Official Title: Exploring the Role of Sarcopenia and Functional Impairment on the Non-Surgical Management of Urinary Incontinence in Older Women
NCT03057834
IRB-Approved Date: 8.5.2019

PROTOCOL TITLE:

The Urinary Incontinence Treatment Study (UNITS): Exploring the role of Sarcopenia and Functional Impairment on the Non-Surgical Management of Urinary Incontinence in Older Women

Principal investigator:

Candace Parker-Autry, MD

Funding mechanism:

Claude D. Pepper Center at Wake Forest University Health Sciences, NIA

National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Award Number UL1TR001420

GEMSSTAR NIA award effective 7/15/2017

Co-Investigators:

Stephen Kritchevsky, PhD, Senior Mentor

Barbara Nicklas, PhD, Exercise Intervention

Iris Leng, PhD, Biostatistician

Study coordinator team:

Kimberly Kennedy, Aging center

Erin Kennedy, Aging center

Consultant:

Lisa Colombo, Physical Therapist

Background, Rationale, and Context:

Growing evidence supports that physical functional limitations can be a cause and result of urinary incontinence in aging adults. Tinetti et al studied a cohort of older community dwelling adults (N=927) to assess predisposing factors associated with UI, falling, and functional dependence. They reported that lower extremity weakness revealed by abnormal performance on timed chair stands showed the strongest relationship.(3) Erekson et al. further clarified this relationship in a secondary cross-sectional analysis that revealed that among women with daily UI, 24% reported specific difficulty or dependence with using the toilet and had 3.3 increased odds of functional difficulty or dependence compared to continent older women.(2) There is great need for revising non-surgical interventions for UI in older women with physical function limitations as the development of functional dependency is an important adverse outcome of UI among older adults.(8) Urinary urgency incontinence has been independently associated with risk of falling [OR 1.26 (1.14-1.40)] and non-spine nontraumatic fractures [relative hazard 1.34 (1.06-1.69).(9) In addition, UI was experienced by 24% of women older than 65 years who participated in the California Health Interview Survey and was significantly associated with poorer overall health (adjusted OR 3.43), decreased mobility (OR, 1.81), and history of falls (OR, 1.53).(10) Understanding the relationship between physical function and UI is critical to effectively treat these conditions as they often occur concomitantly. Sarcopenia may be an important factor contributing both to UI and functional decline in older women and may explain how these two conditions are associated. Women >60 years with stress UI experienced increased pelvic floor muscle strength and functional efficiency with a decline in UI episodes after 12 weeks of intensive pelvic floor physical therapy.(11)

However, only 44% independently adhered, and this has been related to weak muscle function at baseline. Recent reports that UI episodes decrease with increased physical activity (walking) and group based physical fitness in institutionalized older women support our hypothesis that muscle function beyond the pelvic floor is important and needs to be characterized to improve the efficacy of non-surgical therapy for treatment of UI.(12, 13)

Objectives:
AIM 1: To robustly characterize the relationship between physical performance, functional impairment, and sarcopenia status of community-dwelling older women with UI in up to100 women.
Hypothesis 1. Functional impairment and sarcopenia will be prevalent among older women seeking care for UI and will negatively correlate with UI severity in a diverse sub-specialty-based clinic population. Urinary incontinence will be defined as bothersome involuntary leakage of urine at least 2 times/week and characterized by 3 day voiding diary. Physical and functional performance will be measured using the extended Short Physical Performance Battery, a timed 400 meter walk, and Isokinetic dynamometer (Biodex). Sarcopenia status will be determined by the composite of an Appendicular skeletal muscle mass index (ASMI) <5.5 kg/m^2, usual walk speed <1 m/s, and hand-grip strength ≤ 20.5 kg.

AIM 2: To compare a well-characterized cohort of functionally impaired older incontinent women to a control group of functionally normal older incontinent women to assess the impact of sarcopenia and functional impairment on efficacy of a standardized 6 week PFME prescription for treatment of UI.
Hypothesis 2. Functional impairment and sarcopenia status will be independent predictors of efficacy of PFME therapy in a well-characterized cohort of older women with UI. Specifically, older incontinent women without functional impairment will have greater improvement in UI episodes after PFME therapy in comparison to those with functional impairment. Sarcopenia with functional impairment will be defined as a grip strength <16 kg or gait speed <1 m/s. We expect a 6 week PFME prescription to decrease UI episodes by 50% defined in a 3 day bladder diary and the full 12 weeks to decrease UI episodes even more. Pelvic floor strength will be objectively measured using the PERFECT assessment and perineometer.

AIM 3: To explore the relationship between obesity, attitudes (barriers, motivation) towards physical activity, and physical activity levels in a well-characterized longitudinal cohort of older women with UI symptoms. **Hypothesis 3**. Older women with UI view UI severity as a barrier to a high physical activity. Lower physical activity levels (defined as <6.2 MET hours/week) in women with UI impacts on physical performance and is associated with obesity. Physical activity levels will be determined using the Community Healthy Activities Model Program for Seniors questionnaire that reports metabolic equivalent task (MET) hours/week.(6) Questionnaires will assess barriers to and motivations for physical activity.

METHODS AND MEASURES:

Study Design:
We plan a prospective cohort study with an adaptive design based on physical function status. The design will involve tracking the number of women recruited with physical function impairment and those without any functional impairment. We aim to recruit similar numbers of women in each group. If we find unequal numbers, we will adapt our recruitment strategies based on a woman's functional status.

We will compare changes in outcome measures within and between groups after 6 and 12 weeks of PFME. The change in pelvic floor strength/efficiency will be assessed by repeating the pelvic floor PERFECT assessment and will be compared between groups. Changes in UI symptoms, symptom severity, and impact of UI symptoms on quality of life will be determined using standardized measures described above. Data analysis will define associations between changes in PERFECT measures and the change in UI episodes (based on 3-day voiding diary), severity, and type (based on QUID-7), and impact on quality of life (PFIQ-7) within and between groups. Objective measurement of lower-extremity strength will inform the relationship between lower-extremity strength, pelvic floor strength, and UI symptoms at baseline and the 6-week visit. *(See Appendix Figure 1 – Study Flow Chart)*

Setting:
Study visits will take place at the Sticht Center on Aging in the Geriatric Research Clinic. The study coordinator will meet the participants in the GRC to confirm eligibility, describe the study, answer any questions, and administer written informed consent.

Subject selection criteria:

- Inclusion criteria:
  a) Women, age 70 years or older
  b) Symptoms of Urinary Incontinence for greater than 6 months
  (Defined by the QUID assessment as having subscale score for stress ≥4, and/or urge score ≥ 6, and/or total QUID score ≥ 10)
  c) Willing and able to be compliant with pelvic floor muscle exercise intervention (standard of care) for 12 weeks and to log compliance
  d) Willing and able to undergo an extensive physical function evaluation
  e) SPPB ≤9 (for any new screens conducted after amendment 12 is approved)

- Exclusion criteria:
  a) Prior surgical intervention for urinary incontinence within the past 12 months
  b) Hysterectomy within 12 months
  c) Having primarily nocturia
  d) Diagnosis of:
    i) Pelvic Organ Prolapse beyond the hymenal ring
    ii) Urogenital Fistula
    iii) Neurogenic Overactive Bladder (associated with a diagnosis of Multiple Sclerosis or Stroke within past 12 months)
    iv) Incomplete Bladder Emptying/Urinary Retention with PVR >150 ml (measured by bladder scan)
  e) Wheelchair bound
  f) Having significant cognitive impairment or dementia
  g) Unsafe to exercise (severe cardiopulmonary disease)
  h) Unable/unwilling to provide informed consent
  i) Determined otherwise ineligible by the principal investigator

Sample Size Estimate:
With 50 women per group (functional impaired and non-impaired) and assuming a drop-off rate of 15% for a two-sided test, we will be able to detect a 20% difference of improvement of UI episodes (assuming a standard deviation of 32%)[40] with at least a power of 80% at 0.05 significance level for Aim 1.

Interventions and Interactions:

Interaction 1: Mailing of Introductory Letters
Potential participants will be recruited from the community of patients in the Wake Forest Baptist Health System and those in a database of older adults interested in volunteering for research studies on aging (the VITAL database in our Sticht Center on Aging). The electronic health record will be searched using the Translational Data Warehouse (managed by the Wake Forest Clinical and Translational Science Institute [CTSI]). Women > 70 years old with ICD-10 diagnosis codes [R32 (unspecified UI), N39.81 (functional UI), N39.41 (urge UI), N39.46 (mixed UI), and N39.3 (stress UI)] will be identified as having a diagnosis of UI within 6 months of the query. Potential participants will be mailed a letter introducing them to the study and informing them that they may be eligible to participate. The introductory letter includes the 6-item Questionnaire for Urinary Incontinence Diagnosis (**QUID**) validated to establish the diagnosis, distinguish UI type, and measure change in UI severity over time in the letter [18]. It is common for women to self-identify the presence of UI symptoms. Interested women will be instructed to call our study coordinator to learn more. For women in the VITAL database, the diagnosis will be verified over the phone through the QUID.

We plan to mail 100 letters every 2-3 weeks based on the responsiveness and work-load of the study staff.

Interaction 2: Phone Screen
During the screening call, trained study coordinators will determine eligibility using scripted questions and review the results of the QUID. Callers will be asked about their current physical and cognitive function and physical activity through validated questions. Eligibility criteria will be reviewed. Potential participants that screen eligible will then be invited to come for a baseline visit. Women with UI symptoms who screen ineligible for this study will be directed to the website of the American Urogynecology Society (AUGS), to learn more about their symptoms and options for treatment. Those who qualify for participation will be scheduled for a study visit within 1-2 weeks during the phone screen conversation. To help facilitate this process, the personnel performing the phone screen will be given an updated list of available appointments for study visits (Tuesday PM, Wednesday PM) and will be given permission to schedule the visits.

Study introductory packets will be mailed to all women who qualify for participation. These will include the consent form, study related questionnaires, and an introductory letter with details of the upcoming study visit. We may bring people in for a separate pre-screen visit to assess their SPPB score prior to scheduling them for a full study visit 1 since as of amendment 12, the SPPB is part of the eligibility criterion.

Interaction 3 (Study visit 1): (Average duration 3 hours)
Enrollment will take place at the Geriatric Clinical Research Unit in our Claude D. Pepper Older Americans Independence Center supported by the Wake Forest CTSI. A study staff member will confirm eligibility, describe the study, answer any questions, and administer written informed consent.

A. **Demographic and medical characteristics**: age, parity, mode of delivery, history of hormone replacement therapy use, history of vaginal estrogen use, anthropometric body measurements.

B. **Overall health status** and 10-year mortality risk will be assessed using the Charlson Co-morbidity Index. [19] Self-reported health status will be assessed using the Medical Outcomes Study Short-Form 36 (SF-36).[20]

C. **Emotional health** will be determined using the Center for Epidemiologic Studies Depression (CESD). [21]

D. **Pelvic floor assessment:** All participants will undergo a pelvic examination (to evaluate for urogenital atrophy and vaginal prolapse) and pelvic floor muscle assessment performed by the PI or a pelvic floor physical therapist. These assessments are a routine component of the pelvic floor assessment performed by these practitioners during an evaluation for pelvic floor symptoms.

   Participants are placed in the supine position with 1-2 pillows to support the head. Next, the hips are flexed and the abducted and the knees are bent. Use of stirrups may be helpful. A single finger (index) is placed 4-6 cm inside of the vagina and positioned at either 4 or 8 o'clock to monitor muscle activity. Moderate pressure may be applied to the muscle bulk to assist in the initiation of the appropriate muscle contraction.

   The PERFECT scheme will be applied for baseline and follow-up pelvic floor assessment. The PERFECT scheme is a valid and reliable pelvic floor assessment tool to assess pelvic floor muscle strength and efficiency.[22] PERFECT assessment includes the following measures:

   P= power (a measure of muscle strength using digital exam or manometric perineometer). Measured on an modified Oxford scale. A single digit is used to assess power. Power is measured by assessing 3 contractions of maximal effort and obtaining a mean strength measurement. Objective measurement of perineal power will be performed using a perineometer.

Grade 0	**No discernible muscle contraction**
Grade 1	**A flicker of pulsation is felt under the examiner's finger**
Grade 2	**An increase in tension is detected, without any discernible lift**
Grade 3	**Muscle tension is further enhanced and characterized by lifting of the muscle belly and also elevation of the posterior vaginal wall. A grade 3 and stronger can be observed as an in-drawing of the perineum and anus**
Grade 4	**Increased tension and a good contraction are present and are capable of elevating the posterior vaginal wall against resistance with digital pressure applied to the posterior vaginal wall**
Grade 5	**Strong resistance can be applied to the elevation of the posterior vaginal wall; the examining finger is squeezed and drawn into the vagina**

Next, if a perineometer is tolerable, it may be placed 5 cm into the vaginal canal.

E=endurance – expressed as the length of time in seconds up to 10 seconds that the maximum strength can be maintained. When the muscle starts to fatigue, the endurance measurement is terminated. This can be felt as decreased anterior lift digitally. This can be visualized on the perineometer with decrease in calculated strength. Other indications of muscle fatigue that should cause endurance measurement to end are: contraction of hip adductors and glutei, increased contraction of transversus abdominis. Breath holding should be discouraged. If this is occurring, try to ask the participant to contract their muscles with escalation.

R=repetitions - Once fatigue is noted, the participant is given a 4 second rest before being asked to contract with the maximum amount of force again. Power and endurance is measured with each contraction up to 10. The goal of this portion is to determine the number of repetitions needed to overload the muscle. Once the participant is unable to generate the same power, the repetition count ends.

F=fast contractions – After a 1 minute break, the number of 1 second strong contractions up to 10 are counted. Participants are asked to 'contract-relax' as quickly and strongly as possible in their own time until the muscles fatigue.

ECT = every contraction timed – Indicates that the above scheme is repeated up to 10 repetitions with each there is a determination of power, endurance and repetitions.

A prescription will be provided for each participant based on their individual PERFECT assessment; typically this details numbers of repetitions, duration of squeezes, and numbers of sets. Based on physical therapy and exercise science literature, 8-12 repetitions of 3-4 sets over 6 weeks increases strength and efficiency of muscle recruitment.[23]

All participants will use a calendar to record daily compliance with PFMEs.

E. **UI assessment**: UI and pelvic floor symptom assessment will be performed by asking for a history of UI symptoms (years), UI treatment, and number of pads used per day for UI. Participants will complete a 3-day voiding diary to record urinary frequency, urinary urgency and incontinence episodes classified by clinical type (urgency, stress, insensible) along with time of occurrence (day, night).[24] This will be returned during week 2 (baseline), week 6, and week 12. UI symptom impact on daily life will be measured subjectively with the QUID and the Pelvic Floor Impact Questionnaire (PFIQ)-Short Form 7.[25] The Pelvic Floor Distress Inventory (PFDI) short-form 20 will be used to

characterize all pelvic floor symptoms (urinary incontinence, fecal incontinence, voiding dysfunction, overactive bladder, and pelvic organ prolapse).[25]

F. **Physical function assessment**: Participants will undergo the following assessments:
- **Extended version of the Short Physical Performance Battery (expSPPB).** The expSPPB is a standard and robust predictor for disability that includes progressively more challenging standing balance tasks held for 10-30 seconds each (side-by-side, tandem, and semi-tandem, single leg), 4-meter walk to assess usual gait speed, 4-meter narrow walk test of balance, and five chair-stands test.[26, 27] The timed 4-meter walk will be performed as a surrogate for the 6-meter walk; it is associated with urgency/stress UI and its results are strong predictors of falls and fractures in women.
- **Timed 400 meter walk (min:sec)** (22)
- **Isokinetic dynamometer (Biodex®)** as an objective measure of strength, maximal isokinetic knee extensor strength in the right leg will be measured at speeds of 60 degrees/sec. The left leg will be used if the participant has severe knee pain or a joint replacement in the right knee.
- Balance will be measured using a **postural sway test**. Center-of-pressure (COP) trajectory data will be collected using an Advanced Mechanical Incorporated (AMTI) AccuSway biomechanics force platform. Four posturographic parameters (maximum antero-posterior and medio-lateral displacement, average sway velocity, and 95% confidence ellipse) and two statistical mechanics measures (stabilogram diffusion analysis and detrended fluctuation analysis) will be calculated to quantify postural sway according to our previously published methods. [30]

G. **Comprehensive prospective evaluation for physical function limitations** will be assessed with the Pepper Assessment Tool for Disability (PAT-D) and the Mobility Assessment Tool-Short Form (MAT-SF) to measure activities of daily living disability, mobility disability and instrumental activities of daily living disability to assess changes in disability. The MAT-SF is a novel, computerized tool for self-assessment of functional performance designed to reduce bias from factors such as age, gender and body image.[31] [32]

H. **Sarcopenia will be determined using the following validated questionnaires and objective physical function measures with standard cut-offs:**
- Grip-strength and gait speed will objectively measure weakness.[33]
- The “SARC-F” is a short-form questionnaire validated to identify adults with sarcopenia and who are at risk for adverse outcomes and may benefit from a physical function intervention. [34]
- Whole-body DEXA scans will be used to calculate the appendicular lean muscle mass.[35, 36]

I. **Physical activity will be assessed using the** Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire assesses weekly frequency and duration of various physical activities common to older adults to evaluate the efficacy of behavioral interventions aimed at increase levels of physical activity. Caloric expenditure (MET hours/week) will be reported.[8] 'Low activity' will be defined as <6.2 MET-hours/week of activity. Women with 6.3-11.4 MET hr/week will be classified as having low-moderate activity. Since only 23% of incontinent women had >11.4 MET hours/week of physical activity, this level will be defined as high activity.[8] Validated questions will be asked to identify potential barriers to physical activity related to UI symptoms.[37]

J. **Cognitive function** will be assessed using the Montreal Cognitive Assessment (MoCA). Mild cognitive impairment will be defined as MoCA score of <26. Severe cognitive impairment will be determined by MoCA score <21.[38]

At the conclusion of the Study Visit 1, participants are given a folder labeled with their study ID. The folder will contain the following:
- ☐ Voiding dairy (toilet hat should accompany this)
- ☐ Pelvic floor muscle exercise compliance log (we explain that this is an observational study, therefore, they should only complete the log reflecting what they actually are able to do at home)
- ☐ Copy of informed consent form
- ☐ Label indicating the time/day of their next appointment

- Sheet cover insert containing the bladder diary OR questionnaires necessary for the upcoming study visit 2 (bladder diary), study visit 3 and 4 (Questionnaires and bladder dairy)

All assessments will be repeated during the 6- week follow-up visit. Questionnaire based assessments and UI voiding diaries will also repeated at week 12. *(see Appendix Table 1 – Assessment schedule)*
*We were mailing the questionnaires, but they would invariably reach the participants in time. Therefore, we are modifying our technique to increase compliance with completing the questionnaires and improve the efficiency of study visits.

Study visit 2 (week 2): (20 minutes) This visit will ensure that pelvic floor muscle strength and contractions are being performed and recorded correctly. The PI will assess each participant by performing a digital vaginal exam, to confirm proper isolation of pelvic floor muscles and ability to complete the PFME prescription. The bladder diary will be reviewed, clarified, and collected. A data abstraction form should be completed at this time. The pelvic floor exercise prescription may be modified at this visit, if that occurs, a new document will be provided and the previous prescription will be stored in the participants chart. The PFME compliance log should be reviewed. A brief visit note should be completed to summarize the events.

Study visit 3 (week 6): (2.5 hours) This visit will take place 6 weeks after initial assessment to assess for changes in pelvic floor strength/function, physical performance, and physical activity. They will bring with them a 3-day voiding diary and 4 weeks of PFME compliance calendars. A subset of assessments from Study Visit 1 will be repeated.(see Table 1) Additionally, self-reported Global Impression of Improvement (GPI), Patient Satisfaction Questionnaire (PSQ), and Estimated Perception of Improvement (EPI) will be assessed using a standardized and validated measure for UI,[39]. To improve recruitment and retention, a $30 gift card or check will be provided at the completion of this visit.

Study Visit 4 (week 12): (2 hours) To observe long-term adherence to PFME therapy and evaluate the sustained effect on UI symptoms, participants will be asked to return for a visit. They will bring with them a 3-day voiding diary and 6 weeks of PFME compliance calendars. A subset of assessments from Study Visit 1 will be repeated (see Table 1). Additionally, self-reported Global Impression of Improvement (GPI), Patient Satisfaction Questionnaire (PSQ), and Estimated Perception of Improvement (EPI) will be assessed using a standardized and validated measure for UI. [39] We will invite 30 participants (15 with poor physical function defined by SPPB < 9 and 15 with normal physical function defined by SPPB >10) to complete repeated physical performance measures (SPPB, grip strength, postural sway) in order to establish variance among this cohort at 12 weeks. To improve recruitment and retention, a $30 gift card or check will be provided at the completion of this visit.

Reminder telephone calls: Our study staff will call participants 3 days prior to study visit 2, study visit 3 and 4 to remind them to complete the diary and of the time/date of the appointment. In addition, compliance calls will be made in between study visits 3 and 4 every 2 weeks to check on adherence to the PFME prescription, remind participants of upcoming visits, and review expected completed documentation.

Data Entry:

Outcome measures:

Pelvic floor assessment	
Pelvic examination	External evaluation of pelvic floor support will be performed by the PI or physical therapist (per mentioned above). The patient will be asked to undress from the waist down. She will be placed in the dorsal lithotomy position. While her head is elevated to 45 degrees, she will be asked to perform the Valsalva maneuver. The labia majora will be parted to allow visualization of the urethra and vaginal introitus. During the Valsalva maneuver, the anterior and posterior vaginal wall will be observed to ensure that pelvic organ prolapse is not present at or below the level of the vaginal

	hymen. The vaginal epithelium will be assessed visually for signs of urogenital atrophy.
Pelvic Floor Muscle Exercise (PFME) prescription using the PERFECT scheme	The PERFECT scheme is a valid and reliable pelvic floor assessment tool to assess pelvic floor muscle strength and efficiency.[22] PERFECT stands for: P= power (a measure of strength using digital exam or manometric perineometer), E=endurance (how long can they hold the contraction), R=repetitions (how many repetitions can they sustain), F=fast contractions (how many contractions can be repeated), ECT = every contraction timed (how long do they hold the fast contractions). Power is measured by assessing 3 contractions of maximal effort and obtaining a mean strength measurement. Objective measurement of perineal power will be performed using a perineometer. A prescription will be provided for each participant based on their individual PERFECT assessment and typically entails a number of repetitions, duration of squeeze, and number of sets. .
Physical function and performance measures	
Extended version of the Short Physical Performance Battery (expSPPB)	The expSPPB is a standard and robust predictor for disability that includes progressively more challenging standing balance tasks held for 10-30 seconds each (side-by-side, tandem, and semi-tandem, single leg), 4-meter walk to assess usual gait speed, 4-meter narrow walk test of balance, and five chair-stands test.[26] It more sensitively detects changes in physical performance by decreasing the ceiling effect present in healthier adults.[27] The timed 4-meter walk will be performed as a surrogate for the 6-meter walk; it is associated with urgency/stress UI and its results are strong predictors of falls and fractures in women.[28]
400 meter walk (min:sec)	The 400m walk is a direct measurement of exercise tolerance AND correlates with measured VO2 peak.[41]
Isokinetic dynamometer (Biodex®)	As an objective measure of strength, maximal isokinetic knee extensor strength in the right leg will be measured at speeds of 60 degrees/sec. The left leg will be used if there is a reason not to measure the right leg.
Postural Sway	Center-of-Pressure (COP) trajectory data will be collected using an Advanced Mechanical Incorporated (AMTI) AccuSway biomechanics force platform. Participants will be barefoot in an upright stance with arms raised comfortably at their sides, feet abducted, and heels separated. Four posturographic parameters (maximum antero-posterior and medio-lateral displacement, average sway velocity, and 95% confidence ellipse) and two statistical mechanics measures (stabilogram diffusion analysis and detrended fluctuation analysis) will be calculated to quantify postural sway according to our previously published methods.
Sarcopenia measures	
Grip-strength	As an objective measure of weakness and marker of sarcopenia.[33]
Gait speed	Determined based on 4-meter walk at usual speed as a marker of sarcopenia.[35]
SARC-F	The SARC-F questionnaire is validated to identify adults with sarcopenia and who are at risk for adverse outcomes and may benefit from a physical function intervention. [34]
Whole Body DEXA scan Time:	The appendicular lean muscle mass/height will be calculated based upon a whole-body DEXA scan performed in the Geriatric Research Unit.
Physical Activity Assessments	
Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire	The CHAMPS questionnaire is a brief valid measure that assesses weekly frequency and duration of various physical activities common to older adults to evaluate the efficacy of behavioral interventions to increase levels of physical activity. Caloric expenditure (MET hours/week) will be reported.[8] 'Low activity' will be defined as <6.2 MET-hours/week of activity. Women with MET hr/week between 6.3 and 11.4 will be classified as low-moderate activity. Since only 23% of incontinent women had >11.4 MET hours/week of physical activity, this level will be defined as high activity.[8]
Barriers to physical activity questionnaire	Questions regarding attitudes towards physical activity considering UI symptoms and perceived barriers will be assessed.
Comprehensive prospective evaluation for physical function limitations	

Pepper Assessment Tool for Disability (PAT-D) Mobility Assessment Tool-Short Form (MAT-SF)	These tools measure activities of daily living disability, mobility disability and instrumental activities of daily living disability to assess changes in disability.[31] [32]	
Obesity (Height and Weight)	Anthropometric measures of abdominal circumference and body mass index will be obtained to determine obesity severity. Overweight = BMI 25-29.9 kg/m2, Obese= BMI ≥ 30 kg/m2; severely obese = BMI ≥ 40 kg/m2.	
Patient satisfaction and Improvement		
Global Impression of Improvement (GPI)	**Patient Satisfaction Question (PSQ)**	**Estimated Perception of Improvement (EPI)**
Cognitive Assessment		
Montreal Cognitive Assessment (MoCA)	30-point test of short-term memory recall task, visuospatial abilities, executive function, attention, concentration, and working memory, language, and orientation. [38]	

Analytical Plan & Statistical considerations: All data except those generated from DEXA and the Accusway will be entered into a web-based database as collected. DEXA and Accusway data will be downloaded to a server and the summery data will be merged with other data. Final analysis datasets will be stored in SAS databases. All data will undergo range checks to detect any outliers and inconsistency, and will be transformed as appropriate before further analyses.

The hypothesis for AIM 1 (Primary) will be tested using analysis of covariance (ANCOVA) to compare differences of efficacy of PFME therapy (i.e. % UI episodes/week reduction at week 6) between women with and without functional impairment, adjusted for age, race/ethnicity, and BMI. Differences in least-squares means and associated 95% confidence intervals will be calculated. For Sub-aim 1(a), attitudes (barrier and motivation) towards physical activity will be compared between higher vs. lower physically active women using Chi-Square tests. For Sub-aim 1(b), association between physical activity (lower vs. higher) and UI severity will be tested using logistic regression, adjusting for age, race/ethnicity and BMI. Odds ratio and associated 95% confidence intervals will be calculated. We will also explore the impact of functional impairment on the association by adding an interaction of functional impairment and UI severity. Similar ANCOVA models as for Aim 1 will be used to compare efficacy of PFME therapy between women with and without sarcopenia (AIM 2) and between women with and without mild cognitive impairment (Aim 3).

Potential Pitfalls and Alternative Solutions:

a) Recruitment**:** Women will be recruited from the community in the catchment area for Wake Forest Baptist Health system, which includes central and western North Carolina and south central Virginia. Last year, we saw 476 women with a urinary incontinence diagnosis. More than 30% of women older than 70 have UI symptoms and an equal number will have functional impairment. Therefore, we do not expect difficulty in recruiting 50 eligible women/year over 24 months. The Wake Forest Sticht Center on Aging has an established database of older volunteers for aging-related research (VITALS database=12,600)) that will also be a source of recruitment. If necessary, we may start targeted recruitment to ensure that ~ 50% of potential participants have a SPPB score > 10 and that 50% have scores of ≤9.

b) Adherence to PFME therapy: Participants will receive a calendar with their PFME prescription on it and places on the calendar to document compliance. They will be contacted by study staff every 2 weeks to assess for compliance and to reinforce adherence to therapy. This approach has resulted in good compliance in other trials of elderly adults run by the Sticht Center.

c) Dropouts: Participants who drop out will be contacted by the PI or study coordinator to assess why. They will be offered assistance to help facilitate study completion (e.g., transportation to get to appointments). If they are not willing to return, we will ask that they complete 3-day voiding diary and PFME therapy and mail in the diaries and compliance calendars to the study staff in an attempt to ensure that we collect our primary outcome data. If they comply, they will be provided with a $30 gift card.

d) Reproducibility and representativeness of participants to general population**:** We plan to recruit from a diverse community of older women, including underserved, underinsured, and insured patients.

We have a mixed ethnic population of black, non-Hispanic white, and Hispanic Americans in the catchment area; the study will reflect the general population (see Human Subjects section).

Human Subjects Protection

Recruitment & Identification of Cohort:
Potential participants will be recruited from the community of patients in the Wake Forest Baptist Health System and those in a database of older adults interested in volunteering for research studies on aging (the VITAL database in our Sticht Center on Aging). We plan to employ 3 specific recruitment approaches:

1) The electronic health record will be searched using the Translational Data Warehouse (managed by the Wake Forest Clinical and Translational Science Institute [CTSI]). Women >70 years old with ICD-10 diagnosis codes [R32 (unspecified UI), N39.81 (functional UI), N39.41 (urge UI), N39.46 (mixed UI), and N39.3 (stress UI)] will be identified as having a diagnosis of UI within 6 months of the query. Potential participants will be mailed a letter introducing them to the study, informing them that they may be eligible to participate and will be contacted within 2 weeks by study staff in order to inquire about their interest to participate. We will include the 6-item Questionnaire for Urinary Incontinence Diagnosis (**QUID**) validated to establish the diagnosis, distinguish UI type, and measure severity of UI in the letter [18]. It is common for women to self-identify the presence of UI symptoms. Interested women will be instructed to call our study coordinator to learn more.
2) Potential participants who are seen by health care providers in the Wake Forest Gynecology, Urology, or Geriatric clinics and are diagnosed with urinary incontinence may be provided a brochure about the study and introduced to the study by their provider. These providers will not be participating in informed consent. Rather, their patients will be asked if we have permission for the study staff to contact them to introduce the study to them over the phone and to inquire about their interest to participate. Alternatively, the patient may contact study staff directly. During the telephone call, the study eligibility will be determined and the QUID will be used to establish the diagnosis, distinguish UI type, and measure severity of UI.
3) Women in the VITAL database will be mailed a letter informing them about this research study. Similar to the first approach, women will be contacted by the study staff 2 weeks after the letter was mailed. They may also call the study staff directly. The QUID will be used to establish the diagnosis, distinguish UI type, and measure severity of UI.

Telephone screening/eligibility:
During the screening call, trained study coordinators will determine eligibility using scripted questions and review the results of the QUID. Callers will be asked about their current physical and cognitive function and physical activity through validated questions. Eligibility criteria will be reviewed. Potential participants that screen eligible will then be invited to come for a baseline visit. Women with UI symptoms who screen ineligible for this study will be directed to the website of the American Urogynecology Society (AUGS) “voicesforpfd.org”, to learn more about their symptoms and options for treatment.

Enrollment: Enrollment will take place in the Sticht Center. A study staff member will confirm eligibility, describe the study, answer any questions, and administer written informed consent.

Informed Consent: Limited waiver of HIPAA authorization to identify potential participants requested. The data abstracted will be limited to the following: medical record number, contact telephone number, e-mail address, mailing address, presence of ICD-10 diagnosis. All data will be electronically stored on a password-protected online database.

Written informed consent will be obtained by the study staff during the enrollment (baseline) visit at the Geriatric Research Unit.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and

confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed three years after closure of the study through institutional shredding and deleting the data. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

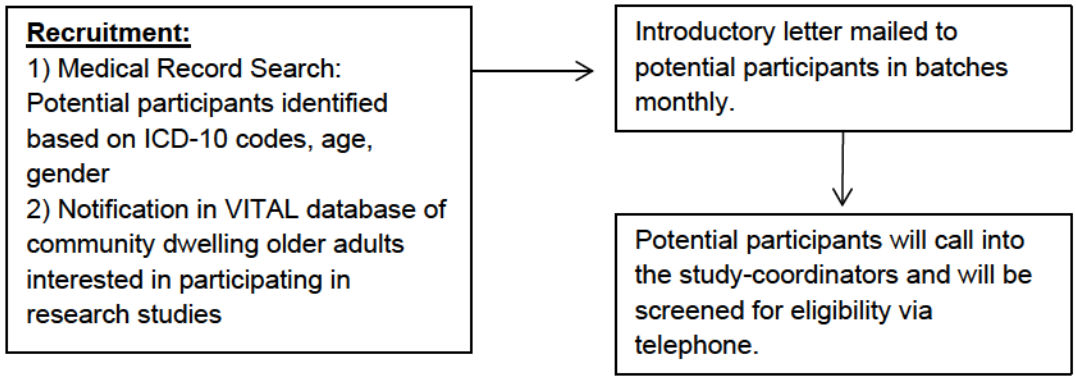
REFERENCES CITED

1. Wu JM, Vaughan CP, Goode PS, Redden DT, Burgio KL, Richter HE, Markland AD. Prevalence and trends of symptomatic pelvic floor disorders in U.S. women. Obstetrics and gynecology. 2014;123(1):141-8. Epub 2014/01/28. doi: 10.1097/aog.0000000000000057. PubMed PMID: 24463674; PubMed Central PMCID: PMCPmc3970401.
2. Erekson EA, Ciarleglio MM, Hanissian PD, Strohbehn K, Bynum JP, Fried TR. Functional Disability and Compromised Mobility Among Older Women With Urinary Incontinence. Female pelvic medicine & reconstructive surgery. 2014. Epub 2014/09/05. doi: 10.1097/spv.0000000000000136. PubMed PMID: 25185600.
3. Tinetti ME, Inouye SK, Gill TM, Doucette JT. Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. Jama. 1995;273(17):1348-53. Epub 1995/05/03. PubMed PMID: 7715059.
4. Goode PS, Burgio KL, Richter HE, Markland AD. Incontinence in older women. Jama. 2010;303(21):2172-81. doi: 10.1001/jama.2010.749. PubMed PMID: 20516418.
5. Borello-France D, Burgio KL, Goode PS, Ye W, Weidner AC, Lukacz ES, Jelovsek JE, Bradley CS, Schaffer J, Hsu Y, Kenton K, Spino C, Pelvic Floor Disorders N. Adherence to behavioral interventions for stress incontinence: rates, barriers, and predictors. Physical therapy. 2013;93(6):757-73. doi: 10.2522/ptj.20120072. PubMed PMID: 23431210; PubMed Central PMCID: PMC3664038.
6. Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. Medicine and science in sports and exercise. 2001;33(7):1126-41. PubMed PMID: 11445760.
7. Brown WJ, Miller YD. Too wet to exercise? Leaking urine as a barrier to physical activity in women. Journal of science and medicine in sport / Sports Medicine Australia. 2001;4(4):373-8. Epub 2002/03/22. PubMed PMID: 11905931.
8. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. The journals of gerontology Series A, Biological sciences and medical sciences. 2004;59(3):255-63. Epub 2004/03/20. PubMed PMID: 15031310.
9. Brown JS, Vittinghoff E, Wyman JF, Stone KL, Nevitt MC, Ensrud KE, Grady D. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. Journal of the American Geriatrics Society. 2000;48(7):721-5. Epub 2000/07/14. PubMed PMID: 10894308.
10. Bresee C, Dubina ED, Khan AA, Sevilla C, Grant D, Eilber KS, Anger JT. Prevalence and correlates of urinary incontinence among older community-dwelling women. Female pelvic medicine & reconstructive surgery. 2014;20(6):328-33. Epub 2014/09/05. doi: 10.1097/spv.0000000000000093. PubMed PMID: 25185631.
11. Madill SJ, Pontbriand-Drolet S, Tang A, Dumoulin C. Effects of PFM rehabilitation on PFM function and morphology in older women. Neurourology and urodynamics. 2013;32(8):1086-95. Epub 2013/01/30. doi: 10.1002/nau.22370. PubMed PMID: 23359286.
12. Danforth KN, Shah AD, Townsend MK, Lifford KL, Curhan GC, Resnick NM, Grodstein F. Physical activity and urinary incontinence among healthy, older women. Obstetrics and gynecology. 2007;109(3):721-7. Epub 2007/03/03. doi: 10.1097/01.aog.0000255973.92450.24. PubMed PMID: 17329526.
13. Tak EC, van Hespen A, van Dommelen P, Hopman-Rock M. Does improved functional performance help to reduce urinary incontinence in institutionalized older women? A multicenter randomized clinical trial. BMC geriatrics. 2012;12:51. doi: 10.1186/1471-2318-12-51. PubMed PMID: 22953994; PubMed Central PMCID: PMC3495708.
14. Bradley CS, Rahn DD, Nygaard IE, Barber MD, Nager CW, Kenton KS, Siddiqui NY, Abel RB, Spino C, Richter HE. The questionnaire for urinary incontinence diagnosis (QUID): validity and responsiveness to change in women undergoing non-surgical therapies for treatment of stress predominant urinary incontinence. Neurourology and urodynamics. 2010;29(5):727-34. Epub 2009/09/30. doi: 10.1002/nau.20818. PubMed PMID: 19787711; PubMed Central PMCID: PMCPmc2891326.

15. Nygaard I, Holcomb R. Reproducibility of the seven-day voiding diary in women with stress urinary incontinence. International urogynecology journal and pelvic floor dysfunction. 2000;11(1):15-7. Epub 2000/03/30. PubMed PMID: 10738929.
16. Barber MD, Chen Z, Lukacz E, Markland A, Wai C, Brubaker L, Nygaard I, Weidner A, Janz NK, Spino C. Further validation of the short form versions of the Pelvic Floor Distress Inventory (PFDI) and Pelvic Floor Impact Questionnaire (PFIQ). Neurourology and urodynamics. 2011;30(4):541-6. doi: 10.1002/nau.20934. PubMed PMID: 21344495; PubMed Central PMCID: PMC3759146.
17. Laycock J JD. Pelvic Floor Muscle Assessment: The PERFECT Scheme. Physiotherapy. 2001;87(12):631-42.
18. Radaelli R, Fleck SJ, Leite T, Leite RD, Pinto RS, Fernandes L, Simao R. Dose-response of 1, 3, and 5 sets of resistance exercise on strength, local muscular endurance, and hypertrophy. Journal of strength and conditioning research / National Strength & Conditioning Association. 2015;29(5):1349-58. Epub 2014/12/30. doi: 10.1519/jsc.0000000000000758. PubMed PMID: 25546444.
19. Pahor M, Blair SN, Espeland M, Fielding R, Gill TM, Guralnik JM, Hadley EC, King AC, Kritchevsky SB, Maraldi C, Miller ME, Newman AB, Rejeski WJ, Romashkan S, Studenski S. Effects of a physical activity intervention on measures of physical performance: Results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. The journals of gerontology Series A, Biological sciences and medical sciences. 2006;61(11):1157-65. Epub 2006/12/15. PubMed PMID: 17167156.
20. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, Studenski S, Berkman LF, Wallace RB. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. The journals of gerontology Series A, Biological sciences and medical sciences. 2000;55(4):M221-31. PubMed PMID: 10811152.
21. Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott AM, Hausherr E, Meunier PJ, Breart G. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. Lancet. 1996;348(9021):145-9. PubMed PMID: 8684153.
22. Investigators LS, Pahor M, Blair SN, Espeland M, Fielding R, Gill TM, Guralnik JM, Hadley EC, King AC, Kritchevsky SB, Maraldi C, Miller ME, Newman AB, Rejeski WJ, Romashkan S, Studenski S. Effects of a physical activity intervention on measures of physical performance: Results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. The journals of gerontology Series A, Biological sciences and medical sciences. 2006;61(11):1157-65. PubMed PMID: 17167156.
23. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, Ferrucci L, Guralnik JM, Fragala MS, Kenny AM, Kiel DP, Kritchevsky SB, Shardell MD, Dam TT, Vassileva MT. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. The journals of gerontology Series A, Biological sciences and medical sciences. 2014;69(5):547-58. doi: 10.1093/gerona/glu010. PubMed PMID: 24737557; PubMed Central PMCID: PMC3991146.
24. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, Abellan van Kan G, Andrieu S, Bauer J, Breuille D, Cederholm T, Chandler J, De Meynard C, Donini L, Harris T, Kannt A, Keime Guibert F, Onder G, Papanicolaou D, Rolland Y, Rooks D, Sieber C, Souhami E, Verlaan S, Zamboni M. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. Journal of the American Medical Directors Association. 2011;12(4):249-56. doi: 10.1016/j.jamda.2011.01.003. PubMed PMID: 21527165; PubMed Central PMCID: PMC3377163.
25. Rejeski WJ, Ip EH, Marsh AP, Miller ME, Farmer DF. Measuring disability in older adults: the International Classification System of Functioning, Disability and Health (ICF) framework. Geriatrics & gerontology international. 2008;8(1):48-54. doi: 10.1111/j.1447-0594.2008.00446.x. PubMed PMID: 18713189.
26. Williams G, Robertson V, Greenwood K, Goldie P, Morris ME. The concurrent validity and responsiveness of the high-level mobility assessment tool for measuring the mobility limitations of people with traumatic brain injury. Archives of physical medicine and rehabilitation. 2006;87(3):437-42. doi: 10.1016/j.apmr.2005.10.028. PubMed PMID: 16500181.

APPENDIX

Figure 1: Study Flow Chart



WEEK 0

Eligible women will be invited to the Geriatric Research Unit for enrollment and baseline visit.
* Payment provided for completion

Study Visit 1:
Informed consent (coordinator)
Demographic/Clinical characteristics (coordinator)
Study questionnaires administered (coordinator)
Clinical assessment: Incontinence and Pelvic floor assessment (PI, Co-PI)
PFME prescription provided (PI, Co-PI)
Physical function assessment (Pepper staff)
Study participation folder provided with all documents: 3 day voiding diaries, PFME compliance calendars, validated questionnaires. (coordinator)
Voiding diary to be completed the first 3 days by participant

WEEK 2

Study Visit 2:
- Follow-up assessment of PFME prescription by way of digital vaginal exam. 2 week PFME compliance calendar collected
- Voiding diary collected and assessed for compliance.

WEEK 3-5

Biweekly calls by study coordinators to assess compliance with PFME prescription.
Remind patient to fill out voiding diary prior to next visit.

WEEK 6

Study Visit 3:
- Review of study questionnaires (coordinator)
- Follow-up incontinence assessment (PI/Co-I)
- Follow-up pelvic floor assessment (PI/Co-I)
- Follow-up physical function assessment (Pepper staff)

* Payment provided for completion

WEEK 6-10

Biweekly calls by study coordinators to assess compliance with PFME prescription, logging of compliance.
Remind patient to fill out voiding diary on week 12

WEEK 12

Study Visit 4:
- Review of study questionnaires (coordinator)
- Follow-up incontinence assessment (PI/Co-I)
- Follow-up pelvic floor assessment (PI/Co-I)
- Follow-up physical function assessment (Pepper staff)

* Payment provided for completion

Table 1. Assessment schedule

	Baseline	2 weeks	6 weeks	12 weeks
Pelvic floor assessment				
Pelvic examination	X		X	X
Pelvic Floor Muscle Exercise (PFME) using the PERFECT scheme	X	X	X	X
Pelvic Floor Muscle Log		X	X	X
Urinary Incontinence assessment				
Pelvic floor distress inventory (PFDI) short form 20	X		X	X
3 day bladder diary	X		X	X
Pelvic Floor Impact Questionnaire (PFIQ)	X		X	X
Physical function and performance measures				
Extended version of the Short Physical Performance Battery (expSPPB)	X		X	X*
400 meter walk (min:sec)	X			
Isokinetic dynamometer (Biodex®)	X			
Postural Sway	X		X	X*
Sarcopenia measures				
Grip-strength	X		X	X*
SARC-F	X			X
Whole-body DEXA scan	X			
Physical activity assessments				
Community Healthy Activities Model Program for Seniors (CHAMPS-Modified) questionnaire	X		X	X
Barriers to physical activity questionnaire	X		X	X
Comprehensive prospective evaluation for physical function limitations				
Pepper Assessment Tool for Disability (PAT-D)	X		X	X
Mobility Assessment Tool-Short Form (MAT-SF)	X		X	X
BMI (height/weight)	X			
Cognitive Assessment				
Montreal Cognitive Assessment (MOCA)	X			
Self-reported measure of improvement (GPI/EPI/PGI)			X	X
Overall Health Assessment				
Center for Epidemiologic Studies Depression (CESD-10)	X		X	
Medical Outcomes Study Short Form 36 (SF-36)	X		X	
Total Time/Visit	3 hrs	1 hour	2.5 hours	2 hours

X* - Subset of 30 participants will complete these in addition to other repeated measures.