A Behavioral Slow-Breathing Exercise Program for Female Overactive Bladder

(Public title: Controlling Urgency through Relaxation Exercises-- CURE)

Protocol Version 1.3

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A. SYNOPSIS

Overactive bladder (OAB), a syndrome defined by recurring strong urges to urinate, frequent trips to the bathroom, and in some cases involuntary urine leakage, affects up to one in five adult women and can have a profound effect on women's day-to-day activities and quality of life. Existing treatments for OAB, such as anti-cholinergic medications, are associated with multiple side effects or have other limitations that limit their usefulness or result in high rates of discontinuation. Because OAB is associated with increased levels of self-reported anxiety and perceived stress, as well as abnormalities in autonomic nervous system control that are linked with anxiety disorders, behavioral interventions that decrease anxiety and improve autonomic nervous system control offer a potentially novel approach to treating this condition.

We previously examined the feasibility of teaching women with OAB symptoms to practice slow-paced respiration, a behavioral technique that involves slowing the resting breathing rate to 5 to 10 breaths per minute to improve autonomic balance. Women were assigned to practice slow-breathing exercises for approximately 15 minutes a day at home for 6 weeks using a small, commercially-available guided-breathing device that is currently FDA-approved for treatment of other conditions associated with autonomic nervous system imbalance (i.e., hypertension). In our pilot trial, recruitment of women was rapid, completion of home slow-breathing exercise sessions was high, and participants randomized to the slow-breathing intervention showed a promising trend toward reduction in OAB-related urine leakage compared to usual care.

To rigorously evaluate the effects of this intervention on female OAB syndrome, we propose to conduct a 12-week randomized controlled trial, in which 160 women with OAB symptoms will be randomized to: 1) use a standard guided-breathing device to practice slowing their breathing rate to 5 to 10 breaths per minute for at least 15 minutes per day, or 2) use an identical-appearing control device that plays relaxing, non-rhythmic music while monitoring their spontaneous breathing rate. All women will complete symptom diaries and questionnaires to monitor the severity and impact of their OAB symptoms, undergo measures of autonomic function, and complete questionnaires about anxiety and stress.

Our goals are to: 1) determine whether the proposed slow-breathing exercise program is effective in reducing the severity of OAB symptoms in women; 2) determine whether this slow-breathing intervention is effective in improving autonomic nervous system control and examine change in autonomic function as a mediator of treatment effects on OAB; and 3) determine whether this slow-breathing intervention is effective in improving anxiety symptoms and explore improvement in anxiety as a mediator of treatment effects on OAB. This study has the potential to significantly advance treatment of OAB in women, as well as change current research paradigms regarding this widely prevalent health problem.

B. SPECIFIC AIMS

We will conduct a rigorous 12-week randomized controlled trial in which 160 women with overactive bladder (OAB) syndrome will be assigned to: 1) use a standard guided-breathing device to slow their respiratory rate to 5 to 10 BPM for at least 15 minutes per day at home, or 2) use an identical-appearing control device that does not guide their breathing but plays relaxing, non-rhythmic music while monitoring their spontaneous breathing pattern. Our aims are:

Aim 1: To determine whether a device-guided slow-breathing exercise program can reduce the frequency and severity of OAB symptoms in women.

Compared to controls, we hypothesize that women randomized to practice slow breathing for at least 15 minutes per day for 12 weeks will report a more than 20% greater reduction in frequency of any voiding or incontinence episodes associated with moderate or severe urgency (measured by a validated voiding diary), in addition to greater improvements in frequency of other OAB symptoms and quality-of-life impact of OAB symptoms (measured by diary or by questionnaire).

Aim 2: To determine whether this slow-breathing intervention can improve autonomic nervous system control in women with OAB, and explore change in autonomic control as a mechanism of treatment effects on OAB symptoms.

Compared to controls, we hypothesize that women randomized to practice slow-breathing will demonstrate significantly improved autonomic control as measured by high-frequency heart rate variability and pre-ejection period parameters, and that treatment effects on OAB symptoms will be at least partly mediated by improvements in autonomic control.

Aim 3: To determine whether this slow-breathing intervention can improve anxiety-related symptoms in women with OAB, and explore changes in anxiety as a mediator of treatment effects on OAB symptoms.

Compared to controls, we hypothesize that women with OAB randomized to practice slow-breathing exercises will report significant improvement in anxiety-related symptoms (as measured by validated questionnaires), and that treatment effects on OAB symptoms will be at least partly mediated by improvement in anxiety.

C. BACKGROUND & JUSTIFICATION

Nearly one in five adult women suffer from overactive bladder, a syndrome characterized by recurrent, strong urges to void, increased frequency of daytime or nocturnal voiding, and in many cases involuntary leakage of urine when women are unable to get to the toilet in time.[1-3] Among women in the community, OAB is associated with sleep disruption, social isolation, decreased work productivity, sexual dysfunction, and depression.[2-9] When further complicated by involuntary urine leakage (i.e., urgency incontinence), OAB can also lead to falls and fractures, increased caregiver burden, and loss of ability to live independently, with potentially devastating consequences for quality of life.[10-12]

Currently, the most widely used treatments for OAB are anticholinergic drugs that can decrease involuntary bladder contractions, but are associated with multiple problematic side effects such as dry mouth, constipation, and even cognitive impairment, especially in older women.[13-17] As a result, many clinicians are

reluctant to prescribe these drugs to older women, and at least half of women who start anticholinergic drugs for OAB discontinue them in less than a year.[18] While behavioral treatments such as pelvic floor exercises can be effective in reducing OAB, these are only modestly effective in the absence of time-intensive, one-on-one training with physical therapists.[19,20] *At this time, there is an urgent need for alternate therapies for OAB that are more effective, better tolerated, and more widely generalizable.*

Recent clinical studies have documented strong associations between self-reported anxiety, perceived stress, and OAB, including an increased risk of new-onset OAB in women with high baseline anxiety.[21-24] Prior research has also shown that many women with OAB have impaired autonomic nervous system control as documented by heart rate variability measures[25-28] that are in turn associated with clinical anxiety disorders. These findings suggest that OAB symptoms, anxiety disorders, and autonomic dysfunction may share important underlying physiologic mechanisms. *As a result, behavioral treatment approaches that decrease anxiety and improve autonomic control may offer a novel way to alleviate OAB symptoms without exposing women to the side effects of anticholinergic drugs.*

To address this possibility, we propose to conduct a randomized trial of a mindfulness-based slow-breathing technique that has previously been shown to decrease anxiety and improve autonomic control. Women with OAB will practice slow-breathing exercises at home using a commercially-available guided-breathing device that requires limited individual instruction, is relatively inexpensive, and is FDA-approved for treatment of hypertension—another chronic condition associated with both autonomic dysfunction and anxiety. To enable rigorous evaluation of efficacy, women will be randomized to: 1) use a standard guided-breathing device to practice slowing their respiratory rate to 5 to 10 breaths per minute (BPM) for a minimum of 15 minutes per day (consistent with recommended use of the device to treat hypertension), or 2) use a visually-identical control device reprogrammed to promote breathing at a normal resting rate of 14 BPM. All women will also receive a pamphlet with information about behavioral self-management of OAB, consistent with usual care.

The proposed work is significant because it will provide new evidence to evaluate the efficacy and tolerability of a behavioral slow-breathing exercise program to treat OAB, and also evaluate autonomic dysfunction and anxiety symptoms as potential mediators of treatment effects. If successful, this research may help decrease the burden of one of the most common chronic health problems in women, as well as reduce morbidity and costs associated with anticholinergic OAB therapy.

D. RESEARCH DESIGN AND METHODS

D.1 General Study Design

We propose to conduct a rigorous, 12-week, randomized controlled trial of a device-guided slow-breathing exercise program in 160 ambulatory women who report an average of at least 3 urgency-associated voiding or incontinence episodes per day, do not have a history of urinary tract surgery, cancer, irradiation, or major neurologic disease, and are not receiving other medical treatments for OAB. Participants will be randomized in a 1:1 ratio to: 1) practice slowing their resting respiratory rate to 5 to 10 breaths per minute for at least 15 minutes/day at home using a portable guided-breathing device; or 2) use an identical-appearing control device that plays non-rhythmic music while monitoring their spontaneous breathing pattern. Women will be told that they are enrolling in a study of two types of relaxation therapy for OAB, and that we do not know which, if either, is effective in treating OAB. All women will also receive a usual care pamphlet providing basic

information about pelvic floor muscle exercises, and other traditional self-management strategies for OAB.

Participants will return to the clinic at 1 week to reinforce correct use of their devices and at 6 and 12 weeks to provide outcomes data; they will also complete a mail-in packet 12 weeks after returning their devices. To address Aim 1, we will assess changes in frequency of voiding and incontinence episodes associated with at least a moderate sensation of urgency as measured by validated voiding diaries, as well as changes in frequency of other OAB symptoms and quality-of-life impact of OAB symptoms measured by both diaries and validated questionnaires. To address Aim 2, we will assess for improvement in autonomic nervous system control using several physiologic measures (heart rate variability, pre-ejection period) and explore change in autonomic control as a mechanism of treatment effects on OAB. For Aim 3, we will assess changes in anxiety-related symptoms using validated questionnaires and assess whether these mediate treatment effects on OAB.

D.2 Study Population and Eligibility Criteria

Overview: Participants will be ambulatory women who have frequent OAB symptoms, report no prior complex urologic history, are not currently using other OAB treatments, and are willing to use the breathing device.

Inclusion criteria

1) Women aged 21 years or older who are able to walk to the bathroom without assistance

2) Report recurrent episodes of urgency (sudden or strong urges to urinate) beginning at least 3 months prior to screening

3) Able to record all voiding and incontinence episodes on a screening 3-day voiding diary[29,30] and rate the severity of urgency associated with each episode using a validated urgency severity scale[31]

4) Document at least 9 voiding or incontinence episodes on the above 3-day voiding diary that are associated with at least moderate sensation of urgency (using the above validated urgency severity scale) [31]

5) Willing to refrain from initiating other treatments that may affect voiding pattern during the trial period

Exclusion criteria

1) Use of anticholinergic OAB medications or other medications known to affect urinary function (i.e., diuretics, tricyclic antidepressants) within 1 month of screening

2) Current urinary tract infection (detected via screening dipstick urinalysis or urine culture) or a history more than 3 urinary tract infections in the preceding 1 year

3) Prior history of lower urinary tract surgery, pelvic cancer, or pelvic irradiation; or other pelvic or abdominal surgery within 6 months of screening

4) History of interstitial cystitis, fistula in the bladder or rectum, or congenital or childhood defect leading to chronic urinary incontinence, retention, or other chronic urinary symptoms

5) Known history of major neurologic conditions likely to have major or permanent effects on bladder function such as stroke, multiple sclerosis, spinal cord injury, or Parkinson's disease

6) Use of bladder botulinum injections, electrostimulation, or other invasive therapies for OAB or incontinence within 3 months of screening

7) Formal pelvic floor rehabilitation or other formal behavioral therapy for bladder symptoms involving a physical therapist or other certified practitioner within 3 months of screening

8) Started, stopped, or changed dosage of a psychoactive medication likely to affect anxiety (SSRIs/SNRIs, tricyclics) within 3 months of screening, or plans to start, stop, or change dosage during the trial

9) Resting blood pressure (average of 2 measures) less than 100/60 at screening (women with baseline low blood pressure may theoretically be at increased risk of hypotension with use of RESPeRATE)

10) Resting breathing rate already below 10 breaths/minute before treatment (as measured during run-in)

11) History of chronic pulmonary disease likely to interfere with breathing exercises (e.g., emphysema)

12) Currently pregnant, gave birth within the past 3 months, or planning pregnancy during the study period

13) Unable or willing to sign an informed consent, fill out questionnaires, or undergo study procedures

D.3 Recruitment and Consent

D.3.1 Recruitment strategies

Participants will be recruited from the greater San Francisco Bay Area community. As with past studies directed at urinary tract symptoms, the investigative team will use a multi-component IRB-approved recruitment approach, including contacting a database of women who have given permission to be contacted about future research opportunities, direct community-based media efforts (newspaper notices, radio advertising, brochures in local clinics, talks to local community groups, notices in churches), social media/networking sites and direct recruitment from physician offices (specifically in gynecology, primary care, and alternative medicine clinics). Recruitment efforts will be based at the UCSF Women's Health Clinical Research Center at the Mt. Zion campus at 300 Frank Ogawa Plaza, in Oakland, CA, where coordinators will bring equipment needed for measurements to a rented private office. To facilitate recruitment, UCSF Women's Health Clinical Research Center includes 2 rooms that are staffed by professional research staff including coordinators, recruiters, and research assistants.

D.3.2 Informed consent & documentation

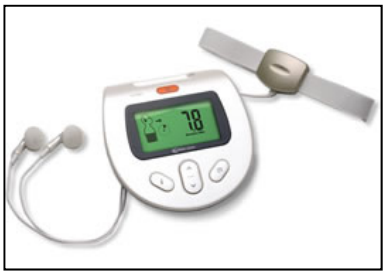
Before entering the study, all study procedures, time requirements, risks and potential benefits will be explained to each potential study participant using the information in the UCSF IRB-approved informed consent form. The potential study participant will be given adequate time to read the informed consent document and ask questions. Eligible participants who choose to enter the study will sign the inform consent form and Health Insurance Portability and Accountability Act (HIPAA) form prior to beginning study treatment. Each participant will be given a copy of the signed documents and the original will be a part of the research

record. All study-specific data will be kept confidential and stored in locked files at the clinical center.

D.4 Interventions, Randomization, and Blinding

D.4.1 Overview of interventions

Participants in this trial will use RESPeRATE, a small, commercially-available guided-breathing device manufactured by Intercure, Ltd. that is currently FDA-approved for treatment of mild hypertension. The



RESPeRATE device includes a belt-type respiration sensor that is placed around the user's chest over the clothing, along with a small computerized box that generates musical tones transmitted through attached earphones. Using the belt-type sensor, the device first senses the user's spontaneous respiratory rate, while playing quiet, relaxing, non-rhythmic music. The device then begins to play distinct musical tones to guide the user in slowing her respiratory rate and prolong her expiratory phase. In the proposed clinical trial, women will be randomized to receive either: 1) a standard, active RESPeRATE device that guides the user in breathing at a rate slower than 10 BPM, or 2) an identical-appearing control device that does not pace respiration but continues to monitor spontaneous breathing rate while playing relaxing, non-rhythmic music. Participants in both groups will be instructed to use their devices for at least 15 minutes per day for 12 weeks.

D.4.2 Active intervention

Participants who are randomized to the active intervention group will receive an active RESPeRATE device at the baseline visit that is programmed to pace respiration at less than 10 BPM (identical to current FDA-approved use of the device for treatment of hypertension). After reading the device instructions, the participant will be asked to place the belt-like elastic strap respiratory sensor around the upper chest over clothing under the axillae and above the breasts. The participant will then place the headphones on the ears and breathe normally until the device recognizes her normal respiratory rate.

After sensing the participant's normal respiratory pattern, the active device will begin to play a distinct musical tone to prompt inspiration and a second tone to prompt expiration. The device will first synchronize its tones to the user's spontaneous respiratory pattern, and then gradually increase the timing and duration of its tones to guide the user in slowing her respiratory rate and prolonging her expiratory phase. The participant will be instructed to simply try to match her inspiration and expiration to the tones. Participants will be asked to use the RESPeRATE device for at least 15 minutes per day at home while sitting quietly and alone in a comfortable location, not listening to other music, watching television, reading, sleeping, or performing any other distracting activity.

During practice sessions, the active device will automatically collect data on: a) the time, date, and number of sessions in which it was used; b) duration of time for each practice session; c) average and range of respiratory rate; d) data quality (i.e., percent time that breathing was detected by the sensor), e) amount of time

that the participant succeeds in slowing respiration to less than 10 BPM in each session, and f) the percentage of time that the participant's breathing pattern follows the device's musical tones. Participants will be instructed to use RESPeRATE for at least 15 minutes per day for a total of 12 weeks.

D.4.3 Control intervention

Participants who are randomized to the control group will a control RESPeRATE device that does not pace respiration, but plays relaxing, non-rhythmic music while monitoring participants' spontaneous breathing rate at home. RESPeRATE devices can be re-programmed by research staff to be either active or control devices using software provided by Intercure, Ltd., and research staff will re-program devices as needed at participants' baseline visits. The control device will look exactly like the active RESPeRATE device, except that the device will not play musical tones synchronized to inspiration and expiration, but will play quiet, non-rhythmic music while monitoring spontaneous breathing.

Like participants in the active group, participants in the control group will be asked to use their devices for at least 15 minutes per day for 12 weeks. Participants in the control group will be given the same instructions as those randomized to use the active RESPeRATE device, except that they will be told to simply listen to the music played by the device rather than using the device as a guide for breathing. Like the active device, the control device will automatically collect data on: a) time, date, and number of sessions in which it was used; b) duration of time for each session; c) average and range of respiratory rate, and d) data quality (i.e., percent time that breathing was detected by the sensor).

This control device will control for the fact that participants will be sitting still and relaxing while wearing the RESPeRATE device breathing sensor belt for at least 15 minutes per day. It will also allow collection of data on spontaneous breathing pattern in the control group and monitoring of adherence to use of the control intervention.

D.4.4 Randomization

Randomization to either the active or control device will be performed by computer at in a 1:1 ratio, using randomly permuted blocks of 2, 4, and 6. Following a brief run-in period in which women use the control device and complete other eligibility assessment procedures, women will be randomized either to: 1) receive a new active RESPeRATE device that paces respiration at a slow rate, or 2) continue using a control device that monitors spontaneous breathing rate while playing non-rhythmic music. Sealed, opaque envelopes will be prepared by the study statistician containing treatment assignment codes. When a participant fulfills study inclusion and exclusion criteria, the next sequential envelope will be opened by study staff and treatment assignment will be irrevocably entered on a participant case report form. A subset of the randomization envelopes will be assigned to the Oakland Satellite office.

D.4.5 Blinding

Because of the behavioral nature of the treatment interventions, study participants cannot be fully blinded to treatment assignment. However, several steps will be taken to minimize possible bias arising from lack of blinding. Participants will be told that they are participating in a study of two different types of relaxation therapy, slow-paced respiration versus music-listening, for treatment of overactive bladder symptoms. They will be told that the investigators do not yet know whether one form of therapy is more effective than the other

in controlling bladder symptoms (which is true). All participant materials will be developed to avoid giving participants the impression that slow-paced respiration is believed to be more effective than relaxing music-listening in controlling overactive bladder. Information listed on clinicaltrials.gov and other public registries will also avoid implying that one form of therapy is more effective than the other.

When interacting with participants, study staff will refer to the RESPeRATE device as the "CURE study relaxation device" rather than a "RESPeRATE device," since the control device will used differently from a standard, commercially-available RESPeRATE device. Participant-oriented study materials will also refer to the device as a "relaxation device" and avoid referring to either RESPeRATE or Intercure Ltd.

The primary outcome, change in frequency of voiding or incontinence episodes associated with at least moderate urgency, will be assessed using 3-day voiding diaries, which are likely to be more resistant to bias than other types of self-report measures. Although clinical staff responsible for conducting study visits will not be blinded to treatment assignment (so that they can assist participants with problems using their RESPeRATE devices), the study investigators will be blinded to treatment assignment., A subset of voiding diaries from both the 2300 Post St. and 300 Frank Ogawa Plaza sites will be reviewed by a blinded analyst for quality control.

D.4.6 Overactive bladder self-management pamphlet

All participants, regardless of treatment assignment, will also receive a pamphlet that provides basic patient-directed information about behavioral self-management of OAB, including pelvic muscle exercises and urge suppression. As information about self-management of OAB is available from multiple websites and public resources, systematic provision of this information will minimize differential use of self-management techniques between treatment groups, and also reflect expected concomitant use of these techniques with slow-paced respiration in clinical practice.

D.5 Measurements

D.5.1 Overactive bladder symptoms (assessed at baseline, 6 weeks, and 12 weeks, and 24 week mail-in)

A. Frequency of voiding or incontinence episodes associated with at least moderate urgency

The primary outcome of this trial, change in frequency of any voiding or incontinence episodes associated with at least a moderate sensation of urgency, will be assessed using a validated 3-day voiding diary.[29,30] At each relevant time point, participants will receive a blank voiding diary along with written instructions and a sample completed diary page. Women will use the diary to record each time they experience a sense of urgency, void in the toilet, or leak urine over 3 days. They will also rate the severity of urgency associated with each of the above episodes using a validated severity scale (the Indevus scale): a) none, b) mild—urgency that is easily tolerated, c) moderate—urgency that interferes with activities, c) severe—extreme urgency that abruptly stops activities).[31] Urgency that results in urine leakage (incontinence) will be assumed to be severe.

B. Frequency of other OAB symptoms

Data abstracted from voiding diaries will also be used to assess secondary voiding outcomes, including

change in frequency of the following additional OAB symptoms: 1) urgency-type incontinence; 2) any voiding or incontinence associated with *severe* urgency, 3) total daytime or nighttime voiding (regardless of association with urgency).

Diary data will also be used to calculate an Overactive Bladder Symptom Composite Score (OAB-SCS), in which points are assigned for each episode of urgency incontinence (5 points each), urgency-associated voiding (2 to 4 points depending on the severity of urgency), and non-urgency-associating voiding (1 point).[32]

C. Bothersomeness and quality-of-life impact of OAB symptoms

Additional secondary voiding outcomes such as bothersomeness and quality-of-life impact of OAB will be assessed using several validated, self-administered, structured-item questionnaires, including:

1) Overactive Bladder Questionnaire (OAB-Q), a 33-item measure of the bothersomness and impact of multiple OAB symptoms (such as urgency, incontinence, nocturia) along a 100-point scale[33]

2) Urgency Severity and Impact Questionnaire (USIQ), a 13-item measure of the severity and impact of urgency validated specifically in patients with OAB[34,35]

3) Urogenital Distress Inventory Short Form (UDI-6), a 6-item measure of the bothersomeness of multiple urinary symptoms, including urgency and incontinence;[36] scores range from

4) Patient Perception of Bladder Condition (PPBC),[37,38] a single-item assessing patient's overall perception of their bladder problems using a 6-point Likert scale

5) Pittsburgh Sleep Quality Index (PSQI),[39,40] an 18-item validated questionnaire evaluating sleep quality, sleep latency, sleep efficiency, and sleep problems over a one-week period. A global sleep quality score ranging from 0 to 21 can be derived from the PSQI, with higher scores reflecting poor sleep quality.

D.5.2 Autonomic nervous system measures (assessed at baseline and 12 weeks)

A. Heart rate variability: Heart rate variability (i.e., fluctuation in instantaneous heart rate that results from autonomic influences on the sinus node) is a well-established measure of overall autonomic balance, and a validated marker of risk for adverse outcomes of other chronic conditions associated with autonomic dysfunction such as coronary disease and heart failure [41]. In particular, the high frequency (0.12-0.40 Hz) component of heart rate variability provides a reliable marker of *parasympathetic* autonomic activity, based on autonomic blockade studies showing that heart rate variability in the high frequency range is influenced by vagal but not sympathetic influences on the heart [42-44]. Measurements will be obtained at baseline and 12 weeks for visits at the 2330 Post St. site only using a Biopac MP150 monitoring system (Santa Barbara, CA), according to protocols established by the North American Society of Pacing and Electrophysiology [45]. Specifically, two electrocardiograph (ECG) electrodes will be attached to participants' torso/chest, and a 20-minute continuous ECG recording will then be taken with the participant in the seated position. Prior to measurement, women will be queried about any history of cardiac arrhythmias that could influence heart rate variability interpretation. To minimize diurnal variation, recordings will be obtained in the same 2-hour time of day at both visits. Women will sit in a quiet, ambient-temperature room, and will also be asked to abstain from tobacco or alcohol for 24 hours prior to recording. For 10 minutes during recording, they will also be asked to perform two computer-based stress tasks designed to assess vagal reactivity and sympathetic nervous system activity. Data will be analyzed using Mindware software (Gahanna, OH), which will calculate multiple time domain heart rate variability parameters (e.g., mean heart rate, standard deviation of N-N interval, square root of mean squared difference of successive N-N

intervals), as well as frequency domain heart rate variability parameters reflecting the distribution of heart rate variability over different frequencies (e.g., high frequency (0.12-0.40 Hz), low frequency (0.04-0.12 Hz), and low frequency/high frequency ratio).

B. Pre-ejection period: Pre-ejection period (i.e., PEP, or, the time period during which the left ventricle of the heart contracts while the aortic and mitral valves are still closed) is an established measure of *sympathetic* autonomic activity that can be measured non-invasively using impedance cardiography [42,44]. Using the same Biopac MP150 monitoring system used to assess heart rate variability (see above), cardiac impedance measurements will be obtained at baseline and at 12 weeks for visits at the 2330 Post St. site only. According to established protocols [46], a standard tetrapolar electrode system will be attached to each participant while in the seated position (two inner electrodes placed at the xiphisternal joint and the base of the neck, outer electrodes place 3 cm distally to the inner electrodes). Impedance cardiogram recordings will be obtained by the Biopac monitor at the same time that heart rate variability recordings. Prior to measurement, women will be queried about any history of heart murmurs suggesting heart valve abnormalities that could influence pre-ejection period interpretation. Cardiac PEP will be determined by calculating the time between ventricular depolarization (assessed by ECG output) and the B point of the dZ/d*t* wave (measured by impedance cardiography). Standard Mindware software will be used to generate the dZ/dt waveform by averaging minute-to-minute ECG and impedance data for each subject.

D.5.3. Anxiety and perceived stress (assessed at baseline, 6 week, 12 weeks, and 24-week mail-in)

Validated self-administered questionnaires will be used to gather additional information about somatic and cognitive anxiety, depression, and perceived stress.

A. Somatic anxiety: 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 Spielberger State Trait Anxiety Inventory (STAI), a 20-item self-administered measure validated in both clinical and psychiatric populations, including patients with bladder symptoms.[47,48] Scores range from 20 to 80, with higher scores indicating greater somatic anxiety.

B. Cognitive anxiety: Cognitive anxiety (i.e., the mental component of anxiety associated with fear of failure) will be measured by the Hospital Anxiety and Depression Scale (HADS), a validated self-administered questionnaire that includes a 7-item Anxiety Subscale[49] shown to be sensitive to change in incontinence trials.[50] Scores range from 0 to 21, with higher scores indicating greater anxiety.

C. Depressive symptoms: Depressive symptoms will be assessed by the Center for Epidemiologic Studies Depression Scale, a 20-item measure that has been widely used in clinical trials, including trials of bladder interventions, and is sensitive to change.[51] Total scores range from 0 to 60, with higher scores indicating greater likelihood of depression.

D. Perceived stress: Perceived stress will be assessed using the Cohen Perceived Stress Scale (PSS), a 10-item self-administered questionnaire assessing subjective feelings and thoughts related to perceived stress in the past month, validated in a probability sample of the United States.[52] Scores range from 0 to 40, with higher scores indicating greater perceived stress.

D.5.4 Respiratory parameters

Respiratory parameters will be measured daily throughout the study by participants' RESPeRATE devices. The RESPeRATE device automatically collects data on respiratory parameters such as average and range of respiratory rate during each practice session. Additionally, the active RESPeRATE device collects data on effectiveness of slow-paced respiration (minutes of breathing in each session in which the respiratory rate was under 10 BPM) and device 'followness' (percent time that breathing was synchronized with the guiding tones). Data are downloaded directly from the device, providing an objective and blinded measurement of respiratory status during sessions. Decrease in respiratory rate with preserved 'followness' indicates that a participant has successfully paced her respiration at a lower rate without holding her breath, and is associated with improvement in blood pressure in prior research [53].

D.5.5 Actigraphy (assessed at baseline and at 12 weeks at the 2330 Post St. site only)

To complement subjective data on sleep quality assessed by questionnaire, actigraphy data will be collected over a 3-day period prior to the Baseline and 12 Week visits using the Motion Logger actigraph (Ambulatory Monitoring, Inc., Ardsley, NY), a small device that designed to be worn on the wrist. This wrist actigraph contains a piezoelectric linear accelerometer (sensitive to 0.003 g and above), a microprocessor, 32K RAM memory, and associated circuitry. The orientation and sensitivity of the accelerometer are optimized for highly effective sleep-wake inference from wrist activity.[54,55] The Motion Logger is able to collect data in three modes simultaneously: the zero-crossing mode, which has been rigorously validated for sleep-wake activity,[54] time-above-threshold, and digital integration mode. The output from the actigraph supplies information about total sleep time, percent sleep, number and duration of awakenings per night, and circadian rhythms.

D.5.6 Demographic and clinical covariates

Structured-item questionnaires will collect data on the following covariates at screening/baseline to provide information on eligibility, characterize the study cohort, provide evidence that treatment groups were comparable at baseline, and guide statistical adjustments in the unlikely situation that groups are not balanced at baseline: demographics (date of birth, race/ethnicity, education, relationship/marital status), urologic history (age of onset of OAB, past urologic surgery, prior treatment of OAB, past response to treatment for OAB), current medications (including psychoactive drugs), gynecologic history (gravidity, parity, menopausal history, hysterectomy, oophorectomy), health-related habits (tobacco and alcohol use, physical activity), and selected co-morbid chronic health conditions (such as diabetes). Height, weight, and seated resting blood pressure, heart rate, and respiratory rate will also be measured at visits. Women will undergo urinalysis testing at baseline to assess for urinary tract infection or hematuria, and to rule out pregnancy.

D.5.7 Safety measures

Because the main potential adverse effect of RESPeRATE is a decrease in blood pressure to symptomatic levels, resting blood pressure will be measured twice in the dominant arm at each study visit, and treatment with RESPeRATE will be discontinued in women with average blood pressure <90/50, and in those with blood pressure <100/60 as well as symptoms suggestive of hypotension such as dizziness. If a participant experiences dizziness while using RESPeRATE, she will also be asked to come to the clinic and practice using RESPeRATE under supervision, with blood pressure measured at the beginning and end of practice. In

published trials of RESPeRATE including a total of 492 participants,[56-63] blood pressure lowering was contingent on higher blood pressure at baseline, such that use of the device in participants with systolic blood pressure <120 mmHg at baseline had no effect on blood pressure; no symptomatic hypotension was reported.

Other unexpected side effects will be assessed using standardized adverse event or serious adverse event forms. At each phone and in-person contact, participants will also be asked about any negative changes in their health. An adverse event will be defined as any undesirable sign, symptom, or medical condition that occurs after starting therapy, whether considered related to the study intervention or not. According to standard practice, adverse events will be classified as mild, moderate, or severe. Events that result in death or disability, are life threatening, or cause hospitalization or prolongation of hospitalization will be classified as serious adverse events and recorded on severe adverse event forms that also note the potential relationship to study interventions and any medical treatment or therapy provided in response to the event.

D.6 Study Visits and Procedures

This clinical trial involves 5 in-person study visits (Screening, Baseline, 1-Week, 6-Week, and 12-Week) and 2 telephone visits (3-Week and 9-Week) over a 12-week period. Additionally, women will complete daily RESPeRATE practice sessions at home, and will complete voiding diaries at home at 3 timepoints over this 12-week period. There is also a 24-week mail-in assessment, in which women will complete an additional voiding diary and packet of questionnaires and return them to study staff by mail.

Study Visits will be conducted in outpatient research facilities associated with the UCSF Women's Health Clinical Research Center at 2330 Post Street on the Mt. Zion campus, where two side-by-side office/exam rooms are equipped with all equipment needed to collect study measurements, or at 300 Frank Ogawa Plaza, in Oakland, CA, where coordinators will bring equipment needed for measurements to a rented private office.

D.6.1 Telephone Screening

Women who respond to study advertisements and notices by calling the study phone number will be provided with a general overview of the study and, if still interested, will complete a brief telephone survey to determine initial eligibility (age, severity of OAB, current and past OAB treatment, exclusionary conditions, availability during the study time period, and willingness to participate). Eligible respondents will be invited to attend a clinic screening visit and will be asked to bring all medications to the visit.

D.6.2 Screening Visit

At the screening visit, the study will be explained in detail, and informed consent will be obtained. Candidate participants will be told that this is a randomized trial of two different forms of relaxation therapy, slow-paced respiration and relaxing music-listening, for treatment of overactive bladder syndrome. They will complete questionnaires assessing demographics, medical history, surgical and gynecological history, medications, alcohol and tobacco use, and OAB symptoms. They will be shown the list of medications that they will need to avoid for the duration of the study. Height, weight, blood pressure, heart and respiratory rate will be measured.

Women will provide a clean-catch urine sample for assessment of urinary tract infection of hematuria, as well as to rule out pregnancy.

If eligible to continue, participants will be given a demo RESPeRATE run-in device and taught how to use it. At the screening visit, the participant will open the box containing the device, sensor strap, earphones, and batteries. After brief instruction (<5 minutes), the research assistant will assist the participant in correctly starting and using the device, answering any questions and making sure the participant is comfortable with device use. The participant will be instructed to place the belt-like elastic strap respiratory sensor around the upper chest over clothing, place the headphones on the ears, and breathe normally until the device recognizes her normal respiratory rate and begins to play background music. Each participant will then be asked to use their device to listen to relaxing music for at least 15 minutes per day at home during a 7-day run-in period.

Each participant will be given a 3-day voiding diary and instructions on using it to record all voiding and incontinence episodes for 3 days during the run-in period and indicate whether episodes were accompanied by a sensation of urgency. Each participant will also be asked to wear a wrist actigraph during the same 3-day period that they complete their voiding diary.

D.6.3 Run-in period

Because previous studies of RESPeRATE for other indications have shown that efficacy improves with adherence,[57,60] all women will complete a 7-day run-in period between the screening and baseline visits in which they will demonstrate willingness to adhere to home RESPeRATE practice. For the run-in, women will be given a demo RESPeRATE run-in device that plays relaxing, non-rhythmic background music but does not pace their breathing. The music played by the demo run-in RESPeRATE devices will be similar but not completely identical to the music played by the regular RESPeRATE control devices that serve as the main control intervention for the study. Like the regular RESPeRATE control device, the demo RESPeRATE control device will automatically collect data on: a) time, date, and number of sessions in which it was used; b) duration of time for each session; c) average and range of respiratory rate during each session; and d) data quality (i.e., percent time that breathing was detected by the sensor). Women will be told to use their run-in RESPeRATE devices for at least 15 minutes each day during the run-in period, while sitting quietly and alone in a comfortable location, and avoiding listening to other music, watch TV, read, sleep, or perform any other distracting activity. For at least 3 days during the run-in period, women will also complete daily voiding diaries, which will be used to further assess women's compliance and to collect data on baseline severity of overactive bladder symptoms. Women will also be asked to wear a wrist actigraph while they complete their voiding diaries, push a button on the actigraph to indicate when they go to bed and when they get up each night, and complete a simple sleep diary over this same 3-day period.

D.6.4 Baseline/Randomization Visit

A baseline visit will be scheduled one to two weeks after the screening visit and completion of the run-in procedures. Participants will return with their completed voiding diary, the demo RESPeRATE run-in device, and the wrist actigraph and sleep diary. Diary data will be abstracted, and data from the run-in device and the actigraph will be downloaded. Those who are non-adherent to RESPeRATE practice or the diary will not be eligible to continue. Blood pressure, heart rate, and respiratory rate will be re-measured; participants who have a blood pressure <100/60 will also be ineligible to continue. If the demo RESPeRATE device indicates

home practice for at least 12 minutes on each of at least 6 days, the voiding diary is completed correctly on at least 3 days, and the diary reveals an average of at least 3 voiding or incontinence episodes per day associated with at least moderate urgency, and the participant meets other eligibility criteria and agrees to enroll in the study, she will be eligible for randomization to a regular active or control RESPeRATE device. Immediately following proof of eligibility, the study coordinator will randomize the participant, using the next sequential randomization envelope.

Following randomization, instruction in use of the active or control RESPeRATE device will be reviewed, and the participant will be asked to use the device for at least 15 minutes per day at home. The participant will be given the study phone number and instructed to call study staff for any questions or problems with the devices. Participants will be given a pamphlet providing brief information about usual care behavioral self-management of overactive bladder symptoms. Participants will be reminded not to take any medications known to affect overactive bladder symptoms during the treatment period.

Participants will also undergo non-invasive measurement of resting heart rate variability and pre-ejection period using the BIOPAC MP150 monitoring device at this visit (if they are randomized). They will complete questionnaires assessing condition-specific quality of life and anxiety and perceived stress symptoms.

D.6.5 Follow-up Visit (1 week)

After one week of treatment, participants will return to the clinic for early follow-up, bringing their RESPeRATE active or control devices. Downloaded RESPeRATE device data will be securely transferred to the study database. The study coordinator will review adherence with use of the active or control device, assess for side effects of treatment, and answer any questions. For safety monitoring, blood pressure, heart rate, and respiratory rate will be reassessed by study staff. Adverse events will be recorded on standardized forms. Each participant will also be given a new, blank voiding diary to complete for 3 days before her 6-week visit.

D.6.6 Follow-up Visit (6 weeks)

After 6 weeks of treatment, women will return to the clinic for follow-up for assessment of adherence, side effects, and concurrent medications, and to address any questions. They will return their 2nd completed voiding diary, in which they will have recorded all voiding and incontinence episodes over a 3-day period and indicated whether these episodes were associated with no, mild, moderate, or severe urgency. Data from RESPeRATE devices will be downloaded before the device is returned to the participant. Blood pressure, heart rate, and respiratory rate will be measured by study staff. Adverse events will be recorded on standardized forms. Participants will complete the same self-administered questionnaires about condition-specific quality of life and anxiety and stress given at baseline visit.

D.6.7 Follow-up Phone Call (9 weeks)

After 9 weeks of treatment, the study coordinator will contact participants by telephone to review adherence with use of the RESPeRATE device, assess for side effects, and answer any questions. At the participant's request, or if there is a safety concern, this visit may also be conducted in person. Participants will be reminded that to start completing their next voiding diary at least 3 days before their 12-week visit, and to wear

the wrist actigraph and complete their sleep diary during this same 3-day period. They will be reminded to bring their completed voiding diary, their RESPeRATE device, and their actigraph and sleep diary with them to that 12-week visit.

D.6.8 12-Week Visit

The final clinic visit will take place approximately 12 weeks after screening or at the time a participant decides to discontinue participation in the trial. Participants will return their third completed voiding diary, the RESPeRATE device, and the wrist actigraph and sleep diary. Participants will complete the same self-administered questionnaires that were given at the baseline and 6-week visits. They will also complete a close-out questionnaire about their satisfaction with the study interventions and procedures. Physical exam measures of blood pressure, heart rate, and respiratory rate will be repeated. Participants will also undergo repeat assessment of heart rate variability and impedance cardiography. Participants will receive instructions and materials for completing and returning the 24-week mail-in voiding diary and questionnaire packet.

D.6.9 24-Week Mail-In

Twelve weeks after returning their guided-breathing devices, women will complete a final voiding diary and set of questionnaires and mail it back to study staff, using a pre-addressed, pre-stamped envelope.

D.6.10 Time commitment

Telephone screening will require approximately 15 minutes. The screening clinic visit will require up to one and a half hours. The baseline clinic visit will require approximately two hours. The 6-week follow-up visit will require one and a half hours. The final (12-week) visit will require approximately two hours. The one-week and 8-week follow-up telephone calls will each require between 5 and 15 minutes. The total estimated time required for study visits is therefore 7 and a half hours, including 7 and hours of clinic visit time, and approximately one half hour of telephone time.

Additionally, participants must practice either slow-paced respiration or music-listening using their RESPeRATE devices for at least 15 minutes per day for 12 weeks, for a total of 21 hours of home RESPeRATE practice time. They must complete voiding diaries at four timepoints in the study (baseline, 6 weeks, 12 weeks, and 24 weeks), adding another 15 minutes at each of these timepoints. They must also complete a mail-in questionnaire packet at 24 weeks, adding another 30 minutes at this timepoint. The total estimated time required of participants at home is therefore 22 and a half hours. In summary, this 12-week study will require a total of 30 hours of participants' time, including 7 and a half hours of visit time, and 22 and a half hours of home time.

D.7 Adherence, Discontinuation, and Reimbursement

D.7.1 Overview

Every effort will be made to assure that participants adhere to the protocol and use the study interventions regularly. Participant contact information including address, phone number(s), fax number(s), and email

address will be obtained. We will also request contact information for two family members or friends who will be able to locate the participant. The study team will encourage retention by educating participants about the importance of the study, maintaining a friendly and efficient clinical center environment, and encouraging excellent staff-participant rapport. All identifying information will be kept confidential, appropriately secured and destroyed at the end of the trial.

D.7.2 Adherence to interventions

Adherence to study interventions will be assessed using data automatically collected by the RESPeRATE device and down-loaded at baseline, 1 week, 6 weeks, and 12 weeks. All participants will be encouraged to use the device as recommended for at least 15 minutes per day. Study staff will ascertain reasons for non-adherence and attempt to help participants find ways to improve adherence. However, participants who are non-adherent with study interventions will still be urged to attend all study visits and complete all study measurements as planned.

D.7.3 Adherence to study visits

All participants will be urged to attend all study visits and complete all study measurements as planned. However, participants can discontinue participation in the study at any time. Participants who miss a visit will be contacted by the study coordinator to reschedule the visit and to provide assistance in completing the visit. Participants who state that they no longer desire to participate in the trial will be asked to undergo final study measurements and complete a close-out questionnaire if possible.

D.7.4 Discontinuation of interventions

The study interventions will be discontinued in women with average blood pressure <90/50 or in those with blood pressure <100/60 as well as symptoms suggestive of hypotension such as dizziness. If possible, the final outcome measurements will be obtained in all participants who discontinue the intervention.

D.7.5 Participant reimbursement

Each participant will receive a $25 gift card at the Baseline Visit and at the Week 6 Visit, a $50 gift card after the Week 12 Visit, and a $20 gift card after returning their mail-in packet at 24 weeks. Participants will therefore receive a total of $120 in gift cards of their choice for their participation in the study. We will also provide parking voucher stickers for participants who wish to park in the UCSF Women's Health Clinical Research Center garage for their study visits.

D.8 Potential Risks and Safety Monitoring

D.8.1 Potential risks of study procedures

A. Paced respiration: RESPeRATE is a commercially-available guided-breathing device (Costco, Amazon) that is FDA-approved for treatment of mild hypertension and widely used without a prescription. Risk to participants from use of RESPeRATE is minimal; in clinical trials that included over 492 participants, no side effects were reported. Additionally, our research team observed no side effects in our other randomized trial of 120 women with menopausal hot flashes treated with slow paced respiration. The effect of RESPeRATE on blood pressure decreases with lower baseline blood pressure such that it does not lower blood pressure in persons with baseline less than about 120 mmHg systolic.

B. Music-listening: There are no known risks to participants associated with use of the RESPeRATE control device for music-listening. Although the music-listening control is designed to be relaxing and pleasant, it is possible that participants randomized to the control group may find this music to be unappealing or irritating.

C. Questionnaires and diaries: Although the information participants provide on data collection forms and diaries is confidential, some participants may feel embarrassed at having to answer questions, especially those related to incontinence symptoms or depression and anxiety symptoms. Completion of diaries and questionnaires will involve slight inconvenience in time and effort.

D. Physical exam measurements: There are no direct risks associated with undergoing measurement of height, weight, blood pressure, and heart rate at study visits, although some participants may experience this as inconvenient or unpleasant.

E. Heart rate variability and impedance cardiography: Heart rate variability and cardiac impedance measurements will be obtained using a non-invasive BIOPAC MP150 electronic monitoring system. The only adverse effect that may result from these measurements is mild skin irritation at the site of the ECG or cardiac impedance electrodes, which generally disappears within 24 hours of removing the electrodes. Although noninvasive, measurement of heart rate variability and cardiac impedance may be experienced by participants as inconvenient or mildly unpleasant. Women will need to lift their shirts (but not remove their brassieres or underwear) for placement of the electrode sensors. They will also need to complete two brief computer-based tasks (approximately 5 minutes in duration each) that may be perceived as psychologically stressful while undergoing Biopac measurements.

F. Computer-based concentration task: Participants will perform two types of brief, computer-based mental concentration tasks while undergoing heart rate variability and cardiac impedance measurements, including a visual attention and tracking task directed at assessing vagal withdrawal and a navigation task designed to assess sympathetic reactivity. Some participants may perceive these tasks to be stressful or annoying.

G. Wrist actigraphy: There is no risk of injury from the wrist actigraph device to measure sleep activity though participants may find it mildly inconvenient to wear a wrist device for 3 days. It is possible that the strap of the actigraph wrist watch device may leave a small area of red skin or irritation which is usually painless and resolves within a few days.

D.8.2 Protections against risks

Women with low blood pressure (<100/60) at the screening or baseline visit will be excluded from the study. Participants will undergo repeat blood pressure measurement at each follow-up clinic visit (1 week, 6 weeks, and 12 weeks) and will be instructed to come to the study clinic to have their blood pressure re-measured if they develop dizziness, fatigue, or other symptoms suggestive of orthostasis. Use of RESPeRATE will be discontinued in participants with blood pressure <90/50, or in those with blood pressure <100/60 and symptoms consistent with hypotension.

Staff will be trained to be courteous and discrete when administering questionnaires, obtaining physical exam measurements, and assessing heart rate variability and impedance cardiography, and to follow-up with referrals to appropriate medical personnel when measurements are outside allowable ranges. Participants will be told that they can ask to pause or discontinue measurements if they become uncomfortable.

Participants who report an allergy or sensitivity to adhesives can decline to undergo heart rate variability or impedance cardiography measurements. Study staff will be trained to remove the EKG electrodes and tape in ways that minimize skin irritation or reaction. Participants with an allergy to metal can wear the wrist actigraph monitor over their sleeve or use a wrist sports sweat band to protect their skin. They can also decline to undergo wrist actigraphy measurements as a non-essential study procedure.

D.8.3 Adverse event monitoring

At each phone and in-person contact, participants will also be asked about any negative changes in their health, which will be recorded as adverse events or serious adverse events on standardized forms. An adverse event will be defined as any undesirable sign, symptom, or medical condition that occurs after starting therapy, whether considered related to the study intervention or not. Medical conditions or diseases present before starting the intervention will only be considered adverse events if they worsen after starting the therapy. According to standard practice, adverse events will be classified as mild, moderate, or severe. Adverse event forms will also record whether the event resolved or continues.

Serious adverse events will be defined as those that are life threatening, require overnight hospitalization or prolong hospitalization, or cause disability or death. Serious adverse events will be recorded on separate forms that note the potential relationship to the study interventions (i.e., no, unlikely, possible, probably, definitely), the time course of the event, and any medications or therapies provided in response to the event. Any participant deaths will be reported within 24 hours of awareness of the event to the UCSF institutional review board, to the Data and Safety Monitor (see below), and to the NIA program officer. All other serious adverse events that are unanticipated and potentially related to the study interventions or procedures will be reported within 48 hours of awareness of the event to the UCSF institutional review board, the Data and Safety Monitor, and the NIA program officer. In the setting of severe or serious adverse events, the study investigators may decide to terminate participants' involvement in the trial prior to their expected termination date, if early termination is thought to be necessary to safeguard the health of participants.

D.8.4 Data and safety monitor committee

The conduct of the study and safety of participants will be evaluated by an independent Data and Safety Monitor (DSM), Dr. Andrew Avins, Senior Investigator at Kaiser Permanente of Northern California. Dr. Avins is a clinical researcher with experience in clinical trials, research ethics, and statistics. 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 study participants. The DSM is independent of the institution and the investigators participating in the study and has no financial ties to the outcome of the study.

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, evaluate the ability of the trial to reach stated goals, review adherence to visits and protocols, assess data quality and timeliness, evaluate the safety of participants, provide a report to the investigators and the IRB on the scientific progress of the trial and the safety of participants, make recommendations to the investigators on continuation, termination, or other modifications of the trial, and consider factors external to the study (i.e., new scientific or therapeutic developments) when relevant to the safety of the participants or the ethical conduct of the trial.

The DSM will periodically review aggregate and unblinded trial data after 30, 60, 90, and 120 participants complete the 6-week visit. 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.

Given that the study is of short duration, no assessment of interim efficacy will be done, and the study will not be stopped or altered for unexpected efficacy or lack of efficacy. 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. A copy of the interim reports will be retained in a locked, confidential file by the DSM.

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 NIA program officer. All materials, discussions, and proceedings of the DSM process will be completely confidential.

D.9 Data Management Plan

D.9.1 Overview

Data will be entered, managed, edited and secured by the UCSF Data Management Group (DMG) which enables simple real-time electronic data entry, ensures timely identification and resolution of data discrepancies, and facilitates the transformation of data to SAS for viewing, reporting, and analyses. Most of the forms and database management modules required for the proposed trial have already been developed and used in previous studies.

D.9.2 Data collection & editing

Machine-readable data forms created with Teleform® software and available for printing at the clinical site from the study website will be completed by participants and clinic staff and transmitted to the DMG using a standard fax machine. The data forms are received at the DMG as electronic images and are evaluated automatically for duplication errors or incomplete scanned images and verified manually by a staff member using Verifier software. This is an important step in which possible misinterpretations in the automated input of data are corrected (e.g. misreading a particular text entry). As each form is verified, the data are written to a pre-defined Microsoft SQL Server database. All of the original form images can be viewed via the password-protected study website. Every hour, preprogrammed error-checking programs scan incoming forms for completeness, data ranges and logic sequences. The results of the error-checking procedures are posted to the study web site where clinical site personnel monitor successful transmission of forms and address any errors that have been detected. Thus, data cleaning is an ongoing process throughout the trial facilitating rapid analysis of results after the final participant visit.

D.9.3 Data monitoring reports

Data are monitored on an ongoing basis to produce a number of standard reports that are made available on the study website automatically, including recruitment reports comparing goal versus actual recruitment rates; adherence reports comparing the number of expected visits to actual visits; participant retention reports indicating the number of participants active, completed, lost, etc.

D.9.4 Computer & data security

The UCSF DMG follows standard operating procedures for computer system security in compliance with established standards for Information Technology Security. The network is privately maintained, hardware fire-walled and none of the workstations or database servers can be directly addressed from outside the Local Area Network. All study data will be stored on Microsoft SQL servers that are backed-up nightly to disk and mirrored to a “failover” site at a co-location facility in San Francisco. In addition, back-up copies of the entire enterprise are archived in Sacramento, CA by Recall, Inc. to protect study data in case of a natural disaster in the San Francisco Bay Area. All servers are housed in a state-of the-art secure server room with controlled access. All servers are protected from viruses by Network Associates Netshield 4.x, Groupshield, and VirusScan Enterprise 7.x (McAfee, Santa Clara, CA). This software automatically checks for virus signature file updates from Network Associates’ FTP and HTTP sites once an hour.

D.10 Statistical Considerations

D.10.1 Statistical analysis plans

Aim 1: To determine whether a device-guided slow-breathing exercise program can reduce the frequency

and severity of OAB symptoms in women.

Expected outcomes: Compared to controls, women randomized to slow breathing will demonstrate a more than 20% greater reduction in frequency of voiding or incontinence episodes associated with moderate urgency, as well as greater reductions in other OAB symptoms and in impact of symptoms.

The primary outcome will be change in the frequency of any voiding or incontinence episodes associated with at least moderate urgency (measured over 3 days using the validated voiding diary and urgency scale[29-31]) from baseline to 12 weeks. Treatment effects will be estimated using ANCOVA models, adjusting for baseline frequency of the outcome. Analyses will be by intention to treat, according to treatment assignment, and without regard to adherence with use of the active or control interventions. For additional confirmation of treatment effects on this primary outcome, we will also use ANCOVA models to examine treatment effects on frequency of other OAB symptoms, including 1) urgency incontinence, 2) voiding or incontinence episodes associated with a *severe* sensation of urgency, 3) total daytime and nighttime voiding (regardless of whether they are associated with urgency), and 4) Overactive Bladder Symptom Composite Scores, as well as on scores on validated urinary symptom bother and impact questionnaires (i.e., the OAB-Q, USIQ, UDI-6, PPBC, and PSQI). Outcomes will be transformed if Shapiro-Wilk tests for normality of the residuals from initial models are significant at $p < 0.01$. In secondary analyses, if treatment benefits are detected at 12 weeks, we will also assess for persistence of effects 12 weeks post-treatment using data from the 24-week mail-in diary and questionnaires, and assess for dose response in treatment effects based on duration and cumulative time of treatment exposure (see the "Additional statistical issues" section below).

Aim 2: To determine whether this slow-breathing intervention can improve autonomic nervous system control in women with OAB, and explore change in autonomic control as a mechanism of treatment effects on OAB symptoms.

Expected outcomes: Women randomized to practice slow-breathing will demonstrate significantly improved autonomic control as measured by high-frequency heart rate variability and pre-ejection period parameters, and that treatment effects on OAB symptoms will be at least partly mediated by improvements in autonomic control.

Secondary outcomes include 12-week change in autonomic control as assessed by high frequency heart rate variability (RSA) and pre-ejection period (PEP), as the purest available measures of parasympathetic and sympathetic function. Treatment effects on each of these measures will initially be estimated using ANCOVA models, first to examine effects on resting parameters, followed by examination of effects on rest-to-stress change (i.e., reactivity) while adjusting for baseline levels of each parameter. Treatment effects will again be examined by intention to treat, according to treatment assignment, and without regard to adherence. Autonomic parameters will transformed as necessary if their distributions appear significantly skewed. We will then assess for mediation of treatment effects on OAB symptoms by improvement in autonomic control using structural equation modeling. This will involve fitting an initial model that includes both autonomic parameters and anxiety symptoms (as described below in the statistical plan for Aim 2), then extracting coefficients for each of the hypothesized mediating pathways.

Aim 3: To determine whether this slow-breathing intervention can improve anxiety-related symptoms in women with OAB, and explore changes in anxiety as a mediator of treatment effects on OAB symptoms.

Expected outcomes: Women with OAB randomized to practice slow-breathing exercises will report significant improvement in anxiety-related symptoms (as measured by validated questionnaires), and treatment effects on OAB symptoms will be at least partly mediated by improvement in anxiety.

Additional outcomes will include change in anxiety symptoms from baseline to 12 weeks, measured by scores on the validated STAI, HADS, PSS, and BDI questionnaires. Intervention effects will again be estimated using ANCOVA, adjusted for baseline questionnaire scores. Anxiety symptom outcomes will be transformed as necessary if their distributions appear skewed. To assess for mediation of treatment effects on the primary outcome by change in anxiety symptom scores (as well as autonomic parameters as noted in the statistical plan for Aim 2), we will use structural equation modeling as outlined above).

D.10.2 Sample size estimates

Sample size is calculated based on parameter estimates derived from prior trials conducted by the investigators, such as BRIDGES and PRIDE: [64,65] a) mean baseline frequency of urgency- associated voiding or incontinence episodes of 12; b) mean reduction in frequency in controls of 30%; c) standard deviation (SD) of change in urgency-associated voiding or incontinence frequency of 5.8 and d) correlation between baseline and follow-up values of 0.59. We assume that a clinically significant effect in the primary outcome would be a net reduction in the active group of more than 20% than that of controls. Under these assumptions, a sample size of 160 (80 per group) would provide 80% power in 2-sided tests with type-I error of 5% to detect between-group differences of >20% in the active vs. control arm. This accounts for reduction in the residual variance achieved by adjustment for baseline frequency, as well as loss to follow-up of 15%. In comparisons of changes in secondary outcomes (other OAB symptoms, impact scores, anxiety, and autonomic parameters), the sample will provide 80% power in 2-sided tests with type-I error of 5% to detect differences of 0.5 SDs, depending on within-subject correlation of outcomes, assumed to fall in the range of 0.4 to 0.8.

D.10.3 Drop-out rates

Given that the proposed trial is of short duration, dropout levels are expected to be low (i.e., less than 15%). The assumption of non-informative dropout will be examined by comparing baseline and early post-randomization characteristics of dropouts and non-dropouts. If dropout is differential between groups, analyses will be adjusted for maldistributed variables. In a sensitivity analysis, we will also use multiple imputation of missing outcomes, in conjunction with standard methods for calculating summary estimates, confidence intervals, and p-values.[66]

D.10.4 Dose effects

In the event that treatment appears effective in improving OAB symptoms over 12 weeks, we will use a closed test procedure to assess for a dose response in duration of treatment without inflating type-I error:[67] specifically, if we detect a statistically significant benefit over 12 weeks at an alpha of 0.05, we will then assess change from baseline to 6 weeks, and from 6 to 12 weeks, also at alpha of 0.05. In exploratory

analyses, we will also assess for a dose response in cumulative time of effective breathing practice, by examining the relationships between total minutes of effective practice and OAB outcomes at 12 weeks, controlling for baseline levels of outcomes. These analyses will allow for assessment of the extent to which differences in adherence and treatment exposure influence treatment benefits on OAB.

D.10.5 Subgroup analyses

Differences between treatment groups will be analyzed in pre-defined subgroups based on clinicopathologic factors in multivariate analysis. For example, we will explore whether high baseline levels of autonomic imbalance or anxiety, past use of medications or other OAB treatments, or baseline use of psychoactive medications influence treatment-associated changes in outcomes. Subgroup-specific effect estimates will be considered only if the interaction with the subgroup is significant at $p<0.05$.

Appendix A: Summary of Measures & Procedures at Study Visits										
Measures	Telephone Screening	Screening Clinic Visit	Run-in period*	Baseline Clinic Visit	1week Clinic Visit	3-week Phone Call	6-Week Clinic Visit	9-week Phone Call	12-week Final Visit	24-week Mail-in
Brief telephone screening interview	X									
Informed consent and HIPAA documentation		X								
Demographic, medical & surgical history		X								
Review of current and past medications		X							X	
Alcohol and tobacco use questionnaires		X								
Height and weight measurement		X							X	
Heart rate and blood pressure measurement		X		X	X		X		X	
RESPeRATE control device run-in			X							
Review of 3-day voiding diary				X			X		X	X
Overactive Bladder Questionnaire				X			X		X	X
Urgency Severity & Impact Scale				X			X		X	X
Urogenital Distress Inventory				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				X			X		X	X
Randomize to active versus control device				X						
Self-management OAB pamphlet distributed				X						
Heart rate variability measurements				X					X	
Impedance cardiography measurements				X					X	
3-day wrist actigraphy				X					X	
Sleep diary (to accompany actigraphy)				X					X	
Adverse events assessment				X	X	X	X	X	X	
Downloading of RESPeRATE device data				X	X		X		X	
Satisfaction questionnaire									X	

REFERENCES CITED

1. Teleman PM, Lidfeldt J, Nerbrand C, Samsioe G, Mattiasson A. Overactive bladder: prevalence, risk factors and relation to stress incontinence in middle-aged women. *BJOG.* Jun 2004;111(6):600-604.
2. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol.* May 2003;20(6):327-336.
3. Sexton CC, Coyne KS, Thompson C, Bavendam T, Chen CI, Markland A. Prevalence and effect on health-related quality of life of overactive bladder in older americans: results from the epidemiology of lower urinary tract symptoms study. *J Am Geriatr Soc.* Aug 2011;59(8):1465-1470.
4. Oh SJ, Ku JH, Choo MS, Yun JM, Kim DY, Park WH. Health-related quality of life and sexual function in women with stress urinary incontinence and overactive bladder. *Int J Urol.* Jan 2008;15(1):62-67.
5. Sand PK, Appell R. Disruptive effects of overactive bladder and urge urinary incontinence in younger women. *Am J Med.* Mar 2006;119(3 Suppl 1):16-23.
6. Coyne KS, Margolis MK, Jumadilova Z, Bavendam T, Mueller E, Rogers R. Overactive bladder and women's sexual health: what is the impact? *J Sex Med.* May 2007;4(3):656-666.
7. Wu EQ, Birnbaum H, Marynchenko M, Mareva M, Williamson T, Mallett D. Employees with overactive bladder: work loss burden. *J Occup Environ Med.* May 2005;47(5):439-446.
8. Coyne KS, Sexton CC, Kopp ZS, Ebel-Bitoun C, Milsom I, Chapple C. The impact of overactive bladder on mental health, work productivity and health-related quality of life in the UK and Sweden: results from EpiLUTS. *BJU Int.* Nov 2011;108(9):1459-1471.
9. Sexton CC, Coyne KS, Vats V, Kopp ZS, Irwin DE, Wagner TH. Impact of overactive bladder on work productivity in the United States: results from EpiLUTS. *Am J Manag Care.* Mar 2009;15(4 Suppl):S98-S107.
10. 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.
11. 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.
12. 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.
13. Carriere I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. *Arch Intern Med.* Jul 27 2009;169(14):1317-1324.
14. Chapple C, Khullar V, Gabriel Z, Dooley JA. The effects of antimuscarinic treatments in overactive bladder: a systematic review and meta-analysis. *Eur Urol.* Jul 2005;48(1):5-26.
15. Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. *J Am Geriatr Soc.* Aug 2011;59(8):1477-1483.
16. Geller EJ, Crane AK, Wells EC, et al. Effect of anticholinergic use for the treatment of overactive bladder on cognitive function in postmenopausal women. *Clin Drug Investig.* Oct 1 2012;32(10):697-705.
17. Hartmann KE, McPheeters ML, Biller DH, et al. Treatment of overactive bladder in women. *Evid Rep Technol Assess (Full Rep).* Aug 2009(187):1-120, v.
18. 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.
19. Burgio KL, Robinson JC, Engel BT. The role of biofeedback in Kegel exercise training for stress urinary incontinence. *Am J Obstet Gynecol.* Jan 1986;154(1):58-64.
20. Wyman JF, Fantl JA, McClish DK, Bump RC. Comparative efficacy of behavioral interventions in the management of female urinary incontinence. Continence Program for Women Research Group. *Am J Obstet Gynecol.* Oct 1998;179(4):999-1007.
21. 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.

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. Lim JR, Bak CW, Lee JB. Comparison of anxiety between patients with mixed incontinence and those with stress urinary incontinence. *Scand J Urol Nephrol.* 2007;41(5):403-406.

25. Im HW, Kim MD, Kim JC, Choi JB. Autonomous nervous system activity in women with detrusor overactivity. *Korean J Urol.* Mar 2010;51(3):183-186.

26. Choi JB, Kim YB, Kim BT, Kim YS. Analysis of heart rate variability in female patients with overactive bladder. *Urology.* Jun 2005;65(6):1109-1112; discussion 1113.

27. Hubeaux K, Deffieux X, Ismael SS, Raibaut P, Amarenco G. Autonomic nervous system activity during bladder filling assessed by heart rate variability analysis in women with idiopathic overactive bladder syndrome or stress urinary incontinence. *J Urol.* Dec 2007;178(6):2483-2487.

28. Liao WC, Jaw FS. A noninvasive evaluation of autonomic nervous system dysfunction in women with an overactive bladder. *Int J Gynaecol Obstet.* Jul 2010;110(1):12-17.

29. 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.

30. 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.

31. Nixon A, Colman S, Sabounjian L, et al. A validated patient reported measure of urinary urgency severity in overactive bladder for use in clinical trials. *J Urol.* Aug 2005;174(2):604-607.

32. Zinner N, Harnett M, Sabounjian L, Sandage B, Jr., Dmochowski R, Staskin D. The overactive bladder-symptom composite score: a composite symptom score of toilet voids, urgency severity and urge urinary incontinence in patients with overactive bladder. *J Urol.* May 2005;173(5):1639-1643.

33. Coyne KS, Matza LS, Thompson CL, Kopp ZS, Khullar V. The responsiveness of the Overactive Bladder Questionnaire (OAB-q). *Qual Life Res.* 2005;14(3):849-855.

34. Lowenstein L, FitzGerald MP, Kenton K, et al. Evaluation of urgency in women, with a validated Urgency, Severity and Impact Questionnaire (USIQ). *Int Urogynecol J Pelvic Floor Dysfunct.* Mar 2009;20(3):301-307.

35. Lowenstein L, Rickey L, Kenton K, et al. Reliability and responsiveness of the Urgency Severity and Life Impact Questionnaire (USIQ). *Int Urogynecol J.* Feb 2012;23(2):193-196.

36. 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.

37. 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.

38. 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.

39. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* May 1989;28(2):193-213.

40. Buysse DJ, Reynolds CF, 3rd, Monk TH, Hoch CC, Yeager AL, Kupfer DJ. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep.* Aug 1991;14(4):331-338.

41. Malik M, Bigger JT, Camm AJ, al. e. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology - Heart rate variability: Standard of measurement, physiological interpretation and clinical use. *Circulation.* 1996;93:1043-1065.

42. Cacioppo JT, Berntson GG, Binkley PF, Quigley KS, Uchino BN, Fieldstone A. Autonomic cardiac control. II. Noninvasive indices and basal response as revealed by autonomic blockades. *Psychophysiology.* Nov 1994;31(6):586-598.
43. Berntson GG, Bigger JT, Jr., Eckberg DL, et al. Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology.* Nov 1997;34(6):623-648.
44. Berntson GG, Cacioppo JT, Binkley PF, Uchino BN, Quigley KS, Fieldstone A. Autonomic cardiac control. III. Psychological stress and cardiac response in autonomic space as revealed by pharmacological blockades. *Psychophysiology.* Nov 1994;31(6):599-608.
45. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability; standards of measurement, physiological interpretation and clinical use. *Circulation.* 1996;93:1043-1065.
46. Sherwood A, Allen MT, Fahrenberg J, Kelsey RM, Lovallo WR, van Doornen LJ. Methodological guidelines for impedance cardiography. *Psychophysiology.* Jan 1990;27(1):1-23.
47. 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.
48. 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.
49. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* Jun 1983;67(6):361-370.
50. 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.
51. 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.
52. 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.
53. Gavish B. Device-guided breathing in the home setting: Technology, performance, and clinical outcomes. *Biological Psychology.* 2010;84:150-156.
54. Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Automatic sleep/wake identification from wrist activity. *Sleep.* Oct 1992;15(5):461-469.
55. Ancoli-Israel S, Clopton P, Klauber MR, Fell R, Mason W. Use of wrist activity for monitoring sleep/wake in demented nursing-home patients. *Sleep.* Jan 1997;20(1):24-27.
56. Altena MR, Kleefstra N, Logtenberg SJ, Groenier KH, Houweling ST, Bilo HJ. Effect of device-guided breathing exercises on blood pressure in patients with hypertension: a randomized controlled trial. *Blood Press.* 2009;18(5):273-279.
57. Meles E, Giannattasio C, Failla M, Gentile G, Capra A, Mancia G. Nonpharmacologic treatment of hypertension by respiratory exercise in the home setting. *Am J Hypertens.* Apr 2004;17(4):370-374.
58. Schein MH, Gavish B, Baevsky T, et al. Treating hypertension in type II diabetic patients with device-guided breathing: a randomized controlled trial. *J Hum Hypertens.* May 2009;23(5):325-331.
59. Schein MH, Gavish B, Herz M, et al. Treating hypertension with a device that slows and regularizes breathing: a randomised, double-blind controlled study. *J Human Hypertension.* 2001;15:271-278.
60. Grossman E, Grossman A, Schein MH, Zimlichman R, Gavish B. Breathing-control lowers blood pressure. *J of Human Hypertension.* 2001;15:263-269.
61. Elliot WJ, Izzo JL, Jr., White WB, et al. Graded blood pressure reduction in hypertensive outpatients associated with use of a device to assist with slow breathing. *J Clin Hypertens.* 2004;10:553-559.
62. Anderson DE, McNeely JD, Windham BG. Regular slow-breathing exercise effects on blood pressure and breathing patterns at rest. *J Hum Hypertens.* Mar 4 2010.
63. Logtenberg SJ, Kleefstra N, Houweling ST, Groenier KH, Bilo HJ. Effect of device-guided breathing exercises on blood pressure in hypertensive patients with type 2 diabetes mellitus: a randomized controlled trial. *J Hypertens.* Jan 2007;25(1):241-246.

64. 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.
65. Subak LL, Wing R, West DS, et al. Weight loss to treat urinary incontinence in overweight and obese women. *N Engl J Med.* Jan 29 2009;360(5):481-490.
66. Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res.* Mar 1999;8(1):3-15.
67. Rom DM, Costello RJ, Connell LT. On closed test procedures for dose-response analysis. *Stat Med.* Aug 15 1994;13(15):1583-1596.