomly permuted blocks of sizes 2 and 4, with proof of eligibility required before assignment. To avoid manipulation, standard allocation concealment procedures will be followed (see section 6.2.4. on Randomization for more detail).

To avoid excessive lag time between randomization and the start of the yoga therapy or physical conditioning programs, randomization will take place within two weeks of the yoga or physical conditioning program orientation session. For candidates whose Baseline Clinic Visit falls within this two-week window, randomization will take place directly at the Baseline Clinic Visit. For candidates who complete their Baseline Clinic Visit more than two weeks before the start of the yoga or physical conditioning intervention programs, a Randomization Telephone Call will be scheduled to complete randomization within the two-week window.

5. STUDY INTERVENTIONS

5.1 Yoga Therapy Program

Overview and rationale: The 12-week yoga therapy program will provide instruction and practice in a variety of yoga postures and techniques that have been selected by the study yoga expert consultants for their potential to improve bladder control and safety and feasibility for the target population. The study will feature a therapeutic program based primarily on Iyengar yoga, a form of Hatha yoga that is known for its potential therapeutic applications, has been employed successfully in other studies of yoga for different indications,[32,34,38-44] and differs from other Hatha yoga styles (power yoga, bikram yoga) in multiple ways that are likely to maximize both efficacy and safety for this study. These include: 1) emphasis on precise anatomical and postural alignment during practice of yoga postures; 2) incorporation of props to minimize risk of injury and accommodate those with lower strength or flexibility; 3) emphasis on mindful awareness during practice of postures rather than rapid cycling through postures. The resulting yoga program, which was pre-tested and refined in the investigators' pilot LILY trial,[37] is designed to maximize women's awareness of and control over the pelvic floor and improve underlying stress and anxiety, while still being feasible for ambulatory women across a wide range of ages, as well as grounded in techniques common to Iyengar yoga at large.

Content and postures: The study yoga program will focus on a core set of 14 postures that are widely used in yoga practice, have been pre-tested in the investigators' earlier pilot study, and can be safely adapted for ambulatory women of all ages, including those with moderately decreased flexibility or mobility. These

include both active postures engaging the pelvic floor and more passive postures promoting relaxation: Baddha Konasana (bounded angle pose), Bharadvajasana (seated twist pose), Malasana (squat pose), Parsvokonasana (side angle pose), Parsvottasana (intense side stretch pose), Salabhasana (locust pose), Savasana (corpse pose), Salamba Set Bandhasana (supported bridge pose), Supta Baddha Konasana (reclined cobbler's pose), Utkatasana (chair pose), Supta Padagushthasana (reclined big toe pose), Tadasana (mountain pose), Trikonasana (triangle pose), Viparita Karani Variation (legs up the wall pose), and Virabhadrasana 2 (warrior 2 pose).

Staff qualifications and training: Each yoga therapy class series will be led by a primary instructor who will: 1) have at least 2 years of experience teaching yoga in the community; 2) review a detailed, study-specific written instructor manual describing all of the postures and yoga techniques to be used in the study program; 3) complete at least 2 hours of in-person training in study-specific techniques with one of the study yoga expert consultants (Leslie Howard or Judith Lasater); 4) complete study-specific training in documentation of participant attendance, review of home practice logs, and recording of yoga postures practiced during group classes on appropriate study forms; 5) carry and submit proof of personal liability insurance (minimum of $2 million coverage); and 6) confirm his or her willingness to adhere to the study intervention procedures. To maximize the generalizability of the study results and minimize observed effects due to specific providers, different primary instructors will be sought for each yoga class series. For each class series, a back-up instructor will also be identified who can teach a class in the event that the primary instructor is ill or is unable to teach due to an emergency.

Orientation and classes: Prior to group instruction, participants in each class series will attend a 90-minute group orientation led by an appointed class instructor. This will include an overview of the general principles of Iyengar yoga, an orientation to the structures of the pelvis, spine, and lower extremity, and an introduction to the yoga postures and the props to be used in the study. After the orientation, women will attend 90-minute group classes twice weekly for 12 weeks, led by the same instructor as well as an assistant to provide personalized attention to students. During group classes with an expected size of 8 to 15 participants, the instructor will guide women in practicing yoga postures, calling attention to ways in which postures can improve pelvic floor function and adapt postures to accommodate physical limitations. Women will also be taught to avoid habits that may worsen incontinence during practice, such as squeezing of abdominal rather than pelvic muscles. Following a study-specific guide, instructors will gradually introduce postures as classes progress, with the goal of making participants comfortable with all core postures by the end of 8 weeks and fully confident in performing postures by 12 weeks.

Home practice: In addition to attending group classes, participants will be asked to practice yoga at home at least one additional time per week and will be given a diary to keep track of the dates and times of practice. Women will also be given a written manual, pre-tested in the pilot LILY study,[37] that includes pictures and descriptions of each yoga posture to guide them in home practice. Each participant will be given a limited set of yoga props (a mat, belt, and 2 blocks) for home practice. Women will be encouraged to practice with other members of their classes, but will be discouraged from practicing with individuals who are not in their class and from taking part in non-study yoga activities that might dilute study techniques. After the

end of the main 12-week study period, participants will be encouraged to continue practice yoga at least one hour per week at home, although they will not continue to attend study-specific group classes.

Quality and safety: The study program will incorporate multiple modifications to help women across the age range to perform postures in ways that minimize risk of muscle strain or injury. Participant manuals will include specific instructions on adapting each posture and/or using props to accommodate problems with mobility, flexibility, or balance. To promote quality and safety, the instructors leading classes will be required to have at least 2 years of experience teaching yoga and have completed dedicated, study-specific training with the study's expert consultants. Following procedures established in the pilot study, a consultant will visit at least one class in each series to ensure that postures are being taught according to protocol, evaluate students' success in learning yoga, and ensure fidelity across instructors. Monthly conference calls will be conducted to help instructors trouble-shoot issues that arise in instruction.

5.2 Physical Conditioning Control Program

Overview and rationale: This trial will include a 12-week physical conditioning program that will provide a rigorous time-and-attention control for the yoga program, but has been designed to avoid engaging the pelvic floor or promoting mindful relaxation. To minimize differential expectations of treatment success, women will be told that they are enrolling in a study of two different types of low-impact physical activity-based interventions (yoga versus physical conditioning) to enhance management of incontinence. Physical conditioning exercises have been adapted from exercises used in prior studies conducted by the investigators, such as the PRYSMS trial of restorative yoga vs. stretching for metabolic syndrome (designed by Sarah Pawlowsky, DPT, consultant on this proposal), in which participants maintained good adherence to the stretching program despite a long study period. Similar to postures in the yoga therapy program, the exercises in the physical conditioning program have been selected for their potential to be performed safely by women across a range of ages and flexibility levels.

Content and exercises: After a brief education about sitting and standing posture, the physical conditioning program will focus on a core set of stretching/strengthening exercises that will be performed sitting in a chair: levator scapulae, upper trapezius, scalenes, shoulder horizontal adduction, triceps, pectoral stretch with hands behind head, wrist flexors and extensors, trunk flexion, trunk extension, trunk side-bend, trunk rotation, and hamstring stretches. Additional chair exercises will incorporate a stretching strap: pectoral stretch with strap, gastrocnemius stretch with strap, and hand behind back with strap. A few stretches will be performed on an exercise mat on the floor: supine single knee to chest, supine hamstrings stretch with strap, quadriceps stretch with strap, supine shoulder flexion with stretch strap, and seated adductor stretch. Three exercises will be performed in the standing position: gastrocnemius, soleus, shoulder flexion, and shoulder abduction stretches.

Staff qualifications and training: Each physical conditioning class series will be led by a primary instructor who: 1) is either certified as a personal trainer through the National Academy of Sports Medicine or the American College of Sports Medicine, or licensed as a physical therapist by the Physical Therapy Board of California; 2) has at least 2 years of experience working as a physical therapist or physical trainer in either individual or group settings; 3) will have reviewed a detailed, study-specific

training manual describing all of the stretching/strengthening exercises to be used in the study program; 4) will have completed at least 2 hours of in-person training in study-specific techniques with study expert consultant Sarah Pawlowsky, DPT; 5) will have completed study-specific training in documentation of participant attendance, review of home practice logs (for adherence), and recording of exercises performed during group classes on appropriate study forms; 6) carries and submits proof of personal liability insurance (minimum of $2 million coverage); 7) confirms his or her willingness to adhere to the study intervention procedures. To maximize the generalizability of the study results and minimize observed effects due to specific providers, different primary instructors will be sought for each class series. For each class series, a back-up instructor will also be identified who can teach a class in the event that the primary instructor is ill or is unable to teach due to an emergency.

Group orientation and classes: Similar to the yoga therapy program, the physical conditioning program will begin with a group orientation led by a physical therapist or trainer and an assistant, who will provide an overview of the stretching/strengthening exercises to be covered in the program. This will be followed by 90-minute twice weekly group classes, each with 8 to 15 participants, led by the same therapist and assistant, who will have received in-person study-specific training from consultant Sarah Pawlowsky, DPT. Classes will be designed to make women comfortable with all stretching/strengthening exercises by 8 weeks and fully confident in performing exercises by 12 weeks.

Home practice: In addition to attending group classes, women will be asked to perform stretching/strengthening exercises at home at least one additional time per week and record the dates and times of practice in a log. Women will receive a detailed manual with pictures and descriptions of each stretching/strengthening exercise to guide them in home practice, as well as a stretch strap and exercise mat to use at home. After the end of the main 12-week study period, participants will be encouraged to continue practice stretching/strengthening exercises at least one hour per week at home, although they will not continue to attend study-specific group classes.

Quality and safety: Instructors leading physical conditioning classes will be physical therapists or trainers who have at least 2 years of experience working with adults of a range of ages and have completed dedicated in-person training with Sarah Pawlowsky, DPT. Dr. Pawlowsky will provide quality monitoring and assess women's success in learning stretching/strengthening exercises by making an in-person visit to at least one class in each series. She will also lead monthly conference calls with instructors, similar to quality monitoring for the yoga program.

5.3 Concomitant Interventions

5.3.1 Required Interventions

Participants in both intervention groups will also receive a pamphlet at the Baseline Clinic Visit that provides basic patient-directed information about first-line behavioral self-management of incontinence, including pelvic muscle exercises, timed urination, and urge suppression. This pamphlet is consistent with usual care of incontinence in the general community, and has been used in previous studies of experimental treatments for incontinence conducted by the investigators.[45] Since information about behavioral self-management of incontinence is available from multiple websites and public resources,

systematic provision of this information will help avoid differential use of self-management techniques between treatment groups, and will also reflect expected concomitant use of these techniques with yoga in clinical practice. Participants will be queried about use of these techniques at baseline, at the 8-week and 12-week clinic visits, and as part of the 24-week assessment, so that information about co-interventions can be incorporated into data analyses if appropriate.

5.3.2 Prohibited Interventions

Participants will be asked to refrain from using other clinical treatments for incontinence during the 12-week intervention period as well as the 12-week post-treatment follow-up period. These include medications with the potential to affect incontinence symptoms (anticholinergic bladder medications, selective norepipherine reuptake inhibitors, tricyclic antidepressants, mirabegron), invasive or surgical bladder treatments, medical devices used to improve bladder symptoms (e.g., pessary), and behavioral treatment programs administered by certified practitioners (e.g., pelvic floor rehabilitation therapy, biofeedback programs). Additionally, participants will be asked to refrain from starting or changing the dosage of medications that could affect anxiety and perceived stress symptoms (e.g., antidepressants, sedatives/hypnotics, or antipsychotic agents), although maintenance of stable dosages of these medications will be acceptable.

Participants will be queried about use of these prohibited interventions at baseline, at the 8-week and 12-week clinic visits, and as part of the 24-week assessment. If participants are found to be using prohibited interventions, they will not be required to terminate the study early, but study staff will also re-urge participants to avoid using prohibited interventions if at all possible (although this may not be possible for some types of interventions), and information about use of prohibited interventions can be taken into account in data analyses.

5.4 Adherence Assessment

Adherence to group yoga and physical conditioning classes will be documented by the study class instructors using standardized attendance logs. Attendance logs will be returned to clinical coordinators on at least a weekly basis throughout the yoga therapy and physical conditioning programs. Clinical coordinators will immediately contact any participant who misses a scheduled class to ask about reasons for missing the class, reinforce the importance of class attendance, and troubleshoot any barriers to attendance.

Adherence to home practice of yoga or stretching/strengthening exercises will be tracked using home practice logs. Participants will be instructed to record the date, time, and duration of each home practice session in their logs, as well as the specific yoga poses or stretching/strengthening exercises practiced during each session. Home practice logs will be collected by class instructions and returned to the clinical coordinators on a weekly basis during the 12-week treatment program. Clinical coordinators will contact any participant whose log indicates that she is not practicing yoga or stretching exercises at least one hour a week at home. Additionally, home practice logs will be returned by mail 12 weeks after the end of the intervention program to assess home practice during the post-treatment follow-up period.

Every effort will be made to encourage participants to complete all intervention classes and practice sessions. Prior to randomization, study coordinators will stress the importance of adherence to group classes and home practice, and only those women who indicate that they are available on scheduled class dates and willing to practice yoga or stretching exercises at home as recommended will be eligible for randomization. The importance of adherence will again be stressed at the orientation session for each yoga or physical conditioning series, as well as during follow-up telephone calls 2 weeks and follow-up visits at 8 weeks. Additionally, attendance sheets from yoga and stretching classes will be carefully monitored, and home practice logs will be reviewed weekly, so that study staff can immediately call any women who miss classes or fail to document home practice in order to reinforce the importance of attendance/practice and troubleshoot barriers to adherence.

6. STUDY PROCEDURES

6.1 Study Measures

6.1.1 Urinary Incontinence

The primary efficacy outcome, frequency of any urinary incontinence, will be assessed using a 3-day voiding diary that has been shown to be a valid and reliable method for documenting change in incontinence symptoms and is widely used in clinical trials of incontinence treatments.[46,47] At screening/baseline, 8 weeks, 12 weeks, and 12 weeks after the end of the yoga and physical conditioning programs (24 weeks), each participant will receive written instructions and a blank diary to take home, and will use the diary to record all voiding and incontinence episodes over a 3-day period and classify incontinence episodes by clinical type (urgency, stress, other). Upon return of the diary, an analyst will abstract data to determine the number of total as well as urgency and stress incontinence episodes per day. For diaries that are completed after randomization, data will be abstracted by an analyst who is blinded to treatment assignment.

6.1.2 Condition-Specific Quality of Life

To address incontinence-related quality of life, participants will complete the following validated questionnaire measures at baseline, 8 weeks, and 12 weeks, as well as 12 after the end of the yoga and physical conditioning programs (24 weeks):

A. Incontinence Impact Questionnaire (IIQ)-- a validated, 28-item measure of the impact of incontinence on 4 domains of functioning and quality of life (physical activity, emotional health, relationships, and travel).[48,49] Scores range from 0 to 100; higher scores indicate worse impact.
B. Urogenital Distress Inventory-6 (UDI-6)-- a validated, 6-item measure that assesses subjective distress from frequent urination, urgency incontinence, stress incontinence, small-volume leakage, difficulty emptying the bladder, and genital pain.[49] Scores are scaled from 0 to 100.
C. Patient Perception of Bladder Condition (PPBC)-- a validated single-item measure assessing the degree to which respondents consider their condition to be a problem on a 6-point scale.[50,51]

6.1.3 Anxiety and Perceived Stress

To evaluate anxiety and perceived stress symptoms that may be associated with incontinence, participants will complete the following validated questionnaire measures at screening/baseline, 8 weeks, and 12 weeks, as well as 12 weeks after the end of the yoga and physical conditioning programs (24 weeks):

A. Spielberger State Trait Anxiety Inventory (STAI): Somatic anxiety (i.e., the affective component of anxiety believed to be related to autonomic physiological arousal response) will be measured using the trait component of the STAI, a 20-item self-administered measure validated in clinical populations, including patients with bladder symptoms, with scores ranging form 20 to 80.[52,53]
B. Hospital Anxiety and Depression Scale (HADS): Cognitive anxiety (i.e., the mental component of anxiety associated with fear of failure) will be measured by the HADS, a validated self-administered questionnaire that includes a 7-item Anxiety Subscale[54] shown to be sensitive to change in incontinence trials.[55] Scores range from 0 to 21, with higher scores indicating greater anxiety.
C. Perceived Stress Scale (PSS): Perceived stress will be assessed by the PSS, a 10-item measure of thoughts and feelings related to perceived stress in the past month, validated in a probability sample of the United States.[56] Scores range from 0 to 40; higher scores indicated greater stress.
D. Center for Epidemiologic Studies Depression Scale (CES-D): Depressive symptoms will be assessed by the CES-D, a 20-item measure that has been widely used in clinical trials, including bladder interventions, and is sensitive to change.[57] Total scores range from 0 to 60.

6.1.4 Yoga/Physical Conditioning Self-efficacy and Competency

A. Yoga Posture Self-Efficacy: At 8 weeks and 12 weeks, as well 12 weeks after the end of the yoga therapy program (24 weeks), women in the yoga group will complete a structured questionnaire (modeled after an existing self-efficacy measure [58] and pre-tested in the investigators' previous pilot study) to indicate how confident they are that they can perform each of the postures featured in the program (from 'not at all' to 'extremely confident'). Total scores will range from 0 to 56, with higher scores indicating greater confidence. A corresponding questionnaire will be administered to the physical conditioning group participants.
B. Independent Yoga Competency Assessment: To provide a more objective assessment of women's success in learning yoga, a yoga expert consultant will attend one class at the end of each series and observe women as they practice yoga. The consultant will rate each woman's success in performing each yoga posture on a 5-point scale, ranging from "not at all" to "extremely" successful. Total scores will range from 0 to 56. In the physical conditioning control group, Sarah Pawlowsky, DPT, will provide similar assessments.
C. Yoga Practice Adherence Self-Efficacy: At 8 weeks and 12 weeks, as well 12 weeks after the end of treatment (24 weeks), women will complete a measure of confidence in adhering to yoga or stretching practice, modeled after existing physical activity adherence self-efficacy scales [59] and tested

in the pilot study. Women will indicate on a 5-point scale how confident they are that they can practice yoga or stretching when they: 1) are tired, 2) are in a bad mood, 3) have limited time, 4) are away from home, and 5) are not regularly attending yoga classes. Scores will range from 0 to 20.

D. Credibility and Expectations of Treatment: To assess whether women perceive the yoga and physical conditioning interventions as equally credible and have similar expectations for improvement in incontinence, we will administer a modified version of an expectancy/credibility measure used in other women's health studies at baseline.[60]

6.1.5 Additional Screening and Covariate Measures

The following data will be collected to assess eligibility, assess whether treatment groups are comparable at baseline, and guide statistical adjustments in the event groups are not balanced:

A. Demographic history including date of birth, gender/sex, race/ethnicity, education history, employment history, marital status (screening/baseline)
B. Urologic/urogynecologic history including age of onset of incontinence, past and current treatment of incontinence, history of pelvic surgery, history of pregnancy and delivery, menstrual/menopausal status (screening/baseline)
C. General medical history including general health assessed by the CDC Healthy Days module,[61] selected medical conditions associated with incontinence such as diabetes, and current medication use (screening/baseline and 12 weeks)
D. Health-related habits such as tobacco/alcohol use, prior yoga experience, prior group-based physical activity instruction, physical activity level by the International Physical Activity Questionnaire[62,63] (screening/baseline)
E. Sleep quality assessed using the Pittsburgh Sleep Quality Index (PSQI),[39,40] a validated questionnaire evaluating sleep quality, latency, efficiency, and problems (screening/baseline, 8 weeks, 12 weeks, 24 weeks)
F. Physical exam measures including measured height, weight, heart rate, and blood pressure (screening/baseline, 8 weeks, and 12 weeks)
G. Physical function including self-reported function using the PROMIS Adult Physical Function Profile short-form.[64] Participants will also undergo direct physical mobility evaluation using the Short Physical Performance Battery[65] (screening/baseline, 8 weeks, and 12 weeks).

6.2 Evaluations

6.2.1 Screening Evaluations

Screening evaluations will be conducted by study coordinators based at outpatient facilities at 2330 Post Street on the Mt. Zion campus of UCSF, which contain all equipment needed for screening assessments. Screening procedures will include a brief preliminary Screening Telephone Interview, followed by an in-person Screening Clinic Visit, completion of a 3-day voiding diary at home, and review of the diary at an in-person Baseline Clinic Visit. All screening procedures must be completed within a 90-day period in order for participants to be eligible for randomization. If screening procedures cannot be completed within 90 days, initial screening procedures must be repeated to ensure that participant eligibility has not changed prior to randomization.

6.2.2 Consenting Procedure

Prior to administration of any data collection instruments, signed consent will be obtained by a research coordinator at the beginning of the Screening Clinic Visit. A single informed consent process will be used that will cover both the screening and post-randomization procedures. All participants must be able to read and understand the consent form in English and must provide written informed consent before enrolling in the study. Following the UCSF IRB-approved template (see Appendix A), the consent form will describe the purpose of the study, the procedures involved in recruiting, randomized, and monitoring participants, and the potential risks and benefits associated with participation. A study coordinator will first explain the study procedures to the potential participant, referring as necessary to the detailed IRB-approved consent form. The coordinator will then give a paper copy of the consent form to the potential participant to read. After the potential participant has read the consent form, she will be asked if she has any questions or concerns about the study. Once these questions/concerns have been addressed, the participant will be asked to sign the consent form, and will be given a copy of the consent form to take home for future reference. Coordinators will also have each participant read and sign a HIPAA authorization form granting study staff permission to access protected health information if needed. Pursuant to California Health & Safety Code 24172, each participant will also receive a copy of the Experimental Subject's Bill of Rights. A copy of the signed consent form and HIPAA authorization form will be stored in the participants' chart in locked research offices.

6.2.3 Screening Procedures

<u>Telephone Screening Interview</u>

- Women who call in response to recruitment advertisements or who have previously given permission to be contacted about opportunities to participate in women's health research at UCSF 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/frequency/type of incontinence, current and past incontinence treatment, prior yoga practice, physical mobility, exclusionary conditions and medications, availability for upcoming yoga therapy or physical conditioning classes).

<u>Screening Clinic Visit</u>

- At this visit, a clinical coordinator will explain the requirements of the study while referring to the detailed informed consent form, and candidates will provide written informed consent if they are still interested in proceeding with the study.
- Candidates will complete questionnaires about their demographic, urologic/urogynecologic, and medical history to determine if they meet criteria related to age, gender, duration/frequency/type of incontinence, current and past incontinence treatment, prior yoga practice, exclusionary conditions and medications

- Over-the-counter and prescription medications will be reviewed to determine if candidates are taking any exclusionary medications.
- Height, weight, and resting blood pressure and pulse measurements will be obtained.
- Physical function will be assessed by questionnaire.
- A clean-catch urine sample will be collected to assess for possible urinary tract infection and rule out pregnancy (for the minority of candidates who are still of child-bearing potential).
- Potentially eligible women will be instructed on completing a 3-day voiding diary to document all incontinence and voiding episodes at home.
- A Baseline Clinic Visit will be scheduled at least 3 days later for review of the completed voiding diary and determination of final eligibility.

Baseline Clinic Visit

- Candidates will return with the completed 3-day voiding diary, and results will be reviewed by a clinical coordinator. Candidates whose diaries indicate predominantly urgency, stress, or mixed-type incontinence, document at least 3 incontinence episodes per 3-day diary, and meet all other eligibility criteria will be eligible to continue.
- Women will complete structured questionnaires about anxiety and perceived stress, incontinence-specific quality of life, and sleep quality.
- Physical function will be assessed by direct physical mobility evaluation.
- Participants will be given a brief written pamphlet about usual first-line behavioral management of incontinence (see description in interventions section above).
- If the Baseline Clinic Visit takes place within 2 weeks of the start of the yoga or physical conditioning program orientation session, eligible participants will be randomized to one of the two interventions at this visit.
- If the Baseline Clinic Visit takes place more than 2 weeks before the start of the yoga or physical conditioning program, eligible participants will be scheduled for a Randomization Telephone Call within two weeks of the start of the program to determine their intervention assignment.

6.2.4 Randomization and Blinding

Randomization

Women who are confirmed to be eligible and available to take part in upcoming yoga or physical conditioning group class series will be randomized in a 1:1 ratio to one of the two intervention groups. Randomization will ideally take place within 1 month of completion of screening procedures, and in no cases will be able to take place more than 2 months after completion of screening procedures. Randomization must also take place within 2 weeks of the start of yoga or physical conditioning class series. If the Baseline Clinic Visit occurs within 2 weeks of the start of the yoga therapy or physical conditioning program, eligible participants will be randomized to one of the two interventions directly at this visit. If the Baseline Clinic Visit occurs more than 2 weeks before the start of the intervention program, eligible participants will be scheduled for a Randomization Telephone Call within two weeks of the start of the program to determine their intervention assignment.

During the Baseline Clinic visit or during the Randomization Telephone Call

(whichever is appropriate), randomization will be performed according to a pre-established computer-algorithm using randomly permuted blocks of sizes 2 and 4 (limited block size to ensure that the number of randomized participants within each strata always exceeds the block size). Randomization will be stratified by clinical type of incontinence (i.e., stress, urgency, or mixed) to ensure adequacy of randomization among women with each major incontinence type. Randomization will be implemented. Prior to randomization, the research coordinator will complete a randomization checklist confirming that the participant meets all eligibility criteria. Additionally, participants' availability and willingness to attend upcoming yoga or physical conditioning group classes will be re-confirmed before randomization assignment is obtained.

Standard allocation concealment procedures will be followed to avoid manipulation of randomization.[66] Prior to the start of recruitment, the randomization scheme will be developed by a statistical programmer who will have no contact with participants or role in data entry, cleaning, or analysis. To execute the randomization scheme, a research assistant who will also have no contact with participants or access to study data will then prepare a series of sealed, opaque envelopes containing group assignment, numbered consecutively with the randomization sequence numbers. When the participant is ready for randomization, study coordinators will enter the date, participant name, and study ID in the randomization log and select the next numbered envelope corresponding to the participants' type of incontinence (stress-, urgency-, or mixed-type) to determine group assignment. Once a participant has been randomized, she cannot be re-assigned to a different intervention group. All randomization envelopes will be retained for review; randomization dates and times should follow the order of the sequence numbers, providing a check on validity.

Blinding

Although participants cannot be blinded to treatment assignment (due to the behavioral nature of the intervention), study procedures have been carefully designed to avoid bias associated with knowledge of group assignment. First, to minimize differential expectations of treatment success, participants will be told that they are participating in a study of two different types of low-impact group activity-based interventions to enhance self-management of incontinence, and that we do not know which is more effective (which is true). The primary outcome will be assessed by voiding diaries, a measure that is resistant to reporting bias, and data from returned diaries will be abstracted by blinded analysts. Similarly, data from participant follow-up questionnaires assessing other symptom and quality-of-life outcomes associated with incontinence will be abstracted by blinded analysts.

Only study personnel who are involved in delivering the therapeutic interventions, assessing and promoting adherence to these interventions, and/or monitoring adverse events related to these interventions will be aware of group assignment. All investigators, study analysts involved in abstracting efficacy outcomes data, and statistical programmers involved in ongoing data cleaning will be blinded to treatment allocation. Unless stipulated by the Data and Safety Monitor or required to assist with the clinical management of a participant experiencing a serious adverse event, these investigators and

staff will remain blinded until after all participants have completed their final visit, trial data are edited and cleaned, and the trial dataset is locked. A statistical programmer who is not involved in data collection or cleaning will be appointed to create the unblinded group-specific data tables for closed session Data and Safety Monitor reviews.

6.2.5 Follow-up/Final Evaluations

Follow-up evaluations will consist of a 2-week telephone call, 8-week clinic visit, 12-week clinic visit, and 24-week mail-in assessment:

2-Week Telephone Call

- Two weeks after the start of the yoga therapy or physical conditioning program, coordinators will call women to assess adverse events, address any concerns, and reinforce adherence to group classes and home practice of yoga therapy or stretching/strengthening exercises.
- Adherence to and challenges in performing usual behavioral self-management strategies for incontinence will also be assessed.
- Women will be reminded to continue recording home yoga or physical conditioning practice in their practice logs and return their logs each week to the yoga class instructors. They will also be reminded to start filling out a second voiding diary 3 days before the 8-Week Clinic Visit.

8-Week Clinic Visit

- Eight weeks after the start of the yoga or physical conditioning program, women will return for a follow-up visit, bringing their second completed voiding diary.
- Voiding diaries will be retrieved by the research coordinator and delivered to a blinded analyst for data abstraction.
- Adverse events will be recorded using standardized forms (see safety monitoring section). Adherence to yoga or stretching practice and incontinence self-management strategies will be re-assessed.
- Yoga/physical conditioning posture and practice self-efficacy questionnaire measures will be administered.
- Women will re-self-administer questionnaires about anxiety/stress symptoms, incontinence-specific quality of life, and sleep quality.
- Current use of prescription and over-the-counter medications will be re-reviewed.
- Physical function will be re-assessed by questionnaire as well as by physical mobility testing.
- Women will be given a third voiding diary to complete before the 12-week visit, and the 12-week visit will be scheduled.

12-Week Clinic Visit

- Twelve weeks after the start of the yoga or physical conditioning program, women will return for another clinic visit, bringing their third completed voiding diary.
- Voiding diaries will be retrieved by the research coordinator and delivered to a blinded analyst for data abstraction.
- Adverse events will be recorded using standardized forms (see safety monitoring section).

- Yoga/physical conditioning posture and practice self-efficacy questionnaire measures will be re-administered.
- Women will re-self-administer questionnaires about anxiety/stress symptoms, incontinence-specific quality of life, and sleep quality.
- Current use of prescription and over-the-counter medications will be re-reviewed.
- Physical function will be re-assessed by questionnaire as well as by physical mobility testing.
- A satisfaction questionnaire will be administered to assess overall satisfaction with study procedures and change in incontinence symptoms.
- Women will be encouraged continue practicing yoga or stretching/strengthening exercises for at least an hour per week for the next 12 weeks and record this practice in their home practice logs.

24-Week Assessment

- Approximately twelve weeks after completion of the yoga or physical conditioning program, coordinators will call participants to them to complete their fourth and final voiding diary at home (the blank diary will be mailed in advance to participants at home).
- Adverse events will be assessed by telephone and recorded using standardized forms (see safety monitoring section).
- Women will also be asked to complete questionnaires addressing symptom, quality-of life, and sleep outcomes as well as yoga/physical conditioning practice adherence and self-efficacy at home (questionnaires will be mailed in advance to participants at home).
- Women will also be asked to complete a close-out satisfaction questionnaire addressing their overall satisfaction with study procedures and change in incontinence symptoms.
- Women will return with their final completed voiding diary and questionnaires using a pre-stamped and addressed envelope.

Recommended time windows for completion each of the post-randomization follow-up evaluations will be as follows:

Follow-Up Assessment	Time Window
2-week telephone call	11 to 17 days after the start of the yoga therapy or physical conditioning program
8-week clinic visit	50 to 62 days (i.e., 8 weeks +/- 6 days) after the start of the yoga therapy or physical conditioning program
12-week clinic visit	78 to 90 days (i.e., 12 weeks +/- 6 days) after the start of the yoga therapy or physical conditioning program
24-week telephone and mail-in assessment	Within 189 days (27 weeks) of the start of the yoga therapy or physical conditioning program (allowing time for return of mail-in packet)

6.2.6 Early Termination (also see section 8 below)

If a randomized participant opts to terminate the study before the 12-Week Clinic Visit, or if the principal investigator in consultation with the Data and Safety Monitor determines that early termination is necessary to protect the

safety of a participant, the study coordinator will encourage the participant to complete an early termination visit. This visit will include as many of the procedures originally scheduled to take place at the 12-Week Clinic Visit as possible, including: assessment of adverse events; re-administration of questionnaires about condition-specific quality of life, anxiety/stress symptoms, yoga or physical conditioning self-efficacy; review of current medications; re-assessment of weight, blood pressure, and heart rate; re-assessment of physical function; and administration of a satisfaction questionnaire. The participant's reasons for terminating the study early will be explored and documented in her study file.

6.2.7 Table of Measures and Procedures

Summary of Measures and Procedures at Study Visits								
	Screening Phone Call	Screening Clinic Visit	Baseline Clinic Visit	Randomization Phone Call	2-Week Phone Call	8-Week Clinic Visit	12-Week Clinic Visit	12 week post-treatment
Brief telephone screening interview	X							
Informed consent and HIPAA authorization		X						
Demographic/urogynecologic history questionnaires		X						
Health-related habits questionnaire		X						
Review of current medications		X				X	X	
Physical function assessment		X				X	X	
Mobility assessment			X			X	X	
Height, weight, blood pressure, and pulse measures		X					X	
Urine dipstick testing		X						
Urine pregnancy testing (if appropriate)		X						
3-day voiding diary return			X			X	X	X
Review of eligibility and randomization			X*	X*				
Incontinence self-management pamphlet			X					
Assessment of credibility/expectations of treatment				X				
Incontinence Impact Questionnaire			X			X	X	X
Urogenital Distress Inventory-6			X			X	X	X
Patient Perception of Bladder Condition			X			X	X	X
Spielberg State-Trait Anxiety Inventory			X			X	X	X
Hospital Anxiety and Depression Scale			X			X	X	X
Perceived Stress Scale			X			X	X	X
Center for Epidemiologic Studies Depression Scale			X			X	X	X
Pittsburg Sleep Quality Index			X			X	X	X
Adverse events assessment					X	X	X	X
Yoga/physical conditioning self-efficacy questionnaires						X	X	X
Assessment of co-interventions						X	X	X
Satisfaction/close-out questionnaire							X	X

*Randomization will take place at either the Baseline Clinic Visit or the Randomization Phone Call

7. SAFETY ASSESSMENTS

7.1 Potential Risks and Protective Measures

Although participation in this study is not expected to place participants at substantial risk of harm, study procedures may be associated with the following risks:

- Yoga Therapy Intervention: Possible risks associated with group yoga instruction and home yoga practice include muscle soreness and muscle/ligament strain, or other musculoskeletal injury if participants fall or lose their balance while trying to practice the yoga poses.
- Physical Conditioning Control Intervention: Similar to the yoga therapy intervention, possible risks associated with physical conditioning control intervention include muscle soreness and muscle/ligament strain, or musculoskeletal injury if participants fall or lose their balance while trying to learn or practice the exercises.
- 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 incontinence symptoms or anxiety/stress symptoms. However, loss of confidentiality is unlikely to pose any significant legal or financial risk to participants.
- Physical Examination/Performance Measurements: There are no direct risks associated with undergoing measurement of height, weight, blood pressure, or heart rate, or evaluation of physical mobility, although participants may experience this as inconvenient or unpleasant.
- Behavioral Incontinence Self-Management Pamphlet: Provision of standard written information on usual first-line behavioral self-management strategies for incontinence such as pelvic floor muscle exercises and timed urination should pose no risks to participants, although participants may find it inconvenient or unpleasant to read the pamphlet.
- Urine Dipstick and Pregnancy Testing: There are no direct risks associated with collection of the screening urine sample, although some participants may experience this as inconvenient or unpleasant.

To minimize potential risks to participants associated with study interventions and procedures, the following steps will be taken:

- Yoga Therapy Intervention. The instructors leading the group yoga classes will be trained yoga teachers who will have experience in guiding adults from a wide range of ages to learn and practice yoga safely and will undergo specific, in-person training by the study's yoga expert consultants. The study protocol incorporates props such as blocks and straps to help participants perform yoga postures in such a way that will minimize the chance of muscle strain or other injury. The yoga instruction manuals have been designed to include explicit tips on modifying or adapting postures to accommodate problems with mobility, flexibility, or balance.
- Physical Conditioning Control Intervention: Instruction for the physical conditioning control classes will be provided trained physical therapists or

personal trainers who are experienced in teaching patients of all ages to perform stretching and strengthening exercises safely, and who will have completed in-person training with co-investigator Sarah Pawlowsky, PT.
Stretching/strengthening exercises have been selected to be appropriate for middle-aged and older women who may have flexibility or mobility limitations in addition to incontinence.

- Questionnaires and Diaries. All study questionnaires and diaries will be stored in a locked file cabinet in a locked room in our research clinic, or on password-secured servers. All study staff are fully trained in good clinical practice, HIPAA procedures, and the importance of participant confidentiality is emphasized.
- Physical Examination/Performance Measures. Study personnel responsibility for performing physical exam measures and evaluating physical mobility will have prior clinical experience with performing physical exam measurements in middle-aged and older women and will receiving study-specific training to ensure that they perform measurements in a manner that is sensitive and minimizes discomfort to participants.
- Urine Dipstick and Pregnancy Testing. Study coordinators will receive training on obtaining screening urine samples in a manner that is sensitive and minimizes discomfort to participants.
- Behavioral Incontinence Self-Management Pamphlet: Study coordinators will be available to answer participants' questions about the pamphlet if they arise.

7.2 Methods and Timing of Safety Assessments

To monitor participant safety, a clinical coordinator will assess for adverse events at each follow-up telephone and in-person contact following randomization, starting with the 2-Week Telephone Call. Negative changes in health will be recorded as adverse events or serious adverse events on standardized forms as appropriate (see sections 7.3 and 7.4 below for definitions and documentation). Additionally, if participants contact clinical coordinators in between scheduled study visits and calls and report negative changes in their health, these will also be recorded as adverse events or serious adverse events.

Coordinators will not prompt participants to provide information about specific types of adverse events at follow-up visits, but instead 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 by participants will then be recorded on standardized AE or SAE forms, as appropriate (see section 7.3 below).

7.3 Adverse Events and Serious Adverse Events

7.3.1 AE/SAE Definitions

An Adverse Event (AE) is any untoward medical occurrence in participant that occurs during the study or with use of the study interventions. An adverse finding can include a sign, symptom, abnormal assessment, or any combination of these. Medical conditions or diseases present before starting study interventions will only be considered adverse events if they worsen after starting the intervention.

A Serious Adverse Event (SAE) is any AE that results in death, a life-

threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly or birth defect, or any other important medical event that jeopardizes the safety of participants based upon appropriate medical judgment.

7.3.2 AE/SAE Documentation

All negative changes in health reported by participants will be recorded on standardized AE or SAE forms, as appropriate. Each adverse event will be assigned an AE number and will be recorded on a separate AE form to avoid duplication in reporting. For each AE, clinical coordinators will record the date of onset and resolution of the AE and record the nature or type of AE. Based on information provided by the participant, coordinators will also classify the severity of the AE as "mild" if it does not have a noticeable impact on the patient, "moderate" if it causes the patient some inconvenience, or "severe" if it results in substantial disruption to the patient's functioning or well-being. In consultation with the principal investigator, coordinators will also indicate whether any indicate whether any specific action such as discontinuation of the study intervention was taken in response to the AE.

Each serious adverse event will be assigned an SAE number and recorded on an SAE form. Similar to regular AEs, clinical coordinators will record the date of onset and resolution of each SAE and record the nature or type of SAE. Coordinators will also document any treatment provided for the SAE, indicate any laboratory or other clinical data obtained about the SAE, indicate the participant's condition at the time of reporting of the SAE, and indicate whether any specific action such as study discontinuation was taken in response to the SAE. Each SAE form will be reviewed and signed by the principal investigator, who will use a standard attribution scale to indicate the potential relationship between any SAEs and study interventions (not, unlikely, possible, probably, or definitely related to study intervention).

7.4 Reporting Procedures

7.4.1 SAE Reporting

- Clinical coordinators will notify the principal investigator immediately when a SAE is discovered, in addition to filling out a standardized SAE form that will be reviewed and signed by the principal investigator (see section 7.3.3 above regarding SAE documentation).
- The principal investigator will then report any deaths to the institutional review board at the University of California San Francisco, the independent Data and Safety Monitor (DSM), and the NCCIH program officer within 24 hours of awareness of the event.
- Other unexpected serious adverse events that are potentially intervention-related will be reported by the principal investigator to the UCSF IRB, the DSM, and the NCCIH Program Officer within 48 hours of learning of the event.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will also be reported to the UCSF IRB and the DSM within 1 week of awareness of the event, and at least quarterly to the NCCIH Program Officer. Of note, no SAEs that are directly related to the study procedures are currently anticipated.

7.4.2 Non-Serious AE Reporting

- If a clinical coordinator discovers an AE that does not meet the definition of a SAE but may still pose a substantial risk of harm to a participant and is potentially associated with study interventions or procedures, he/she will report the AE to the principal investigator within 1 working day, in addition to filling out a standardized AE form.
- Cumulative trends in all non-serious adverse events will be reviewed by the principal investigator and the DSM at scheduled DSM meetings (see below for DSM meeting schedule). More frequent review of non-serious adverse events may be performed if recommended by the DSM or desired by the principal investigator.
- Although the UCSF IRB does not require reporting of non-serious AEs to the UCSF IRB, the principal investigator may consult the UCSF IRB for input on 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.

7.5 Follow-up for AEs/SAEs

From the time that they are first reported by participants until the end of the study, AEs and SAEs will be followed until resolved or considered stable. At each scheduled follow-up contact after initial discovery of an AE or SAE, a clinical coordinator 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, the clinical coordinator or principal investigator will also make more active attempts to communicate with participants in between scheduled study visits (with their permission) in order to monitor resolution of SAEs.

7.6 Independent Safety Monitoring

The conduct of the study and safety of participants will be evaluated by an independent Data and Safety Monitor (DSM), Dr. Andrew Avins, MD, MPH, Senior Research Scientist at Kaiser Permanente Northern California, who is a clinical researcher experienced with designing, implementing, and monitoring safety in therapeutic interventions studies as well as a practicing clinician. The DSM is independent of the investigators and staff participating in the study, and has no financial ties to the outcome of the study. The DSM will periodically review the conduct and outcomes of the study and provide feedback to the investigators, with particular attention to protecting the safety of the participants.

Prior to initiation of the trial, the DSM will review and approve the study design and plans for recruitment, adherence, interventions, data quality, and safety monitoring. At periodic intervals during the course of the trial, the DSM will evaluate the adequacy and timeliness of participant recruitment, adherence to the protocol, and the potential of the study to meet the stated goals; evaluate the quality and integrity of the data, including adequacy of data management and data security procedures; evaluate participant safety including trends in adverse events and relationship to the study procedures; consider factors external to the study when relevant information, such as scientific developments, may have an impact on the safety of the participants or the ethical conduct of the study; and make recommendations, if

necessary, to the investigators, the UCSF IRB, and the NCCIH on continuation, termination, or other modifications of the study protocol.

The DSM will periodically review aggregate and unblinded trial data according to the Data and Safety Monitoring Plan (DSMP). An emergency meeting may also be called by the principal investigator at any time should questions of participant safety arise. Each review will include an assessment of the adequacy and timeliness of participant recruitment, adherence to the visit and intervention protocols, data quality and timeliness, adverse effects, and participant safety. Interim reports for the DSM will be prepared by an unblinded biostatistician at the Women's Health Clinical Research Center, and sent to the DSM at least 5 days prior to a pre-scheduled meeting or conference call.

After each interim review, the DSM will provide a signed statement that indicates whether the study should continue, terminate, or be altered based on ability to meet study recruitment and data quality goals and participant safety. He will include any recommendations for changes to the protocol if necessary to enhance participant safety or potentiate the ability of the trial to answer the research hypotheses. This statement will be provided to the principal investigator and will be sent to the UCSF IRB and to the NCCIH program officer. All materials, discussions, and proceedings of the DSM process will be completely confidential.

8. INTERVENTION DISCONTINUATION

Participation in the yoga therapy and/or physical conditioning interventions may be discontinued if determined to be necessary to protect the safety of a participant. The decision to discontinue the therapeutic intervention will be made on a case-by-case by the principal investigator, with input from the DSM if needed. Possible reasons for discontinuation of the therapeutic intervention may include: 1) development of a clinically significant adverse event limiting a participant's ability to safety take part in yoga or physical conditioning practice; 2) disruptive behavior exhibited by a participant during group yoga or physical conditioning classes or study visits that endangers the safety or comfort of other study participants, class instructors, or study staff; or 3) decision to terminate the study by the IRB, NCCIH, or other regulatory bodies.

In the event that the yoga therapy or physical conditioning control intervention is discontinued, participants will continue to be followed through the 24-week mail-in assessment (or early termination visit) to collect outcomes data, provided that the participant is willing and the principal investigator (with input from the DSM, if appropriate) judges that it is safe and feasible to do so. If follow-up assessments are continued, no modifications to the schedule of follow-up assessments will be made unless necessary to protect the safety of participants or to accommodate limitations in function resulting from an adverse event. Follow-up assessments in participants who have discontinued the therapeutic interventions will not include continue evaluation of adherence to group classes or home practice, assessment of yoga posture or practice adherence self-efficacy, or independent evaluation of participants' success in performing yoga postures.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

A parallel-group, superiority trial design has been selected as the being the most appropriate for the overall scientific goals of this research. Although this pilot trial will

not be powered to prove or disprove any scientific hypotheses, it will provide a means of testing and refining procedures for a future full-scale parallel-group superiority trial to determine the efficacy of the therapeutic yoga intervention for improving urinary incontinence in middle-aged and older women.

To control for the time and attention that participants will spend on group classes and home practice, a physical conditioning exercise program has been selected as an active behavioral control intervention for this trial. Although this control program may offer non-specific benefits for participants' overall health, the investigators believe that it is unlikely to substantially improve women's incontinence. Inclusion of the physical conditioning program will also minimize differential expectations of treatment benefit between the two groups, in an effort to promote equal adherence to study interventions and visits in both groups.

9.2 Sample Size and Randomization

The investigative team plans to randomize and monitor up to 90 participants, with approximately 45 randomized to the yoga therapy group and 45 to the physical conditioning control group. No formal sample size estimates or power analyses have been performed for this pilot study, as one of the goals of this pilot is to collect preliminary data that may be used to guide sample size estimates for a larger clinical trial, if indicated. Study data on the standard deviation, intra-class correlation, and between-group difference in change in incontinence frequency and other efficacy outcomes will be used to guide sample size projections for a future full-scale trial powered to detect a 25% greater reduction in incontinence frequency associated with yoga therapy.

9.3 Intervention Assignment Procedures

Randomization to the yoga therapy or physical conditioning control group will be performed by computer algorithm, with proof of eligibility required before assignment. Randomization will be implemented using randomly permuted blocks of sizes 2 and 4, and will also be stratified by clinical type of incontinence (i.e., stress, urgency, or mixed), to ensure adequacy of randomization within types. To avoid manipulation, standard allocation concealment procedures will be followed.[66] A study analyst will prepare sealed, opaque envelopes containing group assignment, numbered consecutively with the randomization sequence numbers. At the baseline visit, when eligibility and incontinence type have been confirmed, coordinators will enter the date, participant name, and study ID in the randomization log and select the next numbered envelope to determine group assignment. All envelopes will be retained for review; randomization dates and times should follow the order of the sequence numbers, providing a check on validity. Although participants cannot be blinded to treatment assignment (due to the behavioral nature of the intervention), diary and questionnaire data used to evaluate the primary and secondary efficacy outcomes will be abstracted by blinded analysts.

9.4 Assessment of Feasibility of Recruitment and Retention

The feasibility of recruiting and randomizing ambulatory middle-aged and older women with incontinence into a randomized controlled trial of a yoga therapy versus physical conditioning program will be examined by monitoring the average number of participants recruited and randomized per month and per recruitment wave. The study team will also track the success rate of various recruitment approaches (fliers,

print notices, newspaper ads, etc.) and monitor the costs of recruitment per participant in order to guide future recruitment efforts. The investigators plan to recruit and randomize 15 to 30 women in each 3-month enrollment wave to confirm the feasibility of assembling a class size of 8 to 15 women per group per wave in a future full-scale trial.

The study team will also monitor participant retention rates during both the 12-week treatment period and the 12-week post-treatment follow-up period of the trial. Drop-out rates in both treatment groups are expected to increase over time (i.e., to be greater at 12 weeks than at 8 weeks or 4 weeks), but remain within acceptable parameters at 12 weeks of treatment and 12 weeks of post-treatment follow-up. If drop-out is substantial, the study team will conduct exploratory pooled logistic regression analyses to identify participant characteristics associated with drop-out.

The following parameters will be used to measure the adequacy of retention:

	During the 12-week intervention	12 weeks post-intervention
Optimal	< 10%	< 20%
Expected	< 15%	< 25%
Acceptable	< 20%	< 30%

9.5 Assessment of Adherence to Interventions

The study team will assess the feasibility of maintaining participant adherence to group classes and home practice by tracking the number and percentage of participants in each intervention group who complete at least 75%, 80%, and 90% of the recommended group classes as well as 75%, 80%, and 90% of the recommended home practice hours during the 12-week treatment period. During the 12-week post-treatment follow-up period, the study team will also track the number and percentage of participants who complete 25%, 50%, and 75% of recommended home practice hours; however, it should be noted that the study intervention is designed to be a self-contained 12-week intervention, in which sustained practice of yoga therapy or stretching/ strengthening exercises after the end of classes is encouraged but not considered mandatory. If appropriate, exploratory regression analyses will be used to identify participant characteristics associated with adherence to group classes and home practice.

The following parameters will be used to measure the adequacy of adherence:

	Attendance at group sessions during the 12-week intervention	Completion of home practice hours during the 12-week intervention	Completion of home practice hours post-intervention*
Optimal	≥ 90%	≥ 90%	≥ 75%
Expected	≥ 80%	≥ 80%	≥ 50%
Acceptable	≥ 75%	≥ 75%	any

*Practice of yoga or stretching/strengthening exercises at home after 12 weeks, while desirable and encouraged, will not be considered mandatory to study success.

9.6 Interim Analyses and Stopping Guidelines

Interim analyses and/or stopping for unexpected efficacy: As this is a pilot study that is not powered to prove or disprove any hypotheses regarding efficacy, no formal interim analyses to evaluate efficacy will be performed. Given the short duration of treatment and small size of the study, the investigators believe that there is no scientific or ethical reason to stop the trial early or alter the trial design if treatment appears to be more effective than expected. Thus, as long as no safety issues arise, the trial will not be stopped or altered if the therapeutic intervention appears unexpectedly effective.

Interim analyses and/or stopping for harm: Although this study involves a low-impact behavioral intervention that is not expected to pose a significant risk to participant safety, consideration may be given to stopping the trial early if unexpected and clinically significant adverse effects occur in either treatment group that may endanger the safety of participants. These may take the form of SAEs or non-serious AEs posing a substantial safety risk and warranting early termination of the trial. If evidence of adverse effects emerges, the investigators in consultation with the DSM may determine that these side effects are minor and the study can continue as planned, or may decide to alter or stop the study to prevent these side effects. Because the sample is small, and preservation of the nominal type-I error rate is less important for safety than for efficacy, no formal interim analysis procedures are proposed.

Interim analyses and stopping for futility: Consideration may be given to stopping the trial if recruitment and retention are so poor that the ability to meet recruitment goals or meet retention thresholds is severely compromised. For example, consideration will be given to stopping this study prior to its scheduled completion if recruitment falls more than 30% below planned rates and/or timely follow-up (i.e., completion of study visits within recommended windows) falls below 70%.

9.7 Outcomes

9.7.1 Feasibility Outcomes

The feasibility of recruiting and randomizing middle-aged and older women with urinary incontinence into a randomized trial of yoga therapy versus physical conditioning will be examined by calculating the average number of participants recruited and randomized per month and per recruitment wave. It is assumed that the study team will need to recruit and randomize 15 to 30 women in each 3-month enrollment wave to confirm ability to assemble a class size of 8 to 15 women per group per wave in a future full-scale trial.

The feasibility of retaining participants in this trial design will be assessed by monitoring rates of drop-out or loss-to-follow-up over 8 and 12 weeks of treatment as well as during the 12-week post-treatment follow-up period. Drop-out rates in both treatment groups are expected to increase over time (i.e., to be greater at 12 weeks than at 8 weeks), but remain less than 20% after 12 weeks of treatment and less than 30% at 12 weeks of post-treatment follow-up.

9.7.2 Primary Efficacy Outcome

Although this pilot study will not be powered to prove or disprove any

hypotheses regarding efficacy, preliminary data will be gathered to guide planning on a future full-scale trial in which the primary efficacy outcome will be change in the average frequency of urinary incontinence based on a validated 3-day symptom diary. To that end, frequency of incontinence will be assessed based on voiding diaries completed at screening/baseline, 8 weeks, and 12 weeks, as well as 12 weeks after the completion of the yoga therapy or physical conditioning programs. The total number of any, stress-type, and urgency-type incontinence episodes will be calculated for each diary and then divided by the total number of days of recording to calculate the average number of incontinence episodes per day of each type.

9.7.3 Secondary Efficacy Outcomes

Preliminary data will also be gathered to guide planning for a future full-scale trial evaluating secondary efficacy outcomes such as change in other symptom and quality-of-life outcomes associated with incontinence. To that end, changes in anxiety and perceived stress symptoms and incontinence-related quality of life will be assessed using validated questionnaires completed at screening/baseline, 8 weeks, and 12 weeks, as well as 12 weeks after the completion of yoga therapy or physical conditioning programs.

9.8 Data Analyses

To address aim 1 (feasibility), descriptive statistical techniques will be used to describe rates of recruitment, randomization, retention, and adherence for each recruitment wave. If drop-out is substantial, we will conduct exploratory pooled logistic regression analyses to try to identify participant characteristics associated with drop-out. Similarly, if adherence is less than expected, we will use linear, logistic, and/or proportional odds models, depending on the distribution of the outcome, to explore associations of participant characteristics with levels of adherence both to classes and home practice.

To address aim 2 (preliminary efficacy for change in incontinence frequency), we will use linear mixed models with unstructured residual covariance matrix to conduct a preliminary analysis of the 8, 12, and 24 week changes from baseline in incontinence frequency, adjusting for the baseline values, and treating week as categorical. This will provide estimates of the residual standard deviation, intra-class correlation, and fitted between-group differences at each follow-up time point. To assess trends and persistence, we will compare estimated between-group differences across weeks. All estimates will be presented with 95% confidence intervals.

The methods specified for aim 2 will also be used for aim 3 (preliminary efficacy for secondary symptom and quality-of-life outcomes). Outcomes will be normalized as necessary before analysis, and checked for equal variance across group and visit. In previous studies, changes in incontinence frequency and in other symptom and quality-of-life scores have been approximately normally distributed.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Study data will be obtained from participant-completed symptom diaries and logs, participant- or interviewer-administered questionnaires, physical examination and performance measures, and urine sampling/testing. Forms for recording or abstracting data will be developed specifically for this study, including:

- Voiding diary abstraction form: After participants complete their 3-day voiding diary at home, they will return the completed diary to the study clinic, and diary data will be abstracted using a Voiding Diary Abstraction Form. At the Baseline Visit, a clinical coordinator will abstract diary data for eligibility assessment purposes; at all post-randomization follow-up assessments, an analyst who is blinded to intervention assignment will abstract diary data.
- Questionnaires assessing anxiety and perceived stress, condition-specific quality of life, and participant satisfaction: These questionnaire forms will be completed by the participant during clinic visits and returned in person to a clinical coordinator, or completed by the participant at home and then mailed back to the study clinic (in the case of the 12 week post-treatment assessment). Questionnaire data collected after randomization will be entered into the electronic database by an analyst who is blinded to intervention assignment.
- Questionnaires assessing demographic history, general medical and urologic/urogynecologic history, medication use, tobacco and alcohol use, and physical activity and function: These questionnaires will be administered by a clinical coordinator during in-person study visits, and data from questionnaires will subsequently be entered by the coordinator into the electronic database. Because these data will not be used to assess efficacy outcomes, the coordinators who administer and entering data from these forms will not necessarily be blinded to intervention assignment.
- Physical examination, physical performance testing, and urine testing data forms: Clinical coordinators will record the results of height and weight measurements, blood pressure and heart rate measurements, physical performance testing, and urine dipstick and pregnancy testing on study-specific forms, and data from these forms will then be entered by coordinators into the electronic database. Because these data will not be used to assess any efficacy outcomes, the coordinators who are responsible for collecting, recording, and entering these data will not necessarily be blinded to intervention assignment.

10.2 Data Management

Data will be entered, managed, and edited using Research Electronic Data Capture (REDCap), a secure, web-based application developed by a multi-institutional consortium initiated at Vanderbilt University to support data capture for research studies. Data can be entered from any location with secure web authentication, data logging, and Secure Sockets Layer (SSL) encryption. REDCap offers advanced features including auto-validation, branching logic, stop actions, data import functions, and data comparison functions. The REDCap system complies with HIPAA regulations, data will be stored on HIPAA compliant serves, protected by firewalls.

10.3 Quality Assurance

10.3.1 Staff Training

All investigators, project directors, and clinical coordinators involved in the study will complete training in Human Subjects Research offered by the Collaborative Institutional Training Initiative (CITI), which includes specific training modules on assessing risk to subjects, avoiding group harms, conflicts of interest, cultural competence, FDA-regulated research, HIPAA-regulated research, informed consent, IRB member responsibilities, IRB chair responsibilities, records-based research, research with vulnerable subjects, and unanticipated problems and reporting. All investigators, project directors, and coordinators will maintain active CITI certification for the duration of the study.

Coordinators and analysts involved in data collection will also attend a study-specific training meeting led by the principal investigator and the project directors prior to the start of participant recruitment. At a minimum, the training meeting will include: (1) an introduction to the goals, design, and procedures of the LILA study; (2) an overview of goals, structure, and procedures for administering and abstracting data from the voiding diary and other study-specific data collection measures; (3) a review of definitions and procedures for assessing, documenting, and reporting adverse events.

Coordinators and analysts will also receive training and undergo supervised practice in reviewing and abstracting data from the voiding diary as the primary efficacy measure in the trial. They will also receive training and undergo supervised practice performing measurements of blood pressure and heart rate and assessing physical function/performance measures. Following the training, clinical staff will be certified for performing these functions.

10.3.2 Data Quality Assessment

Data collection forms will be reviewed on an ongoing basis for data completeness and accuracy as well as protocol compliance. All forms used to collect data on primary and secondary efficacy outcomes (i.e., voiding diary abstraction forms, questionnaires addressing anxiety and perceived stress and condition-specific quality of life) will be verified against paper-based source forms by a staff member who was not involved in entering the data.

Quality of data entry will be periodically assessed using measures such as number of missing forms, number of missing queries, and proportion of all study variables queried. The results of assessment of data quality will be incorporated into study progress reports for scheduled DSM meetings.

10.3.3 Protocol Deviations

Exceptions to the protocol are expected to occur rarely or not at all and, where possible, will be approved in advance by the principal investigator. Protocol exceptions may occur for the following reasons:

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

- exceptions due to oversight or error on the part of study staff, which are subsequently detected by the investigators, project managers, clinical coordinators, or data analysts.

For each protocol exception, study staff will document the exception on a Protocol Exceptions Log (located in the Regulatory Binder). Entries in the Protocol Exceptions Log should include the participant ID, date of the exception, date exception is being recorded, description of exception, and action taken in response to the exception, if any. The principal investigator will document approval for each exception determined in advance, or acknowledgement for each exception detected after the fact.

For this study, missed yoga therapy or physical conditioning classes will not be considered a protocol deviation, and neither will failure to complete recommended home practice sessions, although study staff will make every effort to promote adherence to classes and home practice (see section 5.4).

10.3.4 Monitoring

If desired by NCCIH, the study team will undergo on-site monitoring by an independent quality monitor who is independent of both the sponsor and UCSF (e.g., Westat). Site monitoring visits may include review of participant records, informed consent forms, source data collection forms, and the electronic study database. The schedule of site monitoring will be agreed upon in advance by NCCIH, the principal investigator, and the independent monitoring organization. The principal investigator, project manager, and study coordinators will be available to meet in person with the independent monitor and provide access to all study-specific forms, materials, and databases.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

The study protocol, informed consent document, data and safety monitoring plan, and data collection forms will be reviewed and approved by the UCSF IRB prior to implementation of study procedures. Any subsequent modifications to these documents will also be reviewed and approved by the UCSF IRB prior to administration in the study.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant at the Screening Visit before in-person data collection procedures are initiated (see section 6.2.2. for description of informed consent procedures). A copy of the consent form will be given to each participant, and documentation of signed consent will be filed in the participant's study file. The template for the form is attached as Appendix A.

11.3 Participant Confidentiality

Study data will be protected to preserve participant confidentiality both during and after the study. Each participant will be assigned a unique numerical study identifier which will be used on study forms instead of names or other identifying information.

The document linking study ID to participant identifiers (name, address, contact names and addresses) will be maintained in a password-protected file stored on a secure server protected by firewalls. Only the clinical coordinators or study investigators who need to get access to participant identifiers to contact participants will have access to the password to this file.

Paper source forms will be stored in a locked cabinet in a locked office at the UCSF Women's Health Clinical Research Center, and only research staff who need to access these forms for data collection, data editing, or quality monitoring purposes will have the key to this cabinet. Information that could identify individual participants will not be released without 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. Paper-based source forms will be securely destroyed 3 years after the end of the study.

11.4 Study Discontinuation

The study may be discontinued at any time at the recommendation of the UCSF IRB, NCCIH, the OHRP, or other government agencies if necessary to protect the safety or confidentiality of research participants.

12. PUBLICATION OF RESEARCH FINDINGS

Any publications resulting from this research will be made available to the public consistent with the NIH public access policy. At the request of the NCCIH program officer, the principal investigator will also provide a copy of any abstracts or manuscripts resulting from this work to the program officer prior to submission.

13. REFERENCES

1. Melville JL, Katon W, Delaney K, Newton K. Urinary incontinence in US women: a population-based study. *Arch Intern Med.* Mar 14 2005;165(5):537-542.
2. Thom DH, Haan MN, Van Den Eeden SK. Medically recognized urinary incontinence and risks of hospitalization, nursing home admission and mortality. *Age Ageing.* Sep 1997;26(5):367-374.
3. Langa KM, Fultz NH, Saint S, Kabeto MU, Herzog AR. Informal caregiving time and costs for urinary incontinence in older individuals in the United States. *J Am Geriatr Soc.* Apr 2002;50(4):733-737.
4. Fultz NH, Fisher GG, Jenkins KR. Does urinary incontinence affect middle-aged and older women's time use and activity patterns? *Obstet Gynecol.* Dec 2004;104(6):1327-1334.
5. Huang AJ, Brown JS, Thom DH, Fink HA, Yaffe K. Urinary incontinence in older community-dwelling women: the role of cognitive and physical function decline. *Obstet Gynecol.* Apr 2007;109(4):909-916.
6. Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I. Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. *Obstet Gynecol.* Dec 2002;100(6):1230-1238.
7. Bogner HR. Urinary incontinence and psychological distress in community-dwelling older African Americans and whites. *J Am Geriatr Soc.* Nov 2004;52(11):1870-1874.
8. Brown JS, Vittinghoff E, Wyman JF, et al. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. *J Am Geriatr Soc.* Jul 2000;48(7):721-725.

9. Wilson L, Brown JS, Shin GP, Luc KO, Subak LL. Annual direct cost of urinary incontinence. *Obstet Gynecol.* Sep 2001;98(3):398-406.
10. Bump RC, Hurt WG, Fantl JA, Wyman JF. Assessment of Kegel pelvic muscle exercise performance after brief verbal instruction. *Am J Obstet Gynecol.* Aug 1991;165(2):322-327; discussion 327-329.
11. Borello-France D, Burgio KL, Goode PS, et al. Adherence to behavioral interventions for urge incontinence when combined with drug therapy: adherence rates, barriers, and predictors. *Physical therapy.* Oct 2010;90(10):1493-1505.
12. Milne JL, Moore KN. Factors impacting self-care for urinary incontinence. *Urologic nursing.* Feb 2006;26(1):41-51.
13. Borello-France D, Burgio KL, Goode PS, et al. Adherence to behavioral interventions for stress incontinence: rates, barriers, and predictors. *Physical therapy.* Jun 2013;93(6):757-773.
14. Imamura M, Abrams P, Bain C, et al. Systematic review and economic modelling of the effectiveness and cost-effectiveness of non-surgical treatments for women with stress urinary incontinence. *Health technology assessment (Winchester, England).* Aug 2010;14(40):1-188, iii-iv.
15. Washington BB, Raker CA, Sung VW. Barriers to pelvic floor physical therapy utilization for treatment of female urinary incontinence. *Am J Obstet Gynecol.* Aug 2011;205(2):152 e151-159.
16. Gopal M, Haynes K, Bellamy SL, Arya LA. Discontinuation rates of anticholinergic medications used for the treatment of lower urinary tract symptoms. *Obstet Gynecol.* Dec 2008;112(6):1311-1318.
17. Diokno A, Yuhico M, Jr. Preference, compliance and initial outcome of therapeutic options chosen by female patients with urinary incontinence. *J Urol.* Nov 1995;154(5):1727-1730; discussion 1731.
18. Shamliyan T, Wyman J, Kane RL. *Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness.* Rockville MD2012.
19. Sultana CJ, Campbell JW, Pisanelli WS, Sivinski L, Rimm AA. Morbidity and mortality of incontinence surgery in elderly women: an analysis of Medicare data. *Am J Obstet Gynecol.* Feb 1997;176(2):344-348.
20. Perry S, McGrother CW, Turner K, Leicestershire MRCISG. An investigation of the relationship between anxiety and depression and urge incontinence in women: development of a psychological model. *Br J Health Psychol.* Sep 2006;11(Pt 3):463-482.
21. Gopal M, Sammel MD, Arya LA, Freeman EW, Lin H, Gracia C. Association of change in estradiol to lower urinary tract symptoms during the menopausal transition. *Obstet Gynecol.* Nov 2008;112(5):1045-1052.
22. Waetjen LE, Ye J, Feng WY, et al. Association between menopausal transition stages and developing urinary incontinence. *Obstet Gynecol.* Nov 2009;114(5):989-998.
23. Knight S, Luft J, Nakagawa S, Katzman WB. Comparisons of pelvic floor muscle performance, anxiety, quality of life and life stress in women with dry overactive bladder compared with asymptomatic women. *BJU Int.* Jun 2012;109(11):1685-1689.
24. Dugan E, Cohen SJ, Bland DR, et al. The association of depressive symptoms and urinary incontinence among older adults. *J Am Geriatr Soc.* Apr 2000;48(4):413-416.
25. Steers WD, Lee KS. Depression and incontinence. *World J Urol.* Nov 2001;19(5):351-357.
26. Melville JL, Delaney K, Newton K, Katon W. Incontinence severity and major depression in incontinent women. *Obstet Gynecol.* Sep 2005;106(3):585-592.
27. Nygaard I, Turvey C, Burns TL, Crischilles E, Wallace R. Urinary incontinence and depression in middle-aged United States women. *Obstet Gynecol.* Jan 2003;101(1):149-156.

28. Freeman RM, Baxby K. Hypnotherapy for incontinence caused by the unstable detrusor. *Br Med J (Clin Res Ed).* Jun 19 1982;284(6332):1831-1834.
29. Garley A, Unwin J. A case series to pilot cognitive behaviour therapy for women with urinary incontinence. *Br J Health Psychol.* Sep 2006;11(Pt 3):373-386.
30. Macaulay AJ, Stern RS, Holmes DM, Stanton SL. Micturition and the mind: psychological factors in the aetiology and treatment of urinary symptoms in women. *Br Med J (Clin Res Ed).* Feb 28 1987;294(6571):540-543.
31. Baker J, Costa D, Nygaard I. Mindfulness-based stress reduction for treatment of urinary urge incontinence: a pilot study. *Female Pelvic Med Reconstr Surg.* Jan-Feb 2012;18(1):46-49.
32. Beddoe AE, Paul Yang CP, Kennedy HP, Weiss SJ, Lee KA. The effects of mindfulness-based yoga during pregnancy on maternal psychological and physical distress. *Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG.* May-Jun 2009;38(3):310-319.
33. Cohen L, Warneke C, Fouladi RT, Rodriguez MA, Chaoul-Reich A. Psychological adjustment and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma. *Cancer.* May 15 2004;100(10):2253-2260.
34. Michalsen A, Grossman P, Acil A, et al. Rapid stress reduction and anxiolysis among distressed women as a consequence of a three-month intensive yoga program. *Med Sci Monit.* Dec 2005;11(12):CR555-561.
35. Rao MR, Raghuram N, Nagendra HR, et al. Anxiolytic effects of a yoga program in early breast cancer patients undergoing conventional treatment: a randomized controlled trial. *Complement Ther Med.* Jan 2009;17(1):1-8.
36. Vempati RP, Telles S. Yoga-based guided relaxation reduces sympathetic activity judged from baseline levels. *Psychol Rep.* Apr 2002;90(2):487-494.
37. Huang AJ, Jenny HE, Chesney MA, Schembri M, Subak LL. A group-based yoga therapy intervention for urinary incontinence in women: a pilot randomized trial. *Female Pelvic Med Reconstr Surg.* May-Jun 2014;20(3):147-154.
38. Banasik J, Williams H, Haberman M, Blank SE, Bendel R. Effect of Iyengar yoga practice on fatigue and diurnal salivary cortisol concentration in breast cancer survivors. *J Am Acad Nurse Pract.* Mar 2011;23(3):135-142.
39. Evans S, Cousins L, Tsao JC, Sternlieb B, Zeltzer LK. Protocol for a randomized controlled study of Iyengar yoga for youth with irritable bowel syndrome. *Trials.* 2011;12:15.
40. Evans S, Cousins L, Tsao JC, Subramanian S, Sternlieb B, Zeltzer LK. A randomized controlled trial examining Iyengar yoga for young adults with rheumatoid arthritis: a study protocol. *Trials.* 2011;12:19.
41. Williams K, Abildso C, Steinberg L, et al. Evaluation of the effectiveness and efficacy of Iyengar yoga therapy on chronic low back pain. *Spine.* Sep 1 2009;34(19):2066-2076.
42. Williams KA, Petronis J, Smith D, et al. Effect of Iyengar yoga therapy for chronic low back pain. *Pain.* May 2005;115(1-2):107-117.
43. Kolasinski SL, Garfinkel M, Tsai AG, Matz W, Van Dyke A, Schumacher HR. Iyengar yoga for treating symptoms of osteoarthritis of the knees: a pilot study. *J Altern Complement Med.* Aug 2005;11(4):689-693.
44. Oken BS, Kishiyama S, Zajdel D, et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. *Neurology.* Jun 8 2004;62(11):2058-2064.
45. Huang AJ, Grady D, Appa A, Subak LL. A pilot randomized trial of a behavioral slow-breathing intervention to treat urgency incontinence in women. American Geriatrics Society Annual Scientific Meeting; May 4, 2012, 2012; Seattle, Washington.

46. Locher JL, Goode PS, Roth DL, Worrell RL, Burgio KL. Reliability assessment of the bladder diary for urinary incontinence in older women. *J Gerontol A Biol Sci Med Sci.* Jan 2001;56(1):M32-35.
47. Brown JS, McNaughton KS, Wyman JF, et al. Measurement characteristics of a voiding diary for use by men and women with overactive bladder. *Urology.* Apr 2003;61(4):802-809.
48. Shumaker SA, Wyman JF, Uebersax JS, McClish D, Fantl JA. Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program in Women (CPW) Research Group. *Qual Life Res.* Oct 1994;3(5):291-306.
49. Uebersax JS, Wyman JF, Shumaker SA, McClish DK, Fantl JA. Short forms to assess life quality and symptom distress for urinary incontinence in women: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program for Women Research Group. *Neurourol Urodyn.* 1995;14(2):131-139.
50. Coyne KS, Matza LS, Kopp Z, Abrams P. The validation of the patient perception of bladder condition (PPBC): a single-item global measure for patients with overactive bladder. *Eur Urol.* Jun 2006;49(6):1079-1086.
51. Matza LS, Thompson CL, Krasnow J, Brewster-Jordan J, Zyczynski T, Coyne KS. Test-retest reliability of four questionnaires for patients with overactive bladder: the overactive bladder questionnaire (OAB-q), patient perception of bladder condition (PPBC), urgency questionnaire (UQ), and the primary OAB symptom questionnaire (POSQ). *Neurourol Urodyn.* 2005;24(3):215-225.
52. Barnes L, Harp D, Jung W. Reliability Generalization of Score son the Spielberger State-Trait Anxiety Inventory. *Educational and Psychological Measurement.* 2002;62(4):603-618.
53. Quek KF, Low WY, Razack AH, Loh CS, Chua CB. Reliability and validity of the Spielberger State-Trait Anxiety Inventory (STAI) among urological patients: a Malaysian study. *Med J Malaysia.* Jun 2004;59(2):258-267.
54. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* Jun 1983;67(6):361-370.
55. Rogers R, Bachmann G, Jumadilova Z, et al. Efficacy of tolterodine on overactive bladder symptoms and sexual and emotional quality of life in sexually active women. *Int Urogynecol J Pelvic Floor Dysfunct.* Nov 2008;19(11):1551-1557.
56. Cohen S, Williamson G. Perceived stress in a probability sample of the United States. In: Sapacapam S, Oskamp S, eds. *The social psychology of health: Claremont Symposium on applied psychology*. Newbury Park, CA: Sage; 1988.
57. WW E, C M, C S, A T, M Y. Center for Epidemiologic Studies Depression Scale: Review and revision (CESD and CESD-R). In: ME M, ed. *The Use of Psychological Testing for Treatment Planning and Outcomes Assessment*. 3rd ed. Mahwah, NJ: Lawrence Erlbaum; 2004:363-377.
58. Junkin S. *Yoga and self-esteem: exploring change in middle-aged women*. Saskatoon: Kinesiology, University of Saskatchewan; 2007.
59. Marcus BH, Selby VC, Niaura RS, Rossi JS. Self-efficacy and the stages of exercise behavior change. *Res Q Exerc Sport.* Mar 1992;63(1):60-66.
60. Borkovec T, SD N. Credibility of analogue therapy rationales. *Journal of Behavior Therapy and Experimental Psychiatry.* 1972;3:257-260.
61. Andresen EM, Fitch CA, McLendon PM, Meyers AR. Reliability and validity of disability questions for US Census 2000. *Am J Public Health.* Aug 2000;90(8):1297-1299.
62. Booth M. Assessment of physical activity: an international perspective. *Res Q Exerc Sport.* Jun 2000;71(2 Suppl):S114-120.

63. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc.* Aug 2003;35(8):1381-1395.
64. Rose M, Bjorner JB, Becker J, Fries JF, Ware JE. Evaluation of a preliminary physical function item bank supported the expected advantages of the Patient-Reported Outcomes Measurement Information System (PROMIS). *J Clin Epidemiol.* Jan 2008;61(1):17-33.
65. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol.* Mar 1994;49(2):M85-94.
66. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet.* Feb 16 2002;359(9306):614-618.

APPENDIX A: INFORMED CONSENT FORM

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO (UCSF)
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Lessening Incontinence through Low-impact Activity (LILA)

This is a research study about two types of low-impact physical activity-based programs to improve urinary incontinence in women. The study researchers, Alison Huang, MD, MAS and Leslee Subak, MD, and their associates from the UCSF Department of Medicine, UCSF Department of Obstetrics, Gynecology, and Reproductive Sciences, and the UCSF Women's Health Clinical Research Center, will explain this study to you.

Medical research studies include only people who choose to take part. Take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask the study staff.

You are being asked to take part in this study because you are a woman with urinary incontinence.

Why is this study being done?

The purpose of this study is to gather information about the effects of a group-based yoga or low-impact physical conditioning program on urinary incontinence in women. The National Center for Complementary and Integrative Health (NCCIH) is providing funding for this study.

How many people will take part in this study?

About 60 women aged 50 years or older will participate in this study at UCSF.

What will happen if I take part in this research study?

The study will require up to 4 in-person clinic visits (screening visit, baseline visit, 8-week visit, and final 12-week visit), 24 yoga or physical conditioning group training sessions (an initial orientation, followed by twice weekly group classes for weeks 1-12), up to 3 telephone visits (Randomization, Week 2, and Week 24), and 1 mail-in visit packet (Week 24).

Before you begin the main part of the study, you will undergo the following procedures to make sure you understand the requirements of the study and that you are eligible:

Screening Visit (located at the UCSF Women's Health Research Office at 2330 Post Street)

If you decide you want to be in the study, you will have the following procedures to find out if you qualify to be in this study:

- The study will be discussed with you, and you will be asked to review and sign the consent form.
- Your medical and gynecologic history will be reviewed, including all medications you are currently taking.
- Your height, weight, blood pressure, and heart rate will be measured.

- You will be asked to give a urine sample to check for signs of urinary tract infection and pregnancy.
- We will give you questionnaires to fill out, which will include information on your race/ethnicity, relationship status, educational history, and health-related behaviors such as drinking alcohol, smoking, and exercise.
- If you qualify so far, you will receive a 3-day voiding diary (a diary in which you will record when you urinate or have accidental urine leakage) and detailed instructions on how to complete it. You will be asked to complete the diary at home bring it with you to your next visit.
- You be given a follow-up appointment for the Baseline Visit.

This screening visit will take about one hour.

Baseline Visit (located at the UCSF Women's Health Research Office at 2330 Post Street)

One to two weeks after the Screening Visit, you will return for the Baseline Visit. You will have the following additional procedures done at this visit:

- You will be asked if you have had any changes in your health or in your medications.
- Your completed 3-day voiding diary will be collected and reviewed by study staff.
- You will be asked to complete questionnaires about your urinary symptoms, stress, mood, and quality of life.
- You will undergo a brief assessment of physical mobility, including walking speed, balance, and ability to rise from the ground and from a chair.
- If the screening procedures show that you are eligible to be in the study, and you still want to take part, then the study coordinator will schedule a Randomization Phone Call, about 1-2 weeks before the start of the yoga or physical conditioning intervention Programs.
- If you complete your screening procedures within 2 weeks of the start of the intervention programs, you may skip the Randomization Phone Call, and the randomization procedures described below will instead take place at the end of the baseline visit.

The complete Baseline Visit will take about one hour.

Randomization Phone Call

If you still want to take part, then you will go on to the main part of the study at this phone call. During the main part of the study:

- You will be randomly assigned to either the Yoga Therapy program or Physical Conditioning program for 12 weeks. This means that you will have a 50/50 chance (like flipping a coin) of being placed in one of two groups. Neither you nor the study doctors can choose the group you will be in. You will have an equal chance of being placed in one of the two possible groups:
- If you are assigned to the Yoga Therapy Program, you will be given an informational pamphlet about urinary incontinence and behavioral strategies for controlling it. You will receive the schedule for the Yoga Therapy Program (described below) and instructions on preparing for that program. The research coordinator will schedule your final visit, to take place about 12 weeks after you start the program. You will be reminded to avoid using any standard medical treatments for incontinence before your final visit.
- If you are assigned to the Physical Conditioning Program, you will be given an informational pamphlet about urinary incontinence and behavioral strategies for controlling it. You will receive the schedule for the Physical Conditioning Program (described below) and

instructions on preparing for that program. The research coordinator will schedule your final visit, to take place about 12 weeks after you start the program. You will be reminded to avoid using any standard medical treatments for incontinence before your final visit.

Yoga Therapy Program (located at TBD)

If you are assigned to the Yoga Therapy Program, you will take part in the following:

Yoga Orientation Session
You will be asked to attend a 90 minute introductory yoga workshop during which a trained yoga teacher will explain the philosophy of yoga and demonstrate some of the postures and breathing techniques that you will be learning during the yoga training visits. You will also be given a yoga guide pamphlet and yoga props (mat, strap, and block) to help you practice at home. You will receive information about urinary incontinence and behavioral strategies.

Yoga Training Sessions
After the Orientation, we will schedule you to attend group yoga training sessions twice a week for 12 weeks (weeks 1-12). The sessions will be offered at regular times throughout the study. The number of individuals in the group will not be more than 15, all of whom will be women with incontinence. Each session will be led by a certified yoga instructor. In these sessions, you will practice a series of yoga postures. You will also practice different yogic breathing techniques, such as breathing slowly through the nose or controlling the rate of your breathing. Part of each session may also be spent doing guided meditation or relaxation. Each of these classes will take about 90 minutes.

Home Yoga Practice
Between the classes, we will ask that you also practice yoga for about one hour one time per week at home. You will be asked to keep a daily log of your home practice of yoga. You will be given instructional materials that describe the yoga poses (participant yoga manual) to help you practice at home.

Physical Conditioning Program (located at TBD)

If you are assigned to the Physical Conditioning Program, you will take part in the following:

Physical Conditioning Orientation Session
You will be asked to attend a 90 minute introductory workshop during which a trained physical therapist will explain the philosophy of the physical conditioning program and demonstrate some of the stretching and strengthening techniques that you will be learning during the training visits. You will also be given a pamphlet to help you practice at home. You will receive information about urinary incontinence and behavioral strategies.

Physical Conditioning Group Training Sessions
After the Orientation, we will schedule you to attend group training sessions twice a week for 12 weeks (weeks 1-12). The sessions will be offered at regular times throughout the study. The number of individuals in the group will not be more than 15, all of whom will be women with incontinence. For each training session, you should wear loose-fitting comfortable clothes. Each session will be led by a certified instructor. In these sessions, you will practice a series of stretching and strengthening exercises.

Home Physical Conditioning Exercises
Between the classes, we will ask that you also practice stretching /strengthening exercises for about one hour one time per week at home. You will be asked to keep a daily log of your home practice of these exercises. You will be given instructional materials that describe the exercises (participant physical conditioning manual) to help you practice at home.

This phone call will take between 5 and 15 minutes.

Week 2 Phone Visit:

During this follow-up telephone call:

- You will be asked if you have had any changes in your health or your medications.
- You will be reminded of your next Clinic Visit appointment (the Week 8 Visit).
- You will discuss your progress with yoga/stretching practice with the coordinator, who will answer questions and provide further instruction if needed.

This phone call will take between 5 and 15 minutes.

Week 8 Clinic Visit:

The following procedures will be done at this visit:

- You will be asked if you have had any changes in your health or in medications.
- Your completed 3-day voiding diary will be collected and reviewed by study staff.
- Your weight, blood pressure, and heart rate will be re-measured.
- You will complete the same questionnaires about your urinary symptoms, stress, mood, and quality of life that you completed at the Baseline Visit.
- You will complete questionnaires about your confidence in performing the yoga or stretching/strengthening exercises.
- You will undergo repeat assessment of assessment of physical mobility, including walking speed, balance, and ability to rise from the ground and from a chair.
- You will discuss your progress with yoga or physical conditioning practice with the coordinator, who will answer questions and provide further instruction if needed.

The Week 8 Visit will take about 1 hour.

Week 12 Clinic Visit (Final Clinic Visit):

The following procedures will be done at this visit:

- You will be asked if you have had any changes in your health or in medications.
- Your completed 3-day voiding diary will be collected and reviewed by study staff.
- Your weight, blood pressure, and heart rate will be re-measured.
- You will complete the same questionnaires about your urinary symptoms, stress, mood, and quality of life that you completed at the Baseline Visit.
- You will complete questionnaires about your confidence in performing the yoga or stretching/strengthening exercises
- You will undergo repeat assessment of assessment of physical mobility, including walking speed, balance, and ability to rise from the ground and from a chair.
- You will be asked some questions about how you felt about the study and the usefulness of yoga or physical conditioning exercises to help your incontinence.

The final visit will take about 1 hour.

Week 24 Phone and Mail-in Packet:

Twelve weeks after completing the yoga or physical conditioning program, a study coordinator will call you. During this follow-up telephone call:

- You will be asked if you have had any changes in your health or your medications.
- You will be reminded to complete and mail a final 3-day voiding diary and set of questionnaires.

You will complete the following procedures while at home:

- You will complete a final 3-day voiding diary.
- You will complete questionnaires about your urinary symptoms, mood, sleep, health, and quality of life.
- You will mail it all of the above completed documents to study staff, using a pre-addressed and stamped envelope.

This will take about 30 minutes to complete.

How long will I be in the study?
Participation in the study will take a total of about 54 hours over a period of about 24 weeks. This includes 4 hours of clinic visit time and about thirty minutes of telephone time. You will be asked to participate in twice weekly yoga or physical conditioning group training sessions for a total of 36 hours (the orientation will require 90 minutes, as well as each of the 23 subsequent group classes). You will be asked to practice the yoga poses or physical conditioning exercises at home for about an hour at least one day per week for 12 weeks, or for a total of 12 hours. Recording in the voiding diary at 4 time points will take approximately 15 minutes each (1 hour total). The final Mail-in Visit packet of questionnaires will take about 30 minutes to complete.

Can I stop being in the study?
Yes. You can decide to stop at any time. Tell the study staff if you are thinking about stopping or decide to stop. They will tell you how to stop your participation.
The study researchers may also stop you from taking part in this study at any time if they believe it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

- **Data Collection and Confidentiality:** All information provided by study participants is confidential. You will be asked some questions about your health history and given some questionnaires about your urinary incontinence, quality of life, stress, and mood. While the information you provide is confidential, some people feel embarrassed at having to answer these types of questions. There will be slight inconvenience in time and effort to complete the questionnaires.

- **Yoga Program:** There is minimal risk associated with participating in the yoga intervention. Risks are rare but may include muscle soreness and muscle or ligament strain, or other musculoskeletal injury if you were to fall or lose balance. The instructors providing instruction for these classes are certified yoga instructors with years of experience

instructing people of a wide range of ages and with chronic health conditions. We will be using props such as blocks and straps to help you to perform the yoga postures, and the instructors will help you modify poses that are uncomfortable.

- **Physical conditioning program:** There is minimal risk associated with participation in the physical conditioning intervention. Rare risks include muscle soreness and muscle or ligament strain, or other musculoskeletal injury if you were to fall or lose balance. The trained instructors will have physical therapy or other qualified backgrounds and will provide instruction on low-impact stretching and strengthening exercises that have been approved for use by our expert Physical Therapist consultant.

- **Physical Examination Measurements:** There are no risks associated with having your height, weight, blood pressure, or heart rate, although you may find this to be inconvenient or unpleasant.

- **Assessment of Physical Mobility**: There are no significant risks associated with evaluation of your walking speed, balance, and ability to rise from the ground and from a chair, but you may find this to be inconvenient or unpleasant.

- **Urine Dipstick and Pregnancy Testing:** There are no direct risks associated with collection of the screening urine sample, although some participants may experience this as inconvenient or unpleasant.
- **Behavioral Incontinence Self-Management Pamphlet:** Provision of standard written information on usual first-line behavioral self-management strategies for incontinence such as pelvic floor muscle exercises and timed urination should pose no risks to participants, although participants may find it inconvenient or unpleasant to read the pamphlet.
- **Unknown Risks:** The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

- For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your urinary incontinence better. While doctors hope that yoga practice or physical conditioning exercises will be effective in improving urinary incontinence, there is no proof of this yet. Low impact physical activity techniques, such as yoga and stretching, have been reported to reduce stress and anxiety and improve sleep as well as improve overall fitness. Information gained from this study may help develop new treatments for individuals with urinary incontinence

What other choices do I have if I do not take part in this study?
Your other choices include:

- Getting no treatment
- Getting standard treatment for your urinary incontinence without being in a study.
    - Regular primary care and gynecologic care is available at UCSF for women with incontinence who choose not to enroll in this study. There are FDA-approved medications for some types of incontinence which are available by prescription.

    - Yoga and physical conditioning classes are available at gyms and studios in the community. These have not yet been proven to be effective for the treatment of incontinence and are not considered to be standard care.
- Getting a different experimental treatment/taking part in another study.

Please talk to your doctor about your choices before deciding if you will take part in this study.

Will information about me be kept private?

We will do our best to make sure that the personal information gathered for this study is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your research records for research, quality assurance, and data analysis include:

- University of California
- The National Institute of Health, and other government agencies involved in keeping research safe for people.

What are the costs of taking part in this study?
You will not be charged for any of the study activities.

Will I be paid for taking part in this study?
You will be reimbursed up to $100 total for your time and effort in this study. You will receive $25 at your baseline visit, Week 8 Visit, and Week 12 Visit upon completion of voiding diaries; and you will receive $25 upon returning your diary and questionnaires at Week 24 ($100 total).

What happens if I am injured because I took part in this study?
It is important that you tell your study doctors, Alison Huang, MD, MAS or Leslee Subak, MD, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call Alison Huang, MD, MAS at (415) 514-8697 or Leslee Subak, MD at (415) 353-9758.

Treatment and Compensation for Injury:
If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California or the study sponsor, the National Institutes of Health, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at (415) 476-1814.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?
You can talk to the study doctor about any questions, concerns, or complaints you have about this study. Contact the study doctors, Alison Huang, MD, MAS at (415) 514-8697 or Leslee Subak, MD at (415) 353-9758.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814.

CONSENT

Please read the sentence below and think about your choice. After reading the sentence, put your initials in the "Yes" or "No" box. If you have any questions about this study, please talk to the study doctor or coordinator.

No matter what you decide to do, it will not affect your care.

Someone may contact me in the future to ask me if I am interested in participating in future research studies.

YES	*NO*

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

_____ _____
Date Participant's Signature for Consent

_____ _____
Date Person Obtaining Consent