

# **Group Learning Achieves Decreased Incidents of Lower Urinary Symptoms (GLADIOLUS)**

**Protocol Version: March 10, 2016**

**National Institute on Aging, National Institutes of Health**

## BACKGROUND AND SIGNIFICANCE

This proposal, "Group Learning Achieves Decreased Incidents of Lower Urinary Symptoms" (GLADIOLUS), involves a novel intervention to treat urinary incontinence (UI) that has the potential for treating large groups of incontinent older women throughout the US, including those with limited access to health care resources. The initial outcomes of pilot studies have shown positive clinical results. After being awarded a planning grant to support development of a multi-site randomized controlled trial assessing the long-term clinical, patient-centered, and economic outcomes of the treatment, the investigators are now ready to embark on a multi-site study to evaluate whether outcomes seen in our pilot studies are reproducible by providers at other sites around the country. This proposal focuses on UI in older women because UI is twice as prevalent in women compared to men<sup>1-4</sup>. This approach is not only suitable for clinical populations, but also has the potential for wider implementation at the community level.

UI is one of the three chronic health conditions that have the greatest effect on a woman's health-related quality of life.<sup>5, 6</sup> More than one in three adult US women suffers from UI.<sup>7</sup> UI is not just a medical problem, but has a social and psychological impact on sufferers and family members. UI is also a source of dependency and a significant factor in nursing home admissions.<sup>8</sup> The economic burden of UI is estimated to be as much as \$16 to \$32 billion (1995 dollars) per year.<sup>9-11</sup> This is greater than the combined direct cost for breast, cervical, and ovarian cancers.<sup>12</sup> These cost figures likely underestimate the real figures since UI is under-reported to physicians and under-treated by health care providers in general.<sup>13</sup>

Although there are several therapeutic options available, behavioral treatments are recommended by most evidence-based guidelines as an initial approach to therapy for stress, urgency and mixed urgency and stress UI. Behavioral treatments may be delivered individually or in groups. Individualized behavioral treatment programs have been studied extensively and demonstrated safety and effectiveness in a significant proportion of UI patients.<sup>14-16</sup> Unfortunately, individual behavioral treatment has been met with resistance among patients and caregivers because it can require multiple visits to a health care provider to reinforce and maintain the acquired technique,<sup>14, 17</sup> making it an inconvenient, time-consuming and costly treatment option. Although there is very limited experience regarding group treatment of UI,<sup>18-21</sup> early and more recent studies report encouraging results of decreased UI symptoms and micturition frequency. However, Group Behavioral Treatment (GBT) has been for the most part theoretical, and the results of these studies, including ours, have not been replicated in a rigorous multi-site study. There is a need to standardize the teaching techniques,<sup>22</sup> content, duration, and interaction with learners and to demonstrate efficacy in a multi-site delivery of this intervention.

GBT could obviate the time consuming disadvantage of individualized instruction, making it more attractive for many consumers and health care providers. Consumers may be better able to fit the GBT into their day-to-day schedule, as it can be scheduled in the evening or on weekends, and at more convenient venues. There is potential gain from the psychological support one gets from group sessions and from being with other people with the same condition. Therefore, GBT may also function as an informal support group.<sup>23</sup>

Once standardized with data to support clinical and cost-effectiveness, GBT could be taught by allied health professionals in senior centers, outreach programs, churches, assisted-living facilities, or other community-based settings for those with limited ability to travel. Offering the intervention in community-based settings may help identify more cases of UI, raise community awareness of the condition and treatment options and improve adherence. For health care providers, treating UI with GBT may increase office productivity by releasing time to focus on other treatments. Thus, GBT has a good potential to significantly reduce the human and economic burden of UI.

Most UI treatments have been assessed in terms of their clinical effectiveness, but lack cost-effectiveness assessment. This proposal will provide cost-effectiveness of GBT and a Control using a schedule of short and long-term outcome evaluations that can be compared with established individual and group treatment. Prior cost evaluations only estimated collective cost and the economic burden of UI, rather than treatment-specific analyses. We aim to address these shortcomings. The opportunity for a dramatic improvement in the quality of life of older women and the potential savings using this group approach should be of great interest to patients and healthcare financing agencies.

In conclusion, the GLADIOLUS Study will enable us to assemble a multidisciplinary team of renowned experts in the field of UI to conduct a multi-site randomized controlled trial of GBT to treat UI in older women, with 12-month follow-up and cost-effectiveness analysis. The GBT approach has been shown to prevent UI in a NIH randomized controlled trial among older women and to improve UI in older women in our pilot study. This multi-site trial will test whether these results are reproducible on a wider scale at other sites and by other professionals. The GBT is a novel group-administered intervention developed by the investigators to treat UI. Once standardized with data to support its clinical effectiveness and cost-effectiveness, group treatment modalities have potential to reach a larger population of older women with UI, not only in medical offices and clinics, but also in community settings, significantly reducing the human and economic burden of UI on patients, health care providers, and the health care system as a whole.

## **OBJECTIVES**

**Aim #1:** The primary aim of this study is to compare the effectiveness of a group-administered behavioral treatment program, the Group Behavioral Treatment (GBT), to no treatment in older women with stress, urgency, or mixed urinary incontinence (UI). UI is a prevalent condition that diminishes quality of life in older women at tremendous social and economic costs. Although there are several therapeutic options available, behavioral treatments are recommended by most guidelines as an initial approach to treatment for stress, urgency, and mixed UI. Behavioral treatments may be delivered in individualized or group sessions. Group treatment modalities have potential to efficiently reach a larger population of older women with UI, not only in traditional medical settings, but also in community settings.

Based on promising outcomes in our pilot studies using a one-time GBT, we propose a three-site, randomized controlled trial to test the effectiveness of this novel group behavioral treatment program. Women with stress, urgency, or mixed urgency and stress UI will be recruited and screened centrally, evaluated clinically at the study sites, and randomly assigned to one of two treatment arms: 1) group treatment or 2) no treatment. The GBT will consist of a single 2-hour group session, in which participants will be given information on bladder health and self-management and instruction in three proven self-management strategies (pelvic floor muscle training, active pelvic floor muscle contraction to prevent stress UI and decrease urinary urgency, and bladder training). Outcomes will be assessed at 3, 6, 9, and 12 months post-randomization. The primary outcome will be self-reported UI severity as measured by the International Consultation on Incontinence Questionnaire Short Form (ICIQ-UI SF), a validated outcome measure for research and practice. Secondary outcome measures will assess frequency of UI episodes, volume of urine loss, type of UI, pelvic floor muscle strength, patient satisfaction, patient perception of improvement, and impact on quality of life. Data will be collected at the clinical sites and transmitted to the data coordinating center where it will be maintained and biostatistical analyses will be performed. We hypothesize that GBT will be more effective than no treatment. The no treatment group will be offered the group treatment and a referral to a continence specialist upon study exit.

**Aim #2:** The second aim of the study is to examine the costs and cost-effectiveness of group behavioral treatment compared to no treatment. We hypothesize that the group treatment will be cost-effective compared to no treatment. Most UI treatments have been assessed in terms of their clinical effectiveness, but lack cost-effectiveness assessment. The proposed study will provide an effectiveness assessment of GBT and a no-treatment control using a schedule of short- and long-term outcome evaluations that can be compared with established individual and group treatment. Prior cost evaluations only estimated collective cost and the economic burden of UI, rather than treatment-specific analyses. We aim to address these shortcomings. The opportunity for a dramatic improvement in the quality of life of older women and the potential savings using this group approach should be of great interest to patients and healthcare financing agencies.

## EXISTING STUDY DATA

Extant literature of group-session UI treatment is encouraging.<sup>18-20</sup> A 2-hour class without further follow-up showed significant reduction in the number of absorbent pads used and decreased symptoms.<sup>18</sup> Other studies reported decreased symptoms and frequency of micturition.<sup>19, 20</sup> The effectiveness of group exercise in improving pelvic floor muscle strength in women with stress UI<sup>24</sup> and in preventing UI during pregnancy<sup>25</sup> has been demonstrated. These limited studies encouraged us to embark on a series of studies to investigate a GBT approach to establish a standardized protocol. We started by: 1) using this approach for preventing UI in older women,<sup>26</sup> 2) testing the transferability of the teaching technique to other professionals,<sup>27</sup> and 3) testing the effectiveness of the approach in treating older women.

### Group Treatment for Prevention

To study the effectiveness of behavioral techniques and bladder training methods in preventing UI, Diokno and Sampsel developed a standardized protocol for continent volunteers who wished to prevent UI.<sup>26</sup> The idea of prevention was partly conceived based on information from a previous NIA-funded epidemiologic study by Diokno and colleagues that revealed UI incidence of about 20% in women 60 years and older.<sup>28</sup> We performed a pilot study to determine the feasibility of group instruction in continent older women living in the community.<sup>29</sup> All participants in the group session were evaluated individually 2 to 4 weeks after the intervention to test their knowledge and assess their skill in bladder training (BT) and pelvic floor muscle training (PFMT). Those who needed further enhancement of knowledge and skills in the technique of pelvic floor muscle control were provided such reinforcement on the spot by a nurse specialist. Results showed that 75% of participants either did not need any further instruction in PFMT or needed only minor reminders, 20% needed 5 minutes of reinforcements and only 1 or 5% could not learn the technique. Only 9% of women could not adhere to the BT program.

With NIA funding, we performed a large scale randomized controlled trial to test GBT UI prevention in continent ambulatory healthy volunteers 55 years and older.<sup>26</sup> In this full-scale prevention study, the teachers were exclusively Drs. Diokno and Sampsel. Participants received baseline evaluation followed by quarterly questionnaires and voiding diaries. At the end of one year, measurements similar to those collected at baseline were repeated. A total of 195 control and 164 treated participants completed the study. Baseline data were not statistically different. Treated participants achieved knowledge scores of 90% for PFMT and 86% for BT after the GBT. Regarding skills in performing pelvic floor muscle contraction, 68% correctly performed the technique, 29% required minor reinforcements, and only 3% were unable to acquire the skill.<sup>30</sup> At 12 months, the treatment group was better than the control group in continence status ( $p=0.01$ ), pelvic floor muscle strength (pressure score  $p=0.0003$  and displacement score  $p=0.0001$ ), and improved micturition frequency ( $p=0.0001$ ).<sup>26</sup>

These promising results demonstrating the effectiveness of GBT in preventing UI gave us the impetus to take it one step further and use the same protocol as a treatment for groups of women who were incontinent. However, before GBT could be widely adapted as a viable treatment for UI, two hurdles had to be overcome. First, we had to determine if the standardized GBT protocol could be taught successfully by other than the two study investigators. Then, we needed to see if there is reasonable evidence that the GBT used for prevention is indeed an effective treatment for incontinent older women.

### Transferability of Group Treatment

To assess the reproducibility of the teaching technique, a pilot study tested the hypothesis that urology nurses with proper training are able to assume the role of teachers and achieve similar outcomes.<sup>27</sup> Two urology nurses were identified and given the standardized slide kit, as well as other handout materials to study. After receiving training from Drs. Diokno and Sampsel, the two nurses served as the teachers to a group of continent older women. Ninety percent of 20 continent volunteers correctly answered the PFMT questions and 93% correctly answered the BT questions. At four to five weeks post intervention, 92% and 91% correctly answered the PFMT and BT questions respectively. At the four-week examination period, 60% achieved perfect pelvic floor muscle exercise technique, 30% needed minimal reinforcements (mainly verbal reminders) and 2% required 5-8 minutes of additional instructions. Regarding BT, 61% achieved optimal voiding interval, 33% improved and only 6% did not do the required BT and did not improve.<sup>27</sup>

### Effectiveness of GBT in Older Women

A second pilot study tested whether similar knowledge and skill transfer would take place in older women with UI. Incontinent volunteers were randomized into a treatment (n=23) or a control group (n=18). Because our earlier study showed women derived considerable content and skill in the GBT and had limited need for individualized instruction, this pilot intervention consisted entirely of group learning. At four to six weeks after baseline the acquisition of knowledge was high (88%) in the treatment group. More than half of the treatment group (52.2%) showed significant improvements in UI severity (change of at least one level on Incontinence Severity Index) as compared to only 16.7% of the control group during the same time period ( $p = 0.025$ ). The treatment group had significant improvement in mean leak diameter on provocative cough test pre- and post-intervention ( $p=0.012$ ). While the control group showed no significant improvements in voiding, the treatment group had a significant decrease in the number of day voids ( $p=0.001$ ), night voids ( $p=0.018$ ), and 24-hour voids ( $p=0.001$ ). Mean knowledge scores immediately after the group session and 2-4 week period after intervention (8.8 and 8.3 out of 10) and acquisition of PFMT skills post intervention (92%; 23/25) were excellent. This translated into improved pelvic floor muscle strength as measured by the mean pressure score ( $p=0.047$ ), mean displacement ( $p=0.001$ ) and mean duration ( $p=0.001$ ) compared to their baseline. The control group showed no statistically significant change except in improved displacement score.<sup>31</sup> These results encourage us to test the GBT in the multi-site GLADIOLUS Study.

### Experience with Phased Mass Mailing as a Recruitment Strategy

In our NIH-funded prevention program,<sup>32</sup> phased mass mailing was the main method of recruiting continent women. A list of names with addresses and phone numbers of women living in targeted counties/communities was purchased from InfoUSA, Inc of Omaha, NE. We mailed 47,440 tri-fold fliers describing the study with a detachable return postage paid card. A total of 2,320 fliers (4.8%) were returned of which 3.3% and 1.5% had positive and negative responses respectively. Of the 1,581(3.3%) + responders, 596 (37.7%) were eligible at telephone screening. At the screening visit, 358 (60%) were eligible and enrolled. These data provided us with a 0.75% ultimate enrollment rate from the total mailings. Assuming that 62% of the population was continent, this represents 1.2% of the continent population (358/29,412).

In the proposed study, we target incontinent rather than continent women, and we are confident that we will recruit an even higher proportion, because the incontinent women will likely be more interested in a treatment trial than the continent women in a prevention trial. In fact, many responses to the prevention study recruitment mailing were from women who were incontinent. Further, in our MESA epidemiological study, we observed that the incontinent respondents were more likely to accept an invitation to participate.<sup>33</sup> In this NIH funded grant, 1,152 women, who responded to our initial phone call, were invited to the clinic for urodynamic study. The acceptance rate for the continent respondents was 9.3% (67/714), whereas for the incontinent respondents, 22.9% (100/437).<sup>34</sup> If we extrapolate this ratio to the 1.2% enrollment for the continent women who received the card, we can estimate about 3% as the enrollment rate for the incontinent women. In the proposed study, we assume a 38% incontinence rate in women in the community (as our previous survey showed), and a 3% enrollment rate among these incontinent women.

### Summary of Preliminary Studies

Our preliminary research establishes the feasibility of conducting group interventions, both for prevention and treatment of UI in older women. The studies have yielded promising results, demonstrating the effectiveness of the group approach and providing a solid foundation for a definitive, multi-site randomized controlled trial of group treatment for UI in older women. We have assembled a strong multidisciplinary team of established investigators with expertise in the field of UI, clinical trial research, and multi-site collaboration. This allows us to build the proposed trial on a strong foundation of experience in the evaluation and treatment of UI, using both individualized and novel group treatments, informed by specialists in geriatric urology, geriatric medicine, nursing, behavioral medicine, health economics, biostatistics, and data collection and coordination. Three study sites representing different regions of the country (North/Midwest, East, and Deep South) will test the reproducibility of our preliminary findings and enhance external generalizability. We are now poised to conduct a definitive multi-site randomized controlled trial to test the effectiveness and cost-effectiveness of group treatment for UI in older women.

## **METHODOLOGY**

### Overview of Experimental Design and Methods

This randomized controlled trial will compare the effectiveness and cost-effectiveness of a group-administered behavioral treatment program and no treatment. Women with stress, urgency, or mixed urgency and stress UI will be recruited and randomized. Outcomes will be assessed at 3, 6, 9, and 12 months post-randomization. The primary outcome will be self-reported UI severity as measured by the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-UI SF), a validated outcome measure for research and practice<sup>35</sup>. The control group will be offered the group treatment or referral to an incontinence specialist after the final 12-month assessment.

### Participants and Recruitment

Participants for the study will be aged 55 years or older with stress, urgency, or mixed urinary incontinence. They will be recruited using targeted, mailed letters of invitation to specific populations in the three geographical areas, a centralized method that proved effective in our earlier randomized controlled trial<sup>32</sup>. Based on prior experience (described in Preliminary Studies), assuming a 38% incontinence rate in community-dwelling women (as our previous survey showed), and a 3% enrollment rate among these incontinent women, we can anticipate that mailing our invitations to 29,000 women in the community will yield 330 participants (29,000 X .38 X .03). We will increase mailings and use other recruitment strategies such as fliers or advertisement as needed to achieve the recruitment goal.

To standardize the screening process, an 800 number will be staffed by a research team at the Beaumont Administrative Core. Coordinators will conduct telephone screening (Appendix 1) to determine potential eligibility and explain the study. Women willing to enroll in the study will be referred to the appropriate study site for clinical evaluation. Referral will be in daily batches.

At each study site, the research coordinator will call participants to provide further information about the study and invite them to participate. Interested women will be scheduled for a clinical evaluation. At this same time the coordinator will obtain telephone consent for the pre-clinic visit assessments, the 3-day voiding diary and the 24-hour pad test, two 'less than minimal risk' assessments. The telephone consent will be attested by the study coordinator at each of the three clinical sites using a standardized form. The assessments will be collected from the subject after the full consenting process is completed. To maintain our proposed timeline, we will consent approximately 675 in order to enroll/randomize up to 465 eligible women (approximately 155 at each site). We will continue the recruitment practice that has proven successful in our prevention study, i.e., emphasizing selected zip codes to enhance minority enrollment. Participants randomized to the intervention group will receive \$60 for attending the baseline visit and bladder health class (\$25 for the baseline visit and \$35 for the attending the bladder health class). Control participants will receive \$60 for the baseline visit. A \$60 stipend will also be provided for the 3- and 12-month assessment, and a \$25 stipend for the 6- and 9-month mailed assessments.

#### Clinical Evaluation at Study Site

A clinical evaluation will be performed to exclude participants who are inappropriate for the study and to characterize participants on relevant dimensions. Prior to the visit, participants will be mailed a packet that contains their appointment information, a 3-day bladder diary with instructions for completing prior to the visit, instructions for completing the 24-hour pad test prior to the visit, Consent Form for review, and site-specific instructions (maps/directions). Upon arrival for the clinical evaluation visit, participants will complete the informed consent process and the instruments completed at home will be collected. The clinical evaluation will consist of the following:

1. Medical and incontinence history
2. ICIQ-UI SF to assess severity of UI
3. Mini Cognitive Test (Mini-Cog) to screen for memory impairment
4. Timed "Up and Go" Test (TUG) to screen for mobility impairment
5. Physical examination (height and weight, provocative cough test, post-void residual urine volume, pelvic examination [including Brink test to assess pelvic floor muscle strength and pelvic organ prolapse assessment])
6. Urinalysis (dipstick)
7. 3-day bladder diary (collected and reviewed for completeness and verification of ability to write in English)
8. 24-hr pad test (collected)

#### Inclusion/Exclusion Criteria

Criteria for inclusion are:

1. Female
2. Aged 55 years or older
3. Ability to understand, read and write English
4. Stress, urgency, or mixed urgency and stress UI (by self report)
5. On the ICIQ-UI SF, frequency of leakage scored at least a 1 ("about once a week or less often") on item #1 and volume of urine loss scored at least a 2 ("a small amount") on item #2.
6. Symptoms of three months duration or longer (on history)
7. Passing score (i.e., categorized as "probably not demented") on the MiniCog Test
8. Timed "Up and Go" Test (TUG) score of  $\leq 20$  seconds

9. Willing to undergo vaginal/pelvic examination
10. Signed informed consent form

Criteria for exclusion are:

1. History of renal, bladder, uterine, ovarian, urethral, anal or rectal cancer, radiation therapy to the pelvis for any cancer/malignancy, or any active cancer/malignancy (except skin cancer).
2. Non-ambulatory (participant confined to bed or wheelchair)
3. Persistent pelvic pain (defined as daily pelvic pain > 3 months)
4. History of neurologic or end-stage diseases (e.g. kidney failure, liver failure, CVA, Parkinson's disease, multiple sclerosis, epilepsy, spinal cord tumor or trauma, spina bifida, symptomatic herniated disc)
5. Previous treatment or current participation in a research study for UI or pelvic organ prolapse, including surgery, pessary or formal behavioral treatment (pelvic floor muscle training, biofeedback, pelvic floor electrical stimulation, percutaneous tibial nerve stimulation, sacral neuromodulation, Botox, or other periurethral injection)
6. Currently taking UI or OAB medications
7. History of other urinary conditions or procedures that may affect continence status (e.g. urethral diverticula, previous augmentation cystoplasty or artificial urinary sphincter; implanted nerve stimulators for urinary symptoms)
8. Participation in any drug/device research study
9. Pelvic organ prolapse protruding past the introitus (at rest or persisting after strain)
10. Evidence of UTI by urine dipstick (leukocytes  $\geq$  +1 nitrites,  $\geq$  +2 leukocytes alone (w/o nitrites), nitrite positive)), or presence of hematuria (>+1). Participants may be re-screened after treatment or if work-up is negative.
11. History of  $\geq$  2 recurrent UTI's within the past year; more than one UTI within past 6 months
12. Post void residual urine volume  $\geq$  150 cc
13. Unstable medical condition (as determined by site PI)

### Design

This three-site, randomized controlled trial will compare the effectiveness and cost-effectiveness of a

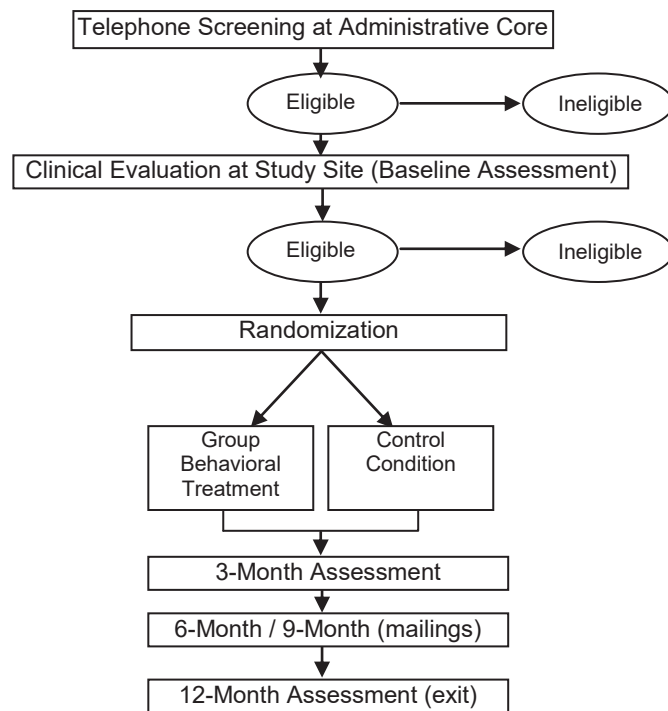


Figure 1: Study

group-administered behavioral treatment program to a no treatment control condition. Within each site, after a woman has been found eligible on evaluation, she will be randomized to one of the two treatment arms as shown in Figure 1. Those in the GBT arm will be scheduled for group treatment in the next convenient GBT session. Treatment will be initiated no later than 4 weeks after randomization. Due to the need for simultaneous participation in the GBT, 2 sessions will be offered each month as needed. Outcomes will be assessed at 3, 6, 9, and 12 months post-randomization. Women in the control arm will receive no treatment, but will be offered GBT and a referral to a continence specialist upon study exit.

At least 55 women will be randomized to GBT and 55 women to the no treatment control condition at each site to achieve



110 participants per site. The random-ization schedule will be concealed so that investigators and staff at the sites will not be able to anticipate experimental group assignments. Evaluators at each site will be blind to group assignment throughout all assessments.

### Power and Sample Size Considerations

We powered our study on Aim 1 to detect a difference of 3 points in ICIQ-UI SF score.<sup>35</sup> Based on the literature, we estimated the standard deviation for the control population to be 6.8.<sup>35-37</sup> We fixed the significance level to 0.05 and power at 90% for two sided comparison using two sample t-test. We assumed that there will 25% drop out at 3 months and by the end of 12 months up to 35% total dropout. We also considered differential dropout rates across the two treatment groups, such as 25% in the treatment group and 35% in the control group. Based on this power analysis, the needed sample size is 165 participants per group for a total sample size of 330 with the expectation that 65% (214-218) women would complete the full study, including the 12 month follow-up visit. We agree that the assumed dropout rate may be conservative but given that some participants may opt for alternative treatment, we wanted to make sure that we will have adequate sample size at the end of the study to draw meaningful conclusions.

### Intervention

Group Behavioral Treatment. The GBT will be modeled after the prevention intervention shown to be effective in our previous randomized trial.<sup>26</sup> Participants will attend a 2-hour group session with other participants. As noted, results of that study and subsequent pilots demonstrated that women gained the essential knowledge and skills in the GBT and had little need for individualized follow-up. At the beginning of the GBT, each participant will be asked to maintain privacy and confidentiality of group members.

In the GBT, participants will be given information on bladder health and self-management, including the anatomic/physiologic basis for continence; instruction in proven self-management strategies, including pelvic floor muscle training (PFMT), the Knack<sup>38</sup> (active pelvic floor muscle contraction during activities that lead to stress UI), urge suppression strategies, and bladder training (BT); and coaching to facilitate incorporation of the strategies into their personal routine. Slides and handouts supplement the content in each. It is designed to provide the four sources of information recommended by Bandura<sup>39, 40</sup> to increase self-efficacy, i.e., verbal persuasion, emotional arousal, vicarious experience, and performance accomplishment.

1. *Verbal persuasion:* The role of pelvic floor muscles in UI and evidence of efficacy for the self-management strategies, the basis for the prescribed PFMT frequency of 5 fast and 10 slow contractions three times a day, and a bladder training goal of 3-4 hour intervals between voids while awake are discussed.
2. *Emotional arousal:* To increase women's interest in how treatment could benefit quality of life, women are invited to give examples of how UI negatively impacts their own lives.
3. *Vicarious experience:* The Interventionist presents case examples, i.e. stories of women who have successfully implemented the self-care strategies.
4. *Performance accomplishment:* PFMT is practiced using a compact disc later presented to each graduate. An attractive magnet is presented also, with advice to place it where it can serve as a visual cue. Women identify personal rewards to enhance adherence.

Group discussion also focuses on inoculation as recommended by Vinokur, et al.<sup>41-43</sup> as a means of sustaining self-efficacy. Women are alerted that it is human nature to occasionally forget or deliberately omit PFMT. Strategies to address lapses are reviewed. The content outline of the Group Behavioral Treatment Session, with specification of the particular source of self-efficacy is presented

in the Manual of Operations. Examples and illustrations appropriate for a diverse older population will be used. Graphics have been simplified and all print and Powerpoint materials are at a 5<sup>th</sup> Grade reading level.

No Treatment Control Condition. Participants in the control arm of the study will receive no treatment, but will be offered the GBT and referral to an incontinence specialist upon study exit.

Standardization of Behavioral Treatment and Assurance of Treatment Fidelity

We recognize that accurate and competent delivery of the interventions is essential to the validity of this trial.<sup>44</sup> Thus, the investigators will conduct in-person, centralized training for all Interventionists. Training will ensure that Interventionists implement the GBT in the same way. A primary Interventionist and a back-up Interventionist from each site will be trained. The same Interventionist will implement each GBT, unless prevented by extended illness, in which case the back-up Interventionist will be available. Interventionists will be certified by role play demonstrations of the critical components of the intervention and must accomplish all critical components and at least 95% of the other checklist items to be certified.

All GBT sessions will be tape-recorded, and a randomly selected sample of 25% of the taped sessions will be reviewed by the geriatric urologic consultant using the checklist in the protocol manual to assess fidelity to protocol.<sup>45</sup> The Interventionist’s consistency with protocol will be assessed, including required presentation of all critical components of the GBT and 95% of other GBT elements. If protocol fidelity falls below 95% of checklist items or any essential components, the site PI will be notified so that remedial interventionist training can be implemented.

Follow-up Assessments

At 3 months and 12 months, participants will return for clinic visits, when they will repeat baseline clinical assessments and questionnaires. In addition, selected questionnaires will be completed by mail at 6 and 9 months (See Table 1 below). The person completing the clinical evaluations (Evaluator) will be blinded to treatment group. At clinic follow-up contact, the participants will be asked about changes in conditions and medications that could potentially affect treatment outcome (e.g., urinary tract infection, cold preparations) so that they can be included as covariates in the statistical analysis. To assist with retention, reminder letters and follow-up telephone calls will be used to promote participation at each follow-up point.

<b>Table 1: Schedule of Measures and Procedures (Venue/Method)</b>	<b>Baseline Evaluation</b>	<b>Pre-Group Session</b>	<b>Post-Group Session</b>	<b>3-month Visit</b>	<b>6-month (Mail)</b>	<b>9-month (Mail)</b>	<b>12-month Visit</b>
Visit Window (plus or minus days)				30	30	30	30
Consent	X						
Demographics	X						
History	X						X
Mini-Cog	X						X
Timed “Up and Go”	X						X
Pelvic exam for prolapse	X			X			X
Brink’s test (pelvic floor muscle strength)	X			X			X
Urine dipstick	X			X			X
24-hour Pad test	X			X			X
Provocative cough test	X			X			X
3-day bladder diary	X			X	X	X	X

Post-Void Residual	X			X			X
Current medications	X			X			X
Eligibility and Randomization	X						
Review changes to medications, medical and surgical procedures (specifically UI treatments/procedures)				X	X	X	X
Assess adverse events				X	X	X	X
<b>Questionnaires</b>							
ICIQ-UI SF	X			X	X	X	X
MESA Questionnaire	X			X			X
*Patient Satisfaction Questionnaire				X	X	X	X
*Participant Comfort with GBT Format			X				
Patient Global Impression of Improvement (PGI-I)				X			X
Incontinence Quality of Life (I-QOL)	X			X			X
*Broome Self-Efficacy Questionnaire			X	X	X	X	X
*Behavioral Knowledge Questionnaire			X				
*UI General Knowledge Questionnaire		X	X				
*Behavioral Adherence /Barrier Questionnaire				X	X	X	X
Euro QOL 5D (EQ-5D)	X			X	X	X	X
Incontinence Resource Use Questionnaire (IRUQ)	X			X	X	X	X
Cost Analysis Questionnaire	X			X			X

\*Intervention group only

### Outcome Measures

The primary outcome will be a change from baseline ICQI score to 3-months post-randomization ICQI score on the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF). Secondary outcome measures will assess frequency of incontinence episodes (3-day bladder diary), volume of urine loss (24-hour pad test), type of incontinence (Medical, Epidemiological, and Social Aspects of Aging Questionnaire (MESA), change in pelvic floor muscle strength (Brink digital assessment), urethral sufficiency (provocative cough test), participant comfort with GBT format, participant satisfaction (Patient Satisfaction Question), participant perception of improvement [Patient Global Impression of Improvement (PGI-I)], and impact on quality of life (Incontinence Quality of Life Questionnaire (I-QOL)). See Table below.

#### International Consultation on Incontinence Questionnaire-UI Short Form (ICIQ-UI SF). <sup>33, 35, 46</sup>

The ICIQ-UI SF is a self-report measure developed by the International Consultation on Incontinence to assess UI and its impact on quality of life. It consists of 4 questions:

1. How often do you leak urine? (rated as 0 never to 5 all the time)
2. How much urine do you usually leak (rated 0 none to 6 a large amount)
3. Overall, how much does leaking urine interfere with your everyday life? (0 "not at all" to 10 "a great deal")

4. When does urine leak? (response options identify precipitants of urine loss)

The first three items are summed to obtain a total score ranging from 0 to 21.

The ICIQ-UI SF has been fully validated and published and recommended by the ICI with a Grade A rating for evidence of validity, reliability, and responsiveness.<sup>47</sup> It is highly correlated with the pad test ( $r=.68$ ;<sup>48</sup>) and Patient Global Impression of Improvement ( $r=.79$ ;<sup>49</sup>). The ICIQ-UI SF is the most widely used module of the ICIQ Modular Questionnaire especially for evaluating female UI. This instrument has been used in epidemiological studies,<sup>50, 51</sup> as well as in intervention trials of various treatments for UI, including surgical trials for SUI,<sup>52</sup> drug trials,<sup>53</sup> and a trial of functional magnetic stimulation.<sup>54</sup>

Participant Comfort with GBT Format.

This four-item, investigator-developed questionnaire assesses overall comfort with the GBT format and will be completed anonymously. Given the findings of Hill et al.,<sup>21</sup> that some women were embarrassed to attend a group session on UI treatment, we believe further exploration of this potential barrier to GBT participation is warranted. Response options range from Strongly Disagree to Strongly Agree:

- 1) I was reluctant to come to a group session about urinary incontinence.
- 2) I found the group session to be a good way to learn how to improve my incontinence symptoms.
- 3) I was embarrassed to be in a group to learn about incontinence treatment.
- 4) I would recommend the group session to a family member or friend.

Table 2. Secondary Outcome Measures.

Instrument	Measures	Psychometrics	Ref
3-day Bladder Diary	Number of UI episodes/day; UI type; mean diurnal voids/24 hours; mean voids during sleeping hours	2-week test-retest results correlate with diurnal micturition ( $r=.89$ , $p<0.001$ ) and UI episodes ( $r=.91$ , $p<0.001$ ). Compared to participant recall of the previous week, Spearman rank correlation = .57 for voiding frequency and .70 for UI episodes.	55-57
24-Hour Pad Test	Total volume (weight) for 24-hour day	The 24-hour pad test is reproducible with two-day correlation coefficients of 0.66-0.82. Older women with both stress and urgency UI have demonstrated capacity to conduct the test at home and provide reliable data.	22, 58-60
Medical, Epidemiological and Social Aspects of Aging Questionnaire (MESA)	Severity of specific types of UI (stress, urgency, mixed). Two subscales, the urgency UI (6 items) and the stress UI (9 items).	Test-retest reliability on “any incontinence” is high (agreement coefficient = .89). Validity (agreement between self-report on the MESA and clinician’s assessment) = 87% in women. Agreement on incontinence = 79%. 69% and 72% accuracy in predicting urodynamic diagnosis of stress UI and uninhibited detrusor contraction.	28, 61
Brink Digital Pelvic Floor Muscle Assessment	Pelvic floor muscle strength as reflected in pressure and displacement	Periodic assessment of inter-rater reliability, in longitudinal studies averaged 95.2% agreement for pressure and 90.5% for displacement. Inter-rater reliabilities = .67-.71, $p<.01$ . Cohen’s kappas very good for displacement (.68) and pressure (.66). Significant differences between nulliparas, primigravidas & secundagravidas ( $F=10.2$ , $p<.0001$ ).	62

Provocative Cough Test	Small volume urine loss	95% agreement within 1ml. within and across visits Wilcoxon Signed Rank Test ( $p < .0001$ ).	22
Participant Comfort with GBT Format	Four-item measure completed following GBT	Investigator developed questionnaire with input from expert panel.	NA
Patient Satisfaction Questionnaire	Single item global rating of satisfaction with progress in the program	Validated and shown to have acceptable convergent & discriminant validity for measuring outcomes in studies of treatment for UI. Response options will be modified to include somewhat dissatisfied and very dissatisfied.	63
Patient Global Impression of Improvement	Global rating of improvement using 7-point scale	Construct validity established in two randomized controlled studies ( $n=1,133$ ) of drug treatment for predominant stress incontinence.	64, 65
Incontinence Quality of Life Questionnaire	Incontinence-specific quality of life (22 questions)	Valid and reproducible. Sensitive to UI frequency in cross-sectional studies and to improvements in UI frequency in intervention trials.	67-71
Broome Self-Efficacy Questionnaire (17-items)	Self-efficacy: confidence that she has the capacity to adopt self-management practices	Overall Cronbach's alpha .98; test-retest .55.	72
Behavioral Knowledge Questionnaire	Knowledge of PFMT, the Knack, urge strategy, and bladder training (10 items)	Group participants demonstrated high levels of knowledge about pelvic floor muscle and bladder training (mean scores of 86% and 90%, respectively). The 3 Knack questions were piloted in a group of 15 older women with 100% correct response on each item.	30
Behavioral Adherence/Barriers Questionnaire	Adherence to PFMT, Knack, urge strategy, bladder training	Higher levels of practice associated with improved pelvic floor muscle pressure (17%, $p=0.0008$ ) and displacement (31%, $p=0.0001$ ) on the Brink's test. Treatment group participants show greater mean voiding intervals ( $p < .0001$ ) vs. controls at 12 months.	26, 72, 73
Mini Cognitive Test (MiniCog)	Brief cognitive screening tool consisting of memory for three words and a clock draw.	High sensitivity (99%) and specificity (96%) in elderly community sample. Performance unaffected by education or language in a multiethnic sample. Sensitivity (75%) and specificity (88%). Test-retest reliability over four weeks ( $r = 0.85$ , $P < 0.01$ ).	74-78
Timed "Up and Go" (TUG)	Brief mobility screening instrument	Predictive of independence with activities of daily living including toilet transfers and ambulation, as well as risk of falls. Inter-rater and intra-rater reliability $> 0.9$ .	79-81

### Measuring Costs and Health Effects for Cost-Effectiveness Analysis

Economic analyses will include investigating participant-incurred costs for incontinence management, estimated by self-reported resource use on the Incontinence Resource Use Questionnaire (IRUQ),<sup>82</sup> Cost Analysis Questionnaire and health-related quality of life (utilities) measured with the Euro QOL 5D (EQ-5D<sup>83</sup>). Participant-incurred costs for incontinence management will be calculated by multiplying units of resources used (recorded on the IRUQ) by an average

national unit cost in dollars, which will permit standardization and later generalization. We will measure resource use and utilities at each data collection time point and compare the change in incontinence management costs and utilities between the treatment groups. The primary cost of group treatment is the interventionist's time. We will measure start time and end time for each group session. The interventionist's time will be translated into costs by applying unit cost estimates. Nationally representative ("average") unit cost estimates will be used, so that results from these setting will be most useful to decision makers in other settings.

#### Clinical Evaluation and Monitoring Instruments

The baseline clinical evaluation will include instruments to screen for exclusion those participants with cognitive or mobility impairment (Mini-Cog and Timed "Up and Go" Test). Because cognitive and mobility deficits negatively impact on continence status, we will repeat these measures at the 12-month visit so that the development of impairments in these domains can be included as covariates in the outcome analyses.

#### Intervening Variables: Self-efficacy, Knowledge, and Adherence

Participants randomized to GBT will complete the Broome Self-Efficacy Questionnaire and the Behavioral Knowledge Questionnaire upon completion of the intervention, and a Behavioral Adherence/Barriers Questionnaire at each follow-up contact. Repeated measures will be collected to document various aspects of domain-specific self-efficacy, and adherence to PFMT, Knack, and BT. Knowledge of PFMT, Knack, and BT is tested immediately after intervention, but not repeated at subsequent data points. (Manual of Operations, Appendix 1). The Interventionist will review participant responses and if more than one item is missed, she will telephone the participant to correct the misunderstanding. The Beaumont Research Coordinating Core will conduct monthly audits of self-efficacy immediately post intervention as a further index of intervention fidelity.

#### Data Management and Quality Control

The Beaumont Research Coordinating Center (BRCC) will be responsible for the development of the database and the transmission and management of the data. This will be accomplished by electronic data capture using an internet-based, custom-designed application called "Crossbreak." The Crossbreak application was developed by the BRCC to support its data management needs and launched in 2007. The electronic data capture process for the proposed study will require the participating clinical sites to connect to the Crossbreak website (<https://crossbreak.pamsearch.com>) via the Microsoft Internet Server. Electronic case report forms (eCRF) will be constructed into "Crossbreak" allowing site personnel to enter data electronically. The data will be de-identified to the coordinating center using study IDs.

To insure accuracy and integrity, data entered for each variable will be validated by an electronic audit procedure, which entails a 3-step process. This is accomplished by assigning numerical ranges to appropriate fields in the database and using validation rules for edit verification. The validation rules are to insure that no data are missing, entries are logical, skip patterns are followed, and non-numerical data entries are appropriate. Crossbreak contains comprehensive reporting services, which will assist in data management. "Real-time" reports provide access to study data, which allow for accurate and efficient monitoring of the study progress. Reports include enrollment (monthly and quarterly), participant follow-up schedules, eCRF completion and delinquencies, query resolutions and delinquencies, protocol deviations, unanticipated problems/adverse events, etc. To ensure accuracy of data entry, Crossbreak entries will be cross-checked against source documents.

#### Statistical Analysis

Data will be inspected using univariate analysis of all key variables for outliers and distributional properties. The data will be cleaned and recodes of variables will be created for analysis. For all

analysis the primary comparison will be between the 2 groups: “GBT” (Group Behavioral Treatment session) and “C” (Control/no treatment). Both groups will be assessed at baseline, 3, 6, 9 and 12 months post-randomization.

Analysis for Aim #1: Effectiveness of Group Session Treatments. We will use a two sample t-test or an equivalent nonparametric approach to compare the two groups on the primary outcome variable, ICIQ score at 3 months post treatment. It is possible that the ICIQ score may not be normally distributed, in which case, we will perform nonparametric analysis using the ranks. We will expand this analysis by using regression models with additional covariates before the randomization to improve efficiency and adjust for any imbalances. It is possible that during the study (i.e. post randomization) some participants may seek alternate treatment outside the study protocol. This may have an impact on the assessment of the true effect of GBT. Though we will perform intent-to-treat analysis, we will also explore the use of marginal structural model<sup>84</sup> and Principal Stratification<sup>85</sup> approaches to estimate the effect of GBT adjusting for post-randomization adoption of treatment options. In fact, time to seeking such intervention (time-to-event) can be treated as an outcome variable. The purpose of analyzing this outcome variable is to evaluate whether there are any differences in the distribution of time to event among the two comparison groups. We will use the Kaplan-Meier analysis and the log-rank test to assess the statistical significance of the differences between the two groups. We will also use Cox proportional hazards model to adjust for additional pre-randomization covariates.

Durability. Given the longitudinal nature of the design, we will be able to assess the individual level changes over time and sustainability of the effect of therapy over time. We will use mixed effects model to assess the change over time and how this change differs by treatment groups. We will use the time as continuous variable, if appropriate and if not, we will use spline models to assess the change over time. We will compare the significance of differences in the curves across the time points to investigate the sustainability of the effect of treatment. In Aim 1, we will test for the differences between the treatment and control groups.

Differential Impact. We will also analyze other outcomes including UI frequency (bladder diary) and impact (I-QOL) using a similar approach. These outcomes are collected longitudinally and they will be analyzed using mixed effects models. For UI frequency, we will use a Poisson or normal mixed effects regression model depending upon the rate of UI. Additionally, the effect of treatment may differ by UI type (stress, urgency or mixed). Because we expect a large number of participants to have mixed UI, we will create a binary covariate indicating whether a participant has stress-predominant versus urge-predominant UI based on pre-randomization data and then perform a stratified analysis or analysis separately for these two groups.

Drop-Outs. As in any longitudinal study, drop-outs may occur leading to missing data. We will make every effort to measure the outcome variables. We will perform intent-to-treat analysis and use multiple imputation techniques for analyzing the data. Dr. Raghunathan is a leading expert in this area and has developed software for performing such analysis ([www.isr.umich.edu/src/smp/ive](http://www.isr.umich.edu/src/smp/ive)).

Analysis for Aim #2: Costs and Cost-Effectiveness. To analyze costs, we will use the cost variables as dependent variables and apply the same procedure as in Aim 1. Cost-effectiveness will be estimated as cost/treatment success, defined as achieving at least a 3-point decrease in ICIQ score. We will secondarily estimate the cost/treatment success with treatment success defined as least a 70% decrease in mean daily frequency of urinary incontinence episode recorded on the 3-day bladder diary, based on data indicating that this is a critical threshold for patient satisfaction<sup>63</sup> Cost-utility will be estimated as cost per quality-adjusted life year (QALY) of the intervention and control conditions with utility assessed by the EQ-5D. These analyses will estimate the incremental cost-effectiveness and cost-utility of the treatment group when compared to the usual care condition. The incremental cost-effectiveness ratio (ICER) will be calculated to estimate the incremental cost

associated with each additional unit of outcome gained within 1-year and lifetime timeframes. The mean ICERs will be calculated using primary data from each time point. Decision modeling will be performed to assess the projected lifetime ICERs.

All methodology will adhere to the “gold standard” guidelines published by the Panel on Cost-Effectiveness in Health and Medicine convened by the US Public Health Service<sup>86</sup>. Methods and decision modeling for the within-trial and lifetime time horizon analyses will be similar. Markov decision models will be constructed using the societal perspective to evaluate the lifetime clinical and economic impact of the alternative strategies within the trial. Costs will be estimated as resource use X unit cost. Primary data for the within-trial time horizon on utilities and probabilities will be available from the trial. For the lifetime analyses, we will use additional cost and utility data abstracted from published efficacy studies and will model the lifetime cost-utility using Markov disease state simulation modeling. For the base case, these analyses will assume persistence of treatment effects on costs and outcomes, and will extensively explore potential attrition in these benefits. Future life expectancy will be computed using standard annual survival probabilities within the Markov simulation (<http://wonder.cdc.gov/>). This standardized approach uses nationally representative statistics and minimizes concerns about selection bias and generalizability of the results. Costs and utilities will be discounted at a rate of 3%. The influence of assumptions will be assessed in sensitivity analyses. Univariate sensitivity analyses will be performed on all variables and assumptions used in the analyses, including health outcomes, costs, and methodological assumptions (e.g., discounting). We will conduct selected multi-way sensitivity analyses to show how different variable values interact. We will also use a Monte Carlo simulation to vary all of the input parameters over their relevant ranges simultaneously and to estimate the 95% confidence intervals of our incremental analyses. DATA 4.0 decision analysis or equivalent software will be used.

Costs will include direct medical costs within and outside the study. Within-study costs are those related to the intervention, including staff time and cost of materials and supplies for the delivery of the intervention (independent of the research component). Outside of study medical care costs include urgent care, outpatient and ER visits, interval hospitalizations, medical procedures and medications. Each of these costs will be estimated as the product of self-report of resource use on questionnaires multiplied by nationally generalizable estimates of cost. Direct non-medical costs will be calculated by multiplying units of resources used (on the IRUQ) by an average unit cost in dollars, which will permit standardization and later generalization. Indirect costs due to lost or impaired productivity specifically associated with the study interventions and visits will be calculated by participant visit and treatment schedules and age-and gender-specific average hourly income.

#### Administrative Core Activities

The Administrative Core, led by the PI will manage the day-to-day operations of the study and will coordinate and serve as the communication center for the 3 clinical sites, the Beaumont Research Coordinating Center (BRCC), the consultant and the biostatistician. This office will be the liaison with the funding agency, as well as any third party company that will interface with the study, such as the vendor InfoUSA.

A steering committee has been established composed of the Principal Investigator as the Chair and membership composed of all the site investigators, director of the BRCC, and the biostatistician. The committee will be responsible for addressing any issues that arise during the trial that need to be clarified or resolved. The committee will decide on assignments for publications, presentations, etc. It will meet by teleconference bi-monthly and face-to-face once a year.



Timeline

Activity	Year 1						Year 2						Year 3						
	1/2	3/4	5/6	7/8	9/10	11/12	13/14	15/16	17/18	19/20	21/22	23/24	25/26	27/28	29/30	31/32	33/34	35/36	
Startup; training;	START -UP																		
Recruitment: N=330			RECRUITMENT																
Screening/Baseline			SCREEN/BASELINE VISITS																
Intervention			INTERVENTION																
Data collection				3, 6, 9 AND 12-MONTH DATA COLLECTION															
Statistical analyses					STATISTICAL AND COST-EFFECTIVENESS ANALYSES														
Final Report																		REPORT	

## **PROTECTION OF HUMAN SUBJECTS**

### **RISKS TO THE SUBJECTS**

*Human Subjects Involvement and Characteristics:*

### **ETHICAL PRINCIPLES**

Each site's Institutional Review Board (IRB) will approve this study. All participants will give informed consent. This study will be conducted pursuant to the Declaration of Helsinki: Recommendations Guiding the Medical Doctors in Biochemical Research Involving Human Subjects. Investigators will follow this clinical investigation plan and follow Good Clinical Practice requirements set by Federal Law and Institutional Review Board regulations at all times.

*Source of materials:*

Research materials will include self-administered questionnaires and face-to-face interviews. Specifically, self-administered questionnaires will be used to measure urinary incontinence and quality of life. Face-to-face visits and telephone interviews will clarify participants' responses on questionnaires.

### **MAINTENANCE OF CONFIDENTIALITY:**

Beaumont Research Coordinating Center (BRCC) will provide oversight of electronic data capture. Measures will be taken to protect the identity of subjects and the confidentiality of collected data. Data that could be used to identify subjects (names, social security numbers) will not be recorded on data collection instruments and no identifying data will be entered into the database. The human subjects' data will be entered into a web-based database and will be identified by number and initials to protect the identities. Research records will be kept in a locked file cabinet or locked room when not being used for data collection or analysis purposes and only members of the research team will have access to the records. Subjects will be informed that their data will be used in combination with other data but they will not be identified individually in any way.

### **ADEQUACY OF PROTECTION FOR HUMAN SUBJECTS**

Recruitment and Informed Consent: Each clinical site will provide the Administrative Core with zip codes, area codes and counties for their respective area. Using this information, a mailing list will be purchased from InfoUSA.com. InfoUSA.com is a marketing company that provides business and consumer data, email and direct mail support, and database processing. Specific zip codes will be targeted for recruitment of traditionally underrepresented populations. The Administrative Core will have oversight over the rate of recruitment through the number and frequency of mailings sent out for each clinical site. Participants will receive a letter inviting them to call an 800 number for further information. We will increase mailings and use other recruitment strategies such as fliers or advertisement as needed to achieve the recruitment goal.

### **CONSENT PROCEDURE:**

Participants who meet the inclusion criteria will be invited to participate. Informed consent will be obtained following all federal guidelines for the protection of human subjects. Prior to obtaining consent, participants will be briefed by the investigators or their designee on the study goals and objectives, including all related procedures. Alternative treatments, risks, and benefits associated with study procedures will be thoroughly discussed with participants. A copy of the signed consent form will be given to the participant and the original will be placed in the research record.

### **PROTECTION AGAINST RISK:**

All participants will be thoroughly screened and evaluated at enrollment and then randomized to one of the two arms of the study. The risk of loss of confidentiality exists. Care will be taken to preserve confidentiality. Only staff personnel will have access to participant records and participants will not be identified in any published study. The study database will be accessed by password protection only. All participants will be asked to follow the principles of privacy and confidentiality.

### **DATA AND SAFETY MONITORING PLAN**

A data and safety monitoring board (DSMB) will be established by the National Institute on Aging (NIA). Per the NIA, the protocol, manual of procedures and informed consents will be reviewed and approved prior to study start. Subsequent data safety monitoring by the DSMB will occur on a periodic basis as determined by the DSMB. The Beaumont Research Coordinating Center will provide data safety reports for review by the DSMB.

### **RISK ASSESSMENT**

This is a multi-centered randomized clinical trial. The risk level for this comprehensive evidenced-based intervention study was determined to be low. The primary risk in the proposed study revolves around privacy and data confidentiality. Privacy and confidentiality of all data will be maintained to the fullest possible extent. Only authorized research personnel will have access to study computers and data. Confidentiality procedures will be strictly adhered to when transferring, managing and analyzing the study data.

There may be a rare (< 1%) risk of discomfort and/or bleeding from the pelvic examinations. Study participants may feel uncomfortable answering questionnaires and/or participating in the group bladder training class. These known risks will be acknowledged in the consent process.

To mitigate any risk of no treatment in the control group and possible inadequate treatment in the intervention group, subjects will not be prohibited from pursuing other UI treatments during the trial. Conversely, subjects will not be encouraged to seek other treatments. At the end of each control subject's participation, she will be offered the group intervention or referral to an incontinence specialist. Participants in the intervention group who are not satisfied with their progress will be offered referral to an incontinence specialist.

### **PLAN FOR MONITORING AND SAFETY REVIEW:**

Members of the DSMB will include an urologist, gerontologist/geriatrician, nurse clinician/social scientist and biostatistician for an independent review of data provided by the BRCC. Members invited to participate on the DSMB will be independent of the GLADIOUS Study and excluded from participation if connected to the GLADIOUS Study. The DSMB will meet periodically and monitor recruitment, subject eligibility, adherence to treatment plan, documentation of dropouts, evaluation of primary and secondary endpoints, unanticipated problems/adverse events (UP/AE), and/or problems with informed consent. Reports from DSMB meetings will be presented to the Steering Committee.

### **PLAN FOR DATA MANAGEMENT**

Electronic data capture process for the proposed study will require the participating clinical sites to connect to the Crossbreak website via the Microsoft Internet Server. To insure accuracy and integrity, data entered for each variable will be validated by an electronic audit procedure, which entails a three-step process. The validation rules are to insure that no data is missing, entries are logical, skip patterns are followed, and that non-numerical data entries are appropriate.

Reports to the DSMB from the BRCC will include enrollment (monthly and quarterly), subject follow-up schedules, eCRF completion and delinquencies, query resolutions and delinquencies, protocol deviations, and unanticipated problems/adverse events.

## **GUIDELINES FOR UNANTICIPATED PROBLEM (UP) / ADVERSE EVENT (AE)/ SERIOUS ADVERSE EVENT (SAE)**

### **DEFINITIONS**

Definitions are from the January 2007 OHRP *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*, OHRP Guidance, <http://www.hhs.gov/ohrp/policy/advevntguid.html>.

#### **Adverse Event (AE):**

Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research. The principal investigator will be responsible for monitoring and reporting the occurrence of these events throughout the study, whether they are anticipated, unanticipated, serious, or not serious.

#### **Serious Adverse Event (SAE):**

Any adverse event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

#### **Unanticipated Problem (UP):**

Defined by DHHS 45 CFR part 46 as any incident, experience, or outcome that meets all of the following criteria:

- unexpected, in terms of nature, severity, or frequency, given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the study population;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);
- suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

## Adverse Events versus Unanticipated Problems

- The vast majority of adverse events occurring in human subjects are not unanticipated problems.
- A small proportion of adverse events are unanticipated problems.
- Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events.

## Pre-Existing Condition

- Any chronic or acute sign, symptom, illness, or condition that the woman has at the time of enrollment of this trial that is unrelated to the UI under treatment is considered a pre-existing condition. (e.g., asthma, diabetes etc.,)
- Information on pre-existing medical conditions will be obtained at the screening visit to allow a comparison to determine potential UP/AE information.

## Expectedness

AEs must be assessed as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the protocol. Categories are:

- **Unexpected** - nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.
- **Expected** - event is known to be associated with the intervention or condition under study.

For this trial, (Group Learning Achieves Decreased Incidents of Lower Urinary Symptoms) there may be a rare (< 1%) risk of discomfort and/or bleeding from the pelvic examinations. Study participants may feel uncomfortable answering questionnaires and/or participating in the group bladder training class. These known risks will be acknowledged in the consent process.

## Relatedness

The potential event relationship to the study intervention and/or participation is assessed by the site investigator. A comprehensive scale in common use to categorize an event is:

- **Definitely Related:** The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- **Possibly Related:** An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.

- *Not Related:* The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

## **REPORTING**

### **Adverse Event Reporting**

All unanticipated problems and adverse events (regardless of relatedness to the study) will be classified and captured on a case report form.

### **Serious Adverse Event Reporting**

All SAEs (regardless of relatedness to the study), unless otherwise specified in the protocol and approved by the IRB and NIA or DSMB (as applicable), require expedited reporting by the Principal Investigator to the study's safety monitoring bodies. Once an SAE is identified obtain pertinent documentation (i.e. hospital discharge summary, death certificate) to complete the SAE review and report. An expedited report of an SAE can be submitted by telephone, fax, or email and must be reported to the independent safety monitoring body (i.e., DSMB or Safety Officer) and the NIA within 24 hours of the event being reported to the Investigator.

## **POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS**

We anticipate that the data collected will translate into improved health and quality of life for others with urinary incontinence. Once standardized with data to support its clinical effectiveness and cost-effectiveness, group treatment modalities have potential to reach a larger population of older women with UI, not only in medical offices and clinics, but also in community settings, significantly reducing the human and economic burden of UI on patients, health care providers, and the health care system as a whole.

## **IMPORTANCE OF KNOWLEDGE TO BE GAINED**

The findings from this study will enhance the current body of knowledge regarding urinary incontinence. Treatment of urinary incontinence utilizing the group session model would provide an alternative treatment for healthcare providers and have the potential to impact economic costs.

### **PROTECTION OF HUMAN PARTICIPANTS:**

Compliance with Informed Consent Regulations (U.S. 21 CFR Part 50) and Relevant Country Regulations will be strictly maintained. Written informed consent is to be obtained from each participant prior to enrollment into the study.

### **COMPLIANCE WITH ELECTRONIC RECORDS:**

Electronic Signatures Regulations: This study is to be conducted in compliance with the regulations on electronic records and electronic signatures and will comply with the Guidance on Computerized Systems Used in Clinical Trials.

The Beaumont Research Coordinating Center (BRCC) will be responsible for the development of the database and the collection and management of the data. This will be accomplished by electronic data capture using an internet-based, custom-designed application called "Crossbreak". The Crossbreak application was developed by the BRCC to support its data management needs and launched in 2007. The BRCC maintains full-time computer programmers on staff to provide ongoing

technical support, daily maintenance, and additional development of the Crossbreak database application. The server for the application is housed at an off-site, secured location and maintained by the Medical Information Services Department (MISD) of William Beaumont Hospital.

The electronic data capture process for the proposed study will require the participating clinical sites to connect to the Crossbreak website (<https://crossbreak.pamisearch.com>) via the Microsoft Internet Server. The electronic case report form (eCRF) will be constructed into "Crossbreak" allowing site personnel to enter data electronically for each of the variables. All data received by the BRCC is de-identified. The data entry fields will appear on a computer screen and mimic the paper version of the case report form. To insure accuracy and integrity, data entered for each variable will be validated by an electronic audit procedure, which entails a three-step process. This is accomplished by assigning numerical ranges to appropriate fields in the database and using validation rules for edit verification. The validation rules are to insure that no data is missing, entries are logical, skip patterns are followed, and that non-numerical data entries are appropriate.

Prior to electronically entering data, the site nurse or research coordinator will review the data contained in the paper version of the case report form for accuracy and completeness. Next, electronically entered data will be scrutinized by the validation process incorporated into "Crossbreak." The first step in the process entails the sequential identification of errors (i.e., numbers outside the predetermined numerical ranges, missing data or inappropriate data entry) as the data is entered. The identification of an error or missing information is signaled on the computer screen to the site operator immediately following that data entry. Upon successful completion of this first verification step, data is imported into the database. The second validation step involves interrogation of the entered data by Data Coordinators at the BRCC. A system of edits and crosschecks are utilized in this process. Data Coordinators will issue electronic queries to each site as inaccuracies are identified. The site personnel will be required to resolve these queries and electronically submit the resolutions. In the third step of the validation process, the resolutions will be reviewed by a member of the BRCC data management team for accuracy and integrity. Should the queries not be resolved appropriately, they will be re-issued to the site until they are satisfactorily resolved. Once this step of the validation process is adequately completed, the data is then encrypted into the secured database. Security of the database is insured using the industry standard 128-bit Secure Sockets Layer (SSL) encryption.

Crossbreak also contains comprehensive reporting services, which will serve to assist in the management of the data. "Real-time" reports provide access to study data, which allow for accurate and efficient monitoring of the study progress. Reports include enrollment (monthly and quarterly), subject follow-up schedules, eCRF completion and delinquencies, query resolutions and delinquencies, protocol deviations, UP/AE reporting, etc.

#### **PARTICIPANT CONFIDENTIALITY:**

A report of the results of this study may be published but participants' names will not be disclosed in these documents. The participants' identities may be disclosed to the governing health authorities or the FDA (Food and Drug Administration) if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

#### **INCLUSION OF WOMEN AND MINORITIES:**

Beaumont Health System maintains a rigorous policy to assure the inclusion of women and minorities into all clinical research being conducted. Each individual investigator along with their staff carefully designs all phases of research to ensure adequate representation of women and minorities in the study. Based upon the research objectives, the inclusion and exclusion criteria are developed based on sound scientific rationale to include the widest possible range of population groups and

assure the appropriate generalization of research results. In collaboration with Beaumont's Office of Corporate Diversity, researchers can obtain assistance developing their strategic plans for outreach and recruitment efforts to improve participation by traditionally underrepresented populations. The Office of Corporate Diversity is committed to supporting principal investigators with this critical element and offers expertise and resources to help clinical trial administrators attain their target enrollments that are appropriately representative in gender, race, ethnicity, and age.

Representative enrollment in clinical research studies is top priority to the Human Investigation Committee (HIC) who reviews each protocol to determine whether the plans for inclusion of women and minorities in the specific study are appropriate and/or adequate. The automatic exclusion of women or minorities without scientific justification is not accepted. The HIC evaluates the proposed plan for the inclusion of minorities for appropriate representation or assesses the scientific strength of the proposed justification if representation is limited or absent. The HIC also evaluates plans for recruitment/outreach for study participants.

Each clinical site identified zip codes, area codes and counties for their respective area. Using this information, a mass-mailing list will be purchased from [InfoUSA.com](http://InfoUSA.com). Specific zip codes will be identified and utilized to target traditionally underrepresented populations.

**University of Alabama at Birmingham:** According to the 2012 estimates of the U.S. Census Bureau, the State of Alabama's population is 70.04 % White, 26.5% African-American. Although the overall population of Alabama is 4.1 % Hispanic or Latino in origin, the vast majority of these women are young enough that incontinence would be rare. Persons 65 years and over account for 14.5% of the population and females account for 51.5% of the population. We will target recruitment to obtain a representative sample of African-American women to the proposed trial.

**University of Pennsylvania:** According to the 2012 estimates of the U.S. Census Bureau, the County of Philadelphia, Pennsylvania is 45.7% White, 44.3% African-American, 13.0 % Hispanic or Latino Origin, 6.6% Asian and has a population of 1.5 million. Persons 65 years and over account for 12.2 % of the population and females account for 52.8% of the population. We will focus our recruitment to target zip codes in Philadelphia County, using a strategy that has been successful in earlier studies. Thus, we anticipate having more than adequate representative sample of African American and Latino women for enrollment in the proposed trial.

**University of Michigan:** According to the 2012 estimates of the U.S. Census Bureau the State of Michigan population is 80.1% White and 14.3% African-American. Southeast Michigan 2010 census data indicates a greater proportion of African-Americans at 21.6%. We will focus our recruitment within Southeast Michigan using a strategy targeting zip codes with higher African-American representation that has been successful in earlier studies. Thus, we anticipate over-sampling African- American women.

**Gender and Minority Inclusion and Non-Discriminatory Statements:** Men are excluded from this clinical trial. While it is equally important to explore group session teachings applicable to men, we hope to establish and demonstrate what works with female incontinent patients before adapting the program to the male population. However, this does represent an interesting opportunity for future research.

**Age:** Urinary Incontinence is a prevalent condition that diminishes quality of life in older women generally over the age of 55 at tremendous social and economic costs. Children (as defined by the NIH) will be excluded from this study because urinary incontinence (stress, urge or mixed) predominantly affects older women.



## REFERENCES

1. Anger JT, Saigal CS, and Litwin MS, The prevalence of urinary incontinence among community dwelling adult women: results from the National Health and Nutrition Examination Survey. *J Urol*, 2006. 175(2): p. 601-4. PMID 16407004
2. Anger JT, Saigal CS, Stothers L, Thom DH, Rodriguez LV, and Litwin MS, The prevalence of urinary incontinence among community dwelling men: results from the National Health and Nutrition Examination survey. *J Urol*, 2006. 176(5): p. 2103-8; discussion 2108. PMID 17070268
3. Diokno AC, Estanol MV, Ibrahim IA, and Balasubramaniam M, Prevalence of urinary incontinence in community dwelling men: a cross sectional nationwide epidemiological survey. *Int Urol Nephrol*, 2007. 39(1): p. 129-36. PMID 17086446
4. Roberts RO, Jacobsen SJ, Rhodes T, Reilly WT, Girman CJ, Talley NJ, and Lieber MM, Urinary incontinence in a community-based cohort: prevalence and healthcare-seeking. *J Am Geriatr Soc*, 1998. 46(4): p. 467-72. PMID 9560070
5. Mittmann N, Trakas K, Risebrough N, and Liu BA, Utility scores for chronic conditions in a community-dwelling population. *Pharmacoeconomics*, 1999. 15(4): p. 369-76. PMID 10537955
6. Schultz SE and Kopec JA, Impact of chronic conditions. *Health Rep*, 2003. 14(4): p. 41-53. PMID 14608795
7. Diokno AC, Burgio K, Fultz H, Kinchen KH, Obenchain R, and Bump RC, Prevalence and outcomes of continence surgery in community dwelling women. *J Urol*, 2003. 170(2 Pt 1): p. 507-11. PMID 12853810
8. Diokno AC, Burgio K, Fultz NH, Kinchen KS, Obenchain R, and Bump RC, Medical and self-care practices reported by women with urinary incontinence. *Am J Manag Care*, 2004. 10(2 Pt 1): p. 69-78. PMID 15011807
9. Hu TW, Impact of urinary incontinence on health-care costs. *J Am Geriatr Soc*, 1990. 38(3): p. 292-5. PMID 2313010
10. Wagner TH and Hu TW, Economic costs of urinary incontinence in 1995. *Urology*, 1998. 51(3): p. 355-61. PMID 9510336
11. Wilson L, Brown JS, Shin GP, Luc KO, and Subak LL, Annual direct cost of urinary incontinence. *Obstet Gynecol*, 2001. 98(3): p. 398-406. PMID 11530119
12. Kirchstein R, Disease-specific estimates of direct and indirect costs of illness and NIH support. , N.I.o.H. Department of Health and Human Services, Office of Director., Editor. 2000: Bethesda, MD.
13. Lapitan MC and Chye PL, The epidemiology of overactive bladder among females in Asia: a questionnaire survey. *Int Urogynecol J Pelvic Floor Dysfunct*, 2001. 12(4): p. 226-31. PMID 11569649
14. Burgio KL, Locher JL, Goode PS, Hardin JM, McDowell BJ, Dombrowski M, and Candib D, Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. *JAMA*, 1998. 280(23): p. 1995-2000. PMID 9863850
15. Dougherty MC, Dwyer JW, Pendergast JF, Boyington AR, Tomlinson BU, Coward RT, Duncan RP, Vogel B, and Rooks LG, A randomized trial of behavioral management for continence with older rural women. *Res Nurs Health*, 2002. 25(1): p. 3-13. PMID 11807915
16. Fantl JA, Wyman JF, McClish DK, Harkins SW, Elswick RK, Taylor JR, and Hadley EC, Efficacy of bladder training in older women with urinary incontinence. *JAMA*, 1991. 265(5): p. 609-13. PMID 1987410
17. Burns PA, Pranikoff K, Nochajski TH, Hadley EC, Levy KJ, and Ory MG, A comparison of effectiveness of biofeedback and pelvic muscle exercise treatment of stress incontinence in older community-dwelling women. *J Gerontol*, 1993. 48(4): p. M167-74. PMID 8315230

18. Gerard L, Group learning behavior modification and exercise for women with urinary incontinence. *Urol Nurs*, 1997. 17(1): p. 17-22. PMID 9110901
19. Janssen CC, Lagro-Janssen AL, and Felling AJ, The effects of physiotherapy for female urinary incontinence: individual compared with group treatment. *BJU Int*, 2001. 87(3): p. 201-6. PMID 11167642
20. McFall SL, Yerkes AM, and Cowan LD, Outcomes of a small group educational intervention for urinary incontinence: health-related quality of life. *J Aging Health*, 2000. 12(3): p. 301-17. PMID 11067699
21. Hill L, Fereday-Smith J, Credgington C, Woodward A, Knight J, Williams A, Doughty G, Lamb S, Pepper J, and Clarke M, Bladders behaving badly, a randomized controlled trial of group versus individual interventions in the management of female urinary incontinence. *Journal of the Association of Chartered Physiotherapists in Women's Health*, 2007. Autumn (101): p. 30-36. PMID
22. Miller JM, Ashton-Miller JA, and Delancey JO, Quantification of cough-related urine loss using the paper towel test. *Obstet Gynecol*, 1998. 91(5 Pt 1): p. 705-9. PMID 9572215
23. Fletcher SG, Clark SJ, Overstreet DL, and Steers WD, An improved approach to followup care for the urological patient: drop-in group medical appointments. *J Urol*, 2006. 176(3): p. 1122-6; discussion 1126. PMID 16890706
24. Bo K, Kvarstein B, and Nygaard I, Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. *Obstet Gynecol*, 2005. 105(5 Pt 1): p. 999-1005. PMID 15863536
25. Morkved S, Bo K, Schei B, and Salvesen KA, Pelvic floor muscle training during pregnancy to prevent urinary incontinence: a single-blind randomized controlled trial. *Obstet Gynecol*, 2003. 101(2): p. 313-9. PMID 12576255
26. Diokno AC, Sampsel CM, Herzog AR, Raghunathan TE, Hines S, Messer KL, Karl C, and Leite MC, Prevention of urinary incontinence by behavioral modification program: a randomized, controlled trial among older women in the community. *J Urol*, 2004. 171(3): p. 1165-71. PMID 14767293
27. Lajiness MJ, Wolfert C, Hall S, Sampsel C, and Diokno AC, Group session teaching of behavioral modification program for urinary incontinence: establishing the teachers. *Urol Nurs*, 2007. 27(2): p. 124-7. PMID 17494451
28. Herzog AR, Diokno AC, Brown MB, Normolle DP, and Brock BM, Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults. *J Gerontol*, 1990. 45(2): p. M67-74. PMID 2313045
29. Sampsel CM, Miller JM, Herzog AR, and Diokno AC, Behavioral modification: group teaching outcomes. *Urol Nurs*, 1996. 16(2): p. 59-63. PMID 8826155
30. Sampsel CM, Messer KL, Seng JS, Raghunathan TE, Hines SH, and Diokno AC, Learning outcomes of a group behavioral modification program to prevent urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*, 2005. 16(6): p. 441-6. PMID 16237512
31. Diokno AC, Ocampo MS, Jr., Ibrahim IA, Karl CR, Lajiness MJ, and Hall SA, Group session teaching of behavioral modification program (BMP) for urinary incontinence: a randomized controlled trial among incontinent women. *Int Urol Nephrol*, 2010. 42(2): p. 375-81. PMID 19701691
32. Messer KL, Herzog AR, Seng JS, Sampsel CM, Diokno AC, Raghunathan TE, and Hines SH, Evaluation of a mass mailing recruitment strategy to obtain a community sample of women for a clinical trial of an incontinence prevention intervention. *Int Urol Nephrol*, 2006. 38(2): p. 255-61. PMID 16868693
33. Diokno AC, Brown MB, Brock BM, Herzog AR, and Normolle DP, Clinical and cystometric characteristics of continent and incontinent noninstitutionalized elderly. *J Urol*, 1988. 140(3): p. 567-71. PMID 3411676

34. Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, and Abrams P, ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *Neurourol Urodyn*, 2004. 23(4): p. 322-30. PMID 15227649
35. Padros J, Peris T, Salva A, Denkinger MD, and Coll-Planas L, Evaluation of a urinary incontinence unit for community-dwelling older adults in Barcelona: implementation and improvement of the perceived impact on daily life, frequency and severity of urinary incontinence. *Z Gerontol Geriatr*, 2008. 41(4): p. 291-7. PMID 18695974
36. Seckiner I, Yesilli C, Mungan NA, Aykanat A, and Akduman B, Correlations between the ICIQ-SF score and urodynamic findings. *Neurourol Urodyn*, 2007. 26(4): p. 492-4. PMID 17304520
37. Miller JM, Sampsel C, Ashton-Miller J, Hong GR, and DeLancey JO, Clarification and confirmation of the Knack maneuver: the effect of volitional pelvic floor muscle contraction to preempt expected stress incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*, 2008. 19(6): p. 773-82. PMID 18204797
38. Bandura A, Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev*, 1977. 84(2): p. 191-215. PMID 847061
39. Bandura A, Health promotion by social cognitive means. *Health Educ Behav*, 2004. 31(2): p. 143-64. PMID 15090118
40. van Ryn M and Vinokur AD, How did it work? An examination of the mechanisms through which an intervention for the unemployed promoted job-search behavior. *Am J Community Psychol*, 1992. 20(5): p. 577-97. PMID 1485612
41. Vinokur AD and Schul Y, Mastery and inoculation against setbacks as active ingredients in the JOBS intervention for the unemployed. *J Consult Clin Psychol*, 1997. 65(5): p. 867-77. PMID 9337505
42. Vinokur AD and Schul Y, The web of coping resources and pathways to reemployment following a job loss. *J Occup Health Psychol*, 2002. 7(1): p. 68-83. PMID 11827235
43. Santacroce SJ, Maccarelli LM, and Grey M, Intervention fidelity. *Nurs Res*, 2004. 53(1): p. 63-6. PMID 14726779
44. Resnick B, Inguito P, Orwig D, Yahiro JY, Hawkes W, Werner M, Zimmerman S, and Magaziner J, Treatment fidelity in behavior change research: a case example. *Nurs Res*, 2005. 54(2): p. 139-43. PMID 15778656
45. Abrams P, Avery K, Gardener N, and Donovan J, The International Consultation on Incontinence Modular Questionnaire: [www.iciq.net](http://www.iciq.net): *J Urol*, 2006. 175(3 Pt 1): p. 1063-6; discussion 1066. PMID 16469618
46. Diokno AC, Brock BM, Brown MB, and Herzog AR, Prevalence of urinary incontinence and other urological symptoms in the noninstitutionalized elderly. *J Urol*, 1986. 136(5): p. 1022-5. PMID 3490584
47. Abrams P, Cardozo L, Khoury S, and Wein A, Patient-reported Outcomes Assessment, in *International Consultation on Incontinence*, Health Publication Ltd 2009: Paris.
48. Karantanis E, Fynes M, Moore KH, and Stanton SL, Comparison of the ICIQ-SF and 24-hour pad test with other measures for evaluating the severity of urodynamic stress incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*, 2004. 15(2): p. 111-6; discussion 116. PMID 15014938
49. Twiss CO, Fischer MC, and Nitti VW, Comparison between reduction in 24-hour pad weight, International Consultation on Incontinence-Short Form (ICIQ-SF) score, International Prostate Symptom Score (IPSS), and Post-Operative Patient Global Impression of Improvement (PGI-I) score in patient evaluation after male perineal sling. *Neurourol Urodyn*, 2007. 26(1): p. 8-13. PMID 17016797
50. Araki I, Beppu M, Kajiwara M, Mikami Y, Zakoji H, Fukasawa M, and Takeda M, Prevalence and impact on generic quality of life of urinary incontinence in Japanese working women:

- assessment by ICI questionnaire and SF-36 Health Survey. *Urology*, 2005. 66(1): p. 88-93. PMID 15992871
51. Cetinel B, Demirkesen O, Tarcan T, Yalcin O, Kocak T, Senocak M, and Itil I, Hidden female urinary incontinence in urology and obstetrics and gynecology outpatient clinics in Turkey: what are the determinants of bothersome urinary incontinence and help-seeking behavior? *Int Urogynecol J Pelvic Floor Dysfunct*, 2007. 18(6): p. 659-64. PMID 17164988
  52. Meschia M, Bertozzi R, Pifarotti P, Baccichet R, Bernasconi F, Guercio E, Magatti F, and Minini G, Peri-operative morbidity and early results of a randomised trial comparing TVT and TVT-O. *Int Urogynecol J Pelvic Floor Dysfunct*, 2007. 18(11): p. 1257-61. PMID 17345002
  53. Bent AE, Gousse AE, Hendrix SL, Klutke CG, Monga AK, Yuen CK, Muram D, Yalcin I, and Bump RC, Duloxetine compared with placebo for the treatment of women with mixed urinary incontinence. *Neurourol Urodyn*, 2008. 27(3): p. 212-21. PMID 17580357
  54. Suzuki T, Yasuda K, Yamanishi T, Kitahara S, Nakai H, Suda S, and Ohkawa H, Randomized, double-blind, sham-controlled evaluation of the effect of functional continuous magnetic stimulation in patients with urgency incontinence. *Neurourol Urodyn*, 2007. 26(6): p. 767-72. PMID 17397061
  55. Brown JS, McNaughton KS, Wyman JF, Burgio KL, Harkaway R, Bergner D, Altman DS, Kaufman J, Kaufman K, and Girman CJ, Measurement characteristics of a voiding diary for use by men and women with overactive bladder. *Urology*, 2003. 61(4): p. 802-9. PMID 12670569
  56. Locher JL, Goode PS, Roth DL, Worrell RL, and Burgio KL, Reliability assessment of the bladder diary for urinary incontinence in older women. *J Gerontol A Biol Sci Med Sci*, 2001. 56(1): p. M32-5. PMID 11193230
  57. Wyman JF, Choi SC, Harkins SW, Wilson MS, and Fantl JA, The urinary diary in evaluation of incontinent women: a test-retest analysis. *Obstet Gynecol*, 1988. 71(6 Pt 1): p. 812-7. PMID 3368165
  58. Lose G, Jorgensen L, and Thunedborg P, 24-hour home pad weighing test versus 1-hour ward test in the assessment of mild stress incontinence. *Acta Obstet Gynecol Scand*, 1989. 68(3): p. 211-5. PMID 2618603
  59. Rasmussen A, Mouritsen L, Dalgaard A, and Frimodt-Moller C, Twenty-four hour pad weighing test: reproducibility and dependency of activity level and fluid intake. *Neurourol Urodyn*, 1994. 13(3): p. 261-5. PMID 7920683
  60. Victor A, Larsson G, and Asbrink AS, A simple patient-administered test for objective quantitation of the symptom of urinary incontinence. *Scand J Urol Nephrol*, 1987. 21(4): p. 277-9. PMID 3445124
  61. Herzog AR and Fultz NH, Prevalence and incidence of urinary incontinence in community-dwelling populations. *J Am Geriatr Soc*, 1990. 38(3): p. 273-81. PMID 2179368
  62. Brink CA, Wells TJ, Sampsel CM, Taillie ER, and Mayer R, A digital test for pelvic muscle strength in women with urinary incontinence. *Nurs Res*, 1994. 43(6): p. 352-6. PMID 7971299
  63. Burgio KL, Goode PS, Richter HE, Locher JL, and Roth DL, Global ratings of patient satisfaction and perceptions of improvement with treatment for urinary incontinence: validation of three global patient ratings. *Neurourol Urodyn*, 2006. 25(5): p. 411-7. PMID 16652380
  64. Wagner TH, Patrick DL, Bavendam TG, Martin ML, and Buesching DP, Quality of life of persons with urinary incontinence: development of a new measure. *Urology*, 1996. 47(1): p. 67-71; discussion 71-2. PMID 8560665
  65. Yalcin I and Bump RC, Validation of two global impression questionnaires for incontinence. *Am J Obstet Gynecol*, 2003. 189(1): p. 98-101. PMID 12861145

66. Haywood KL, Garratt AM, Lall R, Smith JF, and Lamb SE, EuroQol EQ-5D and condition-specific measures of health outcome in women with urinary incontinence: reliability, validity and responsiveness. *Qual Life Res*, 2008. 17(3): p. 475-83. PMID 18274881
67. Monz B, Chartier-Kastler E, Hampel C, Samsioe G, Hunskaar S, Espuna-Pons M, Wagg A, Quail D, Castro R, and Chinn C, Patient characteristics associated with quality of life in European women seeking treatment for urinary incontinence: results from PURE. *Eur Urol*, 2007. 51(4): p. 1073-81; discussion 1081-2. PMID 17081676
68. Patrick DL, Martin ML, Bushnell DM, Yalcin I, Wagner TH, and Buesching DP, Quality of life of women with urinary incontinence: further development of the incontinence quality of life instrument (I-QOL). *Urology*, 1999. 53(1): p. 71-6. PMID 9886591
69. Steers WD, Herschorn S, Kreder KJ, Moore K, Strohbehm K, Yalcin I, and Bump RC, Duloxetine compared with placebo for treating women with symptoms of overactive bladder. *BJU Int*, 2007. 100(2): p. 337-45. PMID 17511767
70. van Kerrebroeck P, Abrams P, Lange R, Slack M, Wyndaele JJ, Yalcin I, and Bump RC, Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence. *BJOG*, 2004. 111(3): p. 249-57. PMID 14961887
71. Messer KL, Hines SH, Raghunathan TE, Seng JS, Diokno AC, and Sampsel CM, Self-efficacy as a predictor to PFMT adherence in a prevention of urinary incontinence clinical trial. *Health Educ Behav*, 2007. 34(6): p. 942-52. PMID 17456856
72. Hines SH, Seng JS, Messer KL, Raghunathan TE, Diokno AC, and Sampsel CM, Adherence to a behavioral program to prevent incontinence. *West J Nurs Res*, 2007. 29(1): p. 36-56; discussion 57-64. PMID 17228060
73. Borson S and Scanlan J. Mini-Cog: Improving primary care physicians' detection of milder cognitive syndromes. in *Abstract presented at The 8th International Conference on Alzheimer's Disease and Related Disorders; July 20-25, 2002*. Stockholm.
74. Borson S, Scanlan J, Brush M, Vitaliano P, and Dokmak A, The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. *Int J Geriatr Psychiatry*, 2000. 15(11): p. 1021-7. PMID 11113982
75. Borson S, Scanlan JM, Chen P, and Ganguli M, The Mini-Cog as a screen for dementia: validation in a population-based sample. *J Am Geriatr Soc*, 2003. 51(10): p. 1451-4. PMID 14511167
76. Borson S, Scanlan JM, Watanabe J, Tu SP, and Lessig M, Simplifying detection of cognitive impairment: comparison of the Mini-Cog and Mini-Mental State Examination in a multiethnic sample. *J Am Geriatr Soc*, 2005. 53(5): p. 871-4. PMID 15877567
77. Choi Y. Validity of the Korean version of the Mini-Cog. in *Second International Congress of Biological Psychiatry. Apr 17-21, 2007*. Santiago, Chile.
78. Nordin E, Rosendahl E, and Lundin-Olsson L, Timed "Up & Go" test: reliability in older people dependent in activities of daily living--focus on cognitive state. *Phys Ther*, 2006. 86(5): p. 646-55. PMID 16649889
79. Podsiadlo D and Richardson S, The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*, 1991. 39(2): p. 142-8. PMID 1991946
80. Shumway-Cook A, Brauer S, and Woollacott M, Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther*, 2000. 80(9): p. 896-903. PMID 10960937
81. Subak L, Van Den Eeden S, Thom D, Creasman JM, and Brown JS, Urinary incontinence in women: Direct costs of routine care. *Am J Obstet Gynecol*, 2007. 197(6): p. 596 e1-9. PMID 17880904
82. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy*, 1990. 16(3): p. 199-208. PMID 10109801

83. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, and Russell LB, Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA, 1996. 276(15): p. 1253-8. PMID 8849754
84. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology.2000), Epidemiology, 2000, 11, 550-60. PMID 10955408
85. Frangakis CE, Rubin DB. Principal stratification in causal inference, Biometrics, 2002, 58, 21-29. PMID 11890317
86. Weinstein MC, Siegel JE, Gold MR, et al., Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA, 1996. 276(15): p. 1253-8. PMID 8849754
87. Broome BAS. Psychometric analysis of the Broome Pelvic Muscle Self-Efficacy Scale in African-American women with Incontinence. Urologic Nursing 2001, 21: 289.