Evidence-based Practice Center Systematic Review Protocol

Project Title: Nonsurgical Treatments for Urinary Incontinence in Adult Women: A Systematic Review Update

I. Background and Objectives for the Systematic Review

The current review will update, in part, AHRQ's 2012 systematic evidence review Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness (hereafter referred to as the 2012 AHRQ review).[1]

Epidemiology

Urinary incontinence (UI) is the involuntary loss of urine. About 17 percent of nonpregnant, adult women have experienced UI.[2] The prevalence of UI increases with age, particularly after menopause; about 3.5 percent of women aged 20 to 29 years old have experienced UI, 22 percent of women aged 50 to 59 years old, and 38 percent of women over age 80.[2] The prevalence also increases with higher parity, obesity, comorbidities, and history of hysterectomy.[2] UI can affect a woman's physical, psychological, and social well-being and can impose substantial lifestyle restrictions. The effects of UI range from slightly bothersome to debilitating. Up-to-date data on the economic costs of UI in adult women are lacking, but the American College of Physicians estimated the costs of UI care in the United States at $19.5 billion in 2004 in their 2014 Clinical Practice Guideline.[3] A separate analysis of urge UI alone, however, estimated total national costs of $35.5 billion in 2007, including $28.1 billion in direct medical costs, $1.5 billion in direct nonmedical costs (e.g., for incontinence pads), and $5.9 billion in indirect costs (e.g., lost productivity).[4]

Types of UI and Etiology

This review focuses specifically on women with stress, urgency, or mixed UI. Incontinence types are distinguished by their baseline mechanisms. Stress UI is associated with impaired urethral sphincter function and results in an inability to retain urine during coughing, sneezing, or other activities that increase intraabdominal pressure. Urgency UI is defined as the involuntary loss of urine associated with the sensation of a sudden, compelling urge to void that is difficult to defer. Mixed UI occurs when both stress and urgency UI are present. These definitions reflect the consensus definitions developed by the International Urogynecological Association/International Continence Society.[5] Stress UI is more common in younger women and in association with pelvic floor trauma and uterine prolapse, both of which are often related to vaginal childbirth and may require surgical treatment. Urgency and mixed UI are more common in older women and in association with overactive bladder, with or without sphincter dysfunction.

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The etiology of UI is multifactorial; risk factors include age, pregnancy, pelvic floor trauma after vaginal delivery, menopause, hysterectomy, obesity, urinary tract infections, functional and/or cognitive impairment, chronic cough, and constipation.[6] Several of these etiologies could be most appropriately treated by surgical interventions, which are not addressed by this review. Therefore, etiologies that require surgery, such as pelvic organ prolapse and pelvic masses, will not be addressed by this review update. We will also exclude atypical etiologies or those not amenable to typical treatments for stress or urgency UI, including urinary tract infection or neurogenic bladder (due to, for example, spinal cord injury, stroke, multiple sclerosis, or Parkinson disease).

Treatments

Nonpharmacological therapies aim to strengthen the pelvic floor and change behaviors that influence bladder function, whereas pharmacological therapies address bladder innervation and sphincter function. Standard nonsurgical, nonpharmacological UI treatments for women include: 1) pelvic floor muscle training (to strengthen the pelvic musculature), 2) behavioral training (e.g., bladder training, to teach one to gradually hold urine for longer periods), 3) vaginal cones and bladder supports (to support the bladder and relieve urgency sensation), 4) electrical and magnetic stimulation (possibly to strengthen musculature or to enhance neural control of the bladder), 5) and urethral bulking (by inflating the tissue around the bladder neck and urethra), among others. Numerous categories of drugs that have urinary retention properties or affect pelvic nerves or musculature are also used (see eligibility criteria, below, for a list of pharmacological interventions).

Treatment Outcomes

The 2012 AHRQ review evaluated a wide range of patient outcomes, including objective, subjective, and patient-centered outcomes, and adverse effects (harms). However, the review focused primarily on continence (i.e., "cure," meaning complete remission, not necessarily actual cure), change in symptoms (e.g., improvement), and harms. Definitions of continence (the lack of UI) are generally similar across studies and clinical settings. However, definitions of improvement in UI vary and include different degrees of change in frequency and severity of symptoms.[7] Furthermore, patients and researchers differ as to what constitutes UI improvement. Patients often define improvement as reduced lifestyle restrictions or improved overall perception of bladder symptoms, especially complete resolution of urine leakage. Conversely, researchers define improvement as a decrease in the amount of UI based on objective tests, including any statistically significant decrease in the frequency of UI episodes (which may not always translate into clinically important changes from the patient perspective).[7] Ideally, the determination of treatment success should be patient-centered and based on factors important to women, rather than on the results of invasive tests. Thus, treatment success and failure should be evaluated according to what women report to be significant symptom changes based on objective tests or subjective validated questionnaires or scales. Ultimately, discussions of UI improvement are complicated by the wide variety of measures used to describe the problem and its treatment outcomes. This review will examine improvement thresholds of clinical importance in validated scales and checklists that can be applied to judge UI treatment success according to women's own perceptions.

Stakeholder Input

PCORI held a multi-stakeholder virtual workshop on December 7, 2016, to discuss potential scoping for the updated review, including the prioritization of key questions, a discussion of where the evidence base has accumulated since the prior review, and emerging issues of importance to the field. Stakeholders included patients, clinicians, and allied health professionals, professional organizations, research funders, payers, and industry. The full participant list, presentation slides from the meeting, and an audio recording of the entire discussion can be found at the PCORI Web site (http://www.pcori.org/events/2016/updating-systematic-reviews-pcori-virtual-multi-stakeholder-workshop-nonsurgical).

Stakeholders agreed that the questions regarding treatment of UI still represented critical issues. Several specific interventions were brought up during the meeting as important for the review to address, including: 1) mirabegron, 2) Impressa®, a vaginal insert manufactured by Poise®, 3) botulinin A toxin injections, 4) nerve stimulation interventions, and 5) "lifestyle" interventions (e.g., bladder irritant reductions, fluid management). Stakeholders were particularly interested in treatment effectiveness in specific patient populations, including: 1) women athletes and those engaging in high-impact physical activity, 2) older women, 3) military women or veterans, and 4) racial and ethnic minorities.

Based on stakeholder input, the 2012 AHRQ review Key Question 1 on the diagnostic evaluation of UI was deemed to be of lower priority for updating at this time. Stakeholders also noted that it is important to summarize information on how patients define successful treatment.

Evidence Gaps from the Prior Review

The 2012 AHRQ review found several research gaps, including: 1) whether specific subpopulations may benefit more from, or have differential adherence to, specific interventions; 2) a need for better matching of trial endpoints with outcomes that truly matter to patients; 3) a need for more research into potential harms of treatments; and 4) a need for new (and more effective) treatment options for women with UI.

Review Update

The update of the 2012 AHRQ review will be similar to the original review with the following exceptions: Key Question 1 (diagnosis) will not be updated. Key Questions 2 and 3 (regarding the effectiveness, comparative effectiveness, and harms of nonpharmacological and pharmacological interventions for all types of UI in adult women) are reorganized for clarity.

Primary Purposes of Review Update

- To update the evidence on the topic of nonsurgical treatments for UI in adult women. (See AHRQ Pub No. 11(12)-EHC074-EF, April 2012).
- To conduct a systematic review and meta-analysis of the efficacy, comparative effectiveness, and harms of nonpharmacological and pharmacological interventions for adult women with all forms of UI.
- To summarize information on how women with UI define a successful outcome, and to highlight data on these outcomes.

II. The Key Questions

The following are the KQs to be addressed by the review:

KQ 1:
What are the benefits and harms of nonpharmacological treatments of UI in women, and how do they compare with each other?

1a. How do nonpharmacological treatments affect UI, UI severity and frequency, and quality of life when compared with no active treatment?

1b. What are the harms from nonpharmacological treatments when compared with no active treatment?

1c. What is the comparative effectiveness of nonpharmacological treatments when compared with each other?

1d. What are the comparative harms from nonpharmacological treatments when compared with each other?

1e. Which patient characteristics, including age, type of UI, severity of UI, baseline diseases that affect UI, adherence to treatment recommendations, and comorbidities, modify the effects of nonpharmacological treatments on patient outcomes, including continence, quality of life, and harms?

KQ 2:
What are the benefits and harms of pharmacological treatments of UI in women, and how do they compare with each other?

2a. How do pharmacological treatments affect UI, UI severity and frequency, and quality of life when compared with no active treatment?

2b. What are the harms from pharmacological treatments when compared with no active treatment?

2c. What is the comparative effectiveness of pharmacological treatments when compared with each other?

2d. What are the comparative harms from pharmacological treatments when compared with each other?

2e. Which patient characteristics, including age, type of UI, severity of UI, baseline diseases that affect UI, adherence to treatment recommendations, and comorbidities, modify the effects of the pharmacological treatments on patient outcomes, including continence, quality of life, and harms?

KQ 3:
What are the comparative benefits and harms of nonpharmacological versus pharmacological treatments of UI in women?

3a. What is the comparative effectiveness of nonpharmacological treatments when compared with pharmacological treatments?

3b. What are the comparative harms of nonpharmacological treatments when compared with pharmacological treatments?

3c. Which patient characteristics, including age, type of UI, severity of UI, baseline diseases that affect UI, adherence to treatment recommendations, and comorbidities, modify the relative effectiveness of nonpharmacological and pharmacological treatments on patient outcomes, including continence, quality of life, and harms?

KQ 4:
What are the benefits and harms of combined nonpharmacological and pharmacological treatment of UI in women?

4a. How do combined nonpharmacological and pharmacological treatments affect UI, UI severity and frequency, and quality of life when compared with no active treatment?

4b. What are the harms from combined nonpharmacological and pharmacological treatments when compared with no active treatment?

4c. What is the comparative effectiveness of combined nonpharmacological and pharmacological treatments when compared with nonpharmacological treatment alone?

4d. What is the comparative effectiveness of combined nonpharmacological and pharmacological treatments when compared with pharmacological treatment alone?

4e. What is the comparative effectiveness of combined nonpharmacological and pharmacological treatments when compared with other combined nonpharmacological and pharmacological treatments?

4f. What are the comparative harms from combined nonpharmacological and pharmacological treatments when compared with nonpharmacological treatment alone, pharmacological treatment alone, or other combined treatments?

4g. Which patient characteristics, including age, type of UI, severity of UI, baseline diseases that affect UI, adherence to treatment recommendations, and comorbidities, modify the effects of combined nonpharmacological and

pharmacological treatments on patient outcomes, including continence, quality of life, and harms?

Table 1. Tabulation of which Key Questions address which intervention comparisons

		KQ (2012 KQ*)			
		Nonpharm	**Pharm**	**Nonpharm+Pharm**	**No active/ Placebo**
Nonpharm	Effect:	1c (3.3)	3a (2.2)	4c (3.2)	1a (3.1)
	Harms:	1d (3.5)	3b (2.4)	4f (3†)	1b (3.4)
Pharm	Effect:		2c (2.2)	4d (2.1, 3.2 ‡)	2a (2.1)
	Harms:		2d (2.4)	4f (3†)	2b (2.3)
Nonpharm+Pharm	Effect:			4e (§)	4a (3.2)
	Harms:			4f (§)	4b (§)

Abbreviations: Effect = effectiveness (benefits), Nonpharm = nonpharmacological treatments, Pharm = pharmacological treatments, Nonpharm+Pharm = combined nonpharmacological and pharmacological treatments, KQ = Key Question.

* In parentheses are the KQs from the 2012 AHRQ review that addressed each comparison. Comparisons (cells) without 2012 KQ numbers in parentheses were not explicitly included in the 2012 AHRQ review KQs, but may have been covered in the text.

† No explicit KQ addressing this topic, but covered in the KQ 3 Results section.

‡ Addressed in the 2012 AHRQ review in the KQ 3 Results section.

§ Not explicitly included in the 2012 AHRQ review KQs and not addressed in the Results section, possibly due to a lack of evidence.

Contextual Question (new):

What is the available evidence concerning adult women's conceptions of what defines a successful outcome in the treatment of UI (i.e., how do patients measure treatment success)?

Eligibility Criteria for the Key Questions

The eligibility criteria for the update are not substantially different from the criteria for the 2012 AHRQ review. The main differences relate to dropping KQ 1 (on diagnosis), explicitly adding subpopulations of interest, and making some criteria more explicit (e.g., fleshing out and adding to the list of interventions of interest).

Changes from the 2012 AHRQ review include the following:

Population: Based on stakeholder input, we will highlight four specific subpopulations of interest (women athletes and those engaging in high-impact physical activities, older women, women in the military or veterans, and racial and ethnic minorities). Studies that either focus on these subpopulations or provide relevant subgroup data will be highlighted.

In addition, we will apply stricter rules about the exclusion criteria, allowing only up to 10 percent of study participants to be among the excluded populations (e.g., men or children); the 2012 AHRQ review allowed up to 25 percent to be men. If we find studies that were included in the 2012 AHRQ review that included between 10 and 25 percent men, we will exclude these from the current review.

Interventions: The list of eligible nonpharmacological interventions is the same as in the 2012 AHRQ review, although we have added some specific interventions to the list that were not explicitly listed *a priori* in the 2012 AHRQ review (e.g., bladder training). Similarly, the list of pharmacological treatments is more complete than the *a priori* list in the 2012 AHRQ review; additional drugs known to be in use have been added, including calcium channel blockers, TRPV1 antagonists, additional antidepressant classes, and mirabegron (a beta-3 adeno-receptor agonist). Although not listed *a priori* in the 2012 AHRQ review, calcium channel blockers and resiniferatoxin (a TRPV1 antagonist) were included in the original review. No studies of SSRI or SNRI antidepressants or of mirabegron were included in the AHRQ 2012 review.

Comparators: No changes are made from the 2012 AHRQ review.

Outcomes: All outcomes reported in the 2012 AHRQ review's eligibility criteria (Appendix D of that document) are included in this update, except for urodynamic testing, which is used in practice only for diagnosis, not for followup outcome assessment. We will add patient-centered outcomes identified from the contextual question on how patients define outcome success.

Study design, Timing, Setting: No substantive changes are made from the 2012 AHRQ review.

Table 1. Eligibility criteria

PICOTS	Inclusion	Exclusion
Population	Adult and elderly (as defined by authors) women with symptoms of UI (as defined by authors) *Subpopulations*: • women athletes and those engaging in high-impact physical activities • older women (whether "elderly" or just older than a younger analyzed subgroup, as defined by authors) • women in the military or veterans • racial and ethnic minorities	*If >10% of study participants* are children or adolescents, men, pregnant women, institutionalized or hospitalized participants, have UI caused by neurological disease or dual fecal and urinary incontinence
Interventions	**Nonpharmacological interventions**: Health education about UI; behavioral therapy, including "lifestyle" interventions (e.g., dietary modifications, weight loss, fluid restriction), bladder training; biofeedback; pelvic floor muscle training and other physical therapy; vaginal cones/weights, bladder supports (e.g., Impressa®); therapeutic pessaries; electrical stimulation (e.g., posterior tibial nerve stimulation, sacral neuromodulation, intravaginal electrical stimulation); magnetic stimulation; urethral plugs and patches; urethral bulking, including transurethral or periurethral injections. **Pharmacological interventions**: Estrogen preparations (topical estrogen); antimuscarinics (e,g, oxybutynin chloride, trospium chloride, darifenacin, solifenacin succinate, fesoterodine, tolterodine, propiverine); calcium channel blockers (e.g., nimodipine); botulinum toxin injections; TRPV1 antagonists (e.g., resiniferatoxin); antidepressants (e.g., tricyclics, SSRI, SNRI); beta-3 adeno-receptor agonists (e.g., mirabegron). **Combinations of eligible nonpharmacological and pharmacological interventions.**	Interventions not available in the United States and surgical treatments
Comparators	Other eligible nonpharmacological interventions, other eligible pharmacological interventions, other eligible combination interventions, no active treatment or placebo.	Noneligible interventions, including surgery

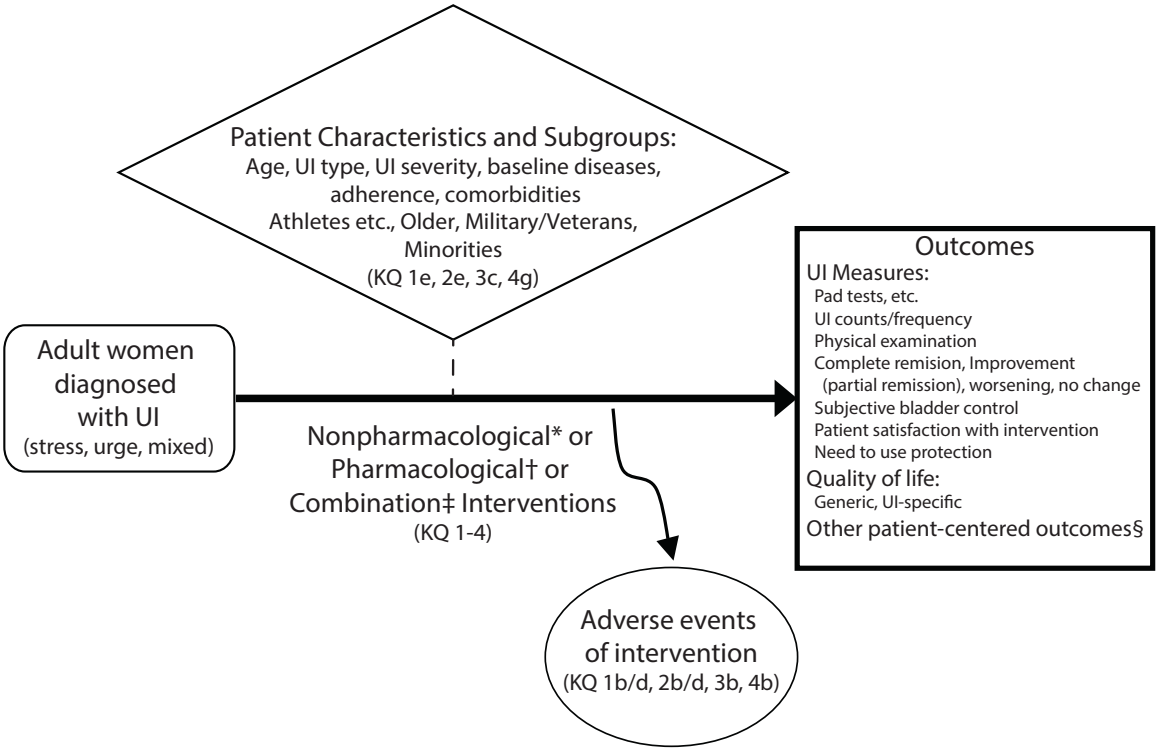
PICOTS	Inclusion	Exclusion
Outcomes	**Measures of UI**: Pad tests and other measures of leakage volumes; incontinence counts/frequency (e.g., by diary), including urgency UI counts/frequency and stress UI counts/frequency; physical examination (e.g., cough stress test); complete remission, improvement (partial remission), worsening, no change; subjective bladder control; patient satisfaction with intervention; need to use protection. **Quality of life and related questionnaires**: Generic, validated; UI-specific, validated. **Other patient-centered outcomes**, based on the findings of the contextual question (what defines a successful outcome). **Adverse events.**	Bladder and pelvic tests that do not measure UI specifically or are used for diagnostic purposes (e.g., urodynamic testing, pelvic muscle strength); urination measures that do not measure UI specifically (e.g., total voids [that include nonincontinence voids], catheterization, postvoid residuals, urinary retention, perceived micturition difficulty)
Timing	Minimum 4 weeks follow up (since the start of treatment)	
Settings	Interventions provided in primary care or specialized clinic or equivalent by any healthcare provider; participants are community-dwelling.	Surgical, institutionalized, or in-hospital settings
Country setting	Any geographic area	None
Study designs	**For effectiveness outcomes**: Randomized controlled trials (RCTs), with no minimum sample size, including pooled individual patient data from RCTs; nonrandomized comparative studies that used strategies to reduce bias (e.g., adjustment, stratification, matching, or propensity scores), N≥50 women per group (N≥100 women total). **For harms outcomes**: RCTs, with no minimum sample size; nonrandomized longitudinal comparative studies (regardless of strategies to reduce bias), including registries or large databases, N≥50 women per group (N≥100 women total); single arm longitudinal studies, including registries, large databases, and large case series N≥100 women; case-control studies (where cases are selected based on presence of harm), N≥50 female cases and ≥50 female controls (N≥100 women total). **All outcomes**: Published, peer-reviewed articles or unpublished data from the Food and Drug Administration (FDA) or from the Web site ClinicalTrials.gov.	**For effectiveness outcomes**: Single group, case-control, and case report/series studies; nonrandomized comparative studies with only crude or unadjusted data.
Publication language	Any	Unable to read or translate.

N = sample size; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; RCT = randomized controlled trial; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TRPV1 = transient receptor potential cation channel subfamily V member 1; UI = urinary incontinence.

III. Analytic Framework for the Key Questions

To guide the assessment of studies that examine the effect of nonpharmacological and pharmacological interventions on clinical and patient-centered outcomes and adverse events in adult women with UI, the analytic framework maps the specific linkages associating the populations, interventions, modifying factors, and outcomes of interest. The analytic framework depicts the chains of logic that evidence must support to link the studied interventions to outcomes of interest.

Figure 1. Analytic framework for the comparative effectiveness and adverse events of nonpharmacological and pharmacological interventions for adult women with urinary incontinence



Abbreviations: KQ = Key Question(s), UI = urinary incontinence.

* Health education about UI; behavioral therapy, including "lifestyle" interventions (e.g., dietary modifications, weight loss, fluid restriction), bladder training; biofeedback; pelvic floor muscle training and other physical therapy; vaginal cones/weights; bladder supports (e.g., Impressa®); therapeutic pessaries; electrical stimulation (e.g., posterior tibial nerve stimulation, sacral neuromodulation, intravaginal electrical stimulation); magnetic stimulation; urethral plugs and patches; urethral bulking, including transurethral or periurethral injections.

† Estrogen preparations (topical estrogen); antimuscarinics (e,g, oxybutynin chloride, trospium chloride, darifenacin, solifenacin succinate, fesoterodine, tolterodine, propiverine); calcium channel blockers (e.g., nimodipine); botulinum toxin injections; TRPV1 antagonists (e.g., resiniferatoxin); antidepressants (e.g., tricyclics, SSRI, SNRI); beta-3 adeno-receptor agonists (e.g., mirabegron).

‡ Combinations of eligible nonpharmacological and pharmacological interventions.

§ Other patient-centered outcomes based on the findings of the Contextual Question.

IV. Methods

The Evidence-based Practice Center (EPC) will conduct the review based on a systematic review of the scientific literature, using established methodologies as outlined in the Agency for Healthcare Research and Quality's (AHRQ) Methods Guide for Comparative Effectiveness Reviews.[8] As described below, the contextual question will be addressed using a nonsystematic approach.

Conducting the Systematic Review (KQ 1-4)

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

To identify new primary research studies meeting our criteria we will conduct literature searches of studies in PubMed, the Cochrane Central Trials Registry, the Cochrane Database of Systematic Reviews, and EMBASE databases. We will also search the FDA Web site (and, if feasible, obtain unpublished study results directly from the FDA), ClinicalTrials.gov, and the International Clinical Trials Registry Platform. We will also review reference lists of existing systematic reviews for additional studies.

The 2012 AHRQ review identified studies published in English that were entered into electronic databases from 1990 until December 30, 2011. The grey literature searches were last conducted in May 2010. Based on these search dates, searches for new primary studies and existing systematic reviews in electronic databases will be limited to January 2011 to the current search date. This time frame will provide a 1-year overlap with the search done for the 2012 AHRQ review. The electronic database search will be updated upon submission of the draft report. Searches of the FDA and ClinicalTrials.gov registries will include studies entered since January 2010. For earlier studies that address the KQs covered by the update, we will fully rely on the 2012 AHRQ review and will make the assumption that the search for the 2012 AHRQ review was complete and accurate. However, if we come across eligible studies that were omitted from the 2012 AHRQ review, we will include these as well. Furthermore, we will include any additional eligible studies made known to us by AHRQ, PCORI, peer reviewers, manufacturers (via Supplemental Evidence and Data for Systematic Reviews [SEADS]/Federal Registry Notices), or other stakeholders.

To the extent possible, the current search will replicate the search reported by the 2012 AHRQ review. However, we will add terms for any listed eligible interventions that were omitted from the 2012 AHRQ review search strategies. We will use the search strategies in Appendix A. Since the terms being added to the 2012 AHRQ review primarily cover interventions that were included in that review (regardless of whether they were explicitly searched for), we will not search for older studies with the newly added terms.

With the exception of studies in the 2012 AHRQ review, studies found from existing systematic reviews will be extracted *de novo*. For studies included in the 2012 AHRQ

review, to the extent feasible, we will rely on their extraction and summary data for study level data, including risk of bias assessment.

All citations (abstracts) found by literature searches and other sources will be independently screened by two researchers. At the start of abstract screening, we will implement a training session, in which all researchers will screen the same articles and conflicts will be discussed. During double-screening, we will resolve conflicts by discussion among the team. All screening will be done in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/). All potentially relevant studies will be rescreened in full text to ensure eligibility.

Data Extraction and Data Management

Each new study will be extracted by one methodologist. The extraction will be reviewed and confirmed by at least one other experienced methodologist. Any disagreements will be resolved by discussion among the team. Data will be extracted into a customized form in Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov) designed to capture all elements relevant to the Key Questions. Upon completion of the review, the SRDR database will be made accessible to the general public (with capacity to read, download, and comment on data). The basic elements and design of the extraction form will be the similar to those used for other AHRQ comparative effectiveness reviews and will include elements that address population characteristics; descriptions of the interventions, exposures, and comparators analyzed; outcome definitions; effect modifiers; enrolled and analyzed sample sizes; study design features; funding source; results; and risk of bias questions.

Assessment of Methodological Risk of Bias of Individual Studies

We will assess the methodological quality of each study based on predefined criteria. We will use the same tools used in the 2012 AHRQ review. For RCTs, we will use the Cochrane risk of bias tool,[9] assessing randomization (yes/no), randomization method and adequacy, allocation concealment method and adequacy, use of intention-to-treat analysis, and masking (blinding). For observational studies, we will use relevant questions from the Newcastle Ottawa Scale.[10] Note that for observational studies, the 2012 AHRQ review only assessed only study strategies to reduce bias and justification of sample size. Thus, assessment of risk of bias of observational studies will differ between older and newer studies. Therefore, we will randomly select a number of observational studies from the 2012 AHRQ review and assess their risk of bias using current methodology. This will allow us to make statements about the risk of bias of observational studies across reviews.

Data Synthesis

All eligible studies from the 2012 AHRQ review and the updated searches will be evaluated together without regard for the source of the study, except to possibly highlight differences in studies or finding since 2012.

All included studies from both the 2012 AHRQ review and the update will be summarized together in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, and results. These will

include descriptions of the study design, sample size, interventions, followup duration, outcomes, results, and study quality.

We expect to conduct random effects model meta-analyses of comparative studies, if they are sufficiently similar in population, interventions, and outcomes. Specific methods and metrics (summary measures) to be meta-analyzed will depend on available, reported study data, but we expect to summarize odds ratios for categorical outcomes and net differences (or standardized mean differences) for continuous outcomes. Possible reasons for statistical heterogeneity will be explored qualitatively, and, if appropriate data are available, we may also conduct metaregression analyses to evaluate study, patient, and intervention features and to evaluate dose-response. We will explore subgroup differences within (and possibly across) studies. For within- and between-study heterogeneity, we will, at a minimum, attempt to evaluate the four specific population subgroups listed in the eligibility criteria.

If time and resources allow, we plan to explore the possibility of conducting network meta-analyses of comparative studies to allow indirect comparisons of interventions that have not been directly compared within studies. These analyses will be feasible only if sufficient studies report on the same outcome(s) in sufficiently similar groups of women. The exact methodology to conduct the network meta-analyses will be determined based on the available studies. Full methodology for conducting the network meta-analyses will be reported, as will all results and assessments of model fit, coherence, and consistency.

Grading the Strength of Evidence

We will grade the strength of the total body of evidence (from the combined 2012 AHRQ review and update) as per the AHRQ methods guide on assessing the strength of evidence (SoE).[11] We plan to assess the SoE for each outcome category (e.g., objective measures of UI, subjective measures of UI, generic quality of life, UI-specific quality of life, adverse events) and specific outcomes for which there are sufficient evidence. Following the standard AHRQ approach, for each comparison of interventions, and for each outcome, we will assess the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, other limitations, and the overall findings across studies. Based on these assessments, we will assign a strength of evidence rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect. The data sources, basic study characteristics, and each SoE dimensional rating will be summarized in a "Summary of Evidence Reviewed" table detailing our reasoning for arriving at the overall SoE rating.

Addressing the Contextual Question

To address the contextual question, we will follow the guidance of the U.S. Preventive Services Task Force.[12] We will conduct targeted literature searches—with key terms for patient values and preferences—for relevant studies of any design, including qualitative studies, surveys, and focus-group studies, including opinion pieces (such as narrative reviews, editorials, and letters). We will also include any relevant studies we find opportunistically from the systematic review searches for KQs 1-4. To supplement the

published literature, we will also informally interview up to nine members of the Society of Gynecologic Surgeons (SGS) Systematic Review Group (of which Drs. Balk and Jeppson are members) and other selected members of SGS and the American Urogynecologic Society for insights or suggested references.

Based on data and input garnered from these sources, we will answer the contextual question in a narrative format. We will not systematically extract or review all eligible studies, create summary tables, or assess the strength of evidence. However, in summarizing the evidence, we will prioritize the findings with a "best evidence" approach, based on the degree to which each study appropriately evaluates patients' opinions and preferences.

The results of the contextual question will be fed back into the assessment of studies and of the evidence base. We will explicitly expand the list of included outcomes based on adult women's conceptions of what defines a successful outcome. In particular, we will highlight identified outcomes that have insufficient (or no) evidence.

V. References

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VI. Definition of Terms

Biofeedback: Training to gain awareness of one's own physiological function, which may help to train the patient to better control her symptoms.

Electrical and magnetic stimulation: Electrical or magnetic pulses used to stimulate, and thus exercise and strengthen, the lower pelvis muscles.

Mixed urinary Incontinence: UI with features of both stress and urge UI.

Pessaries: Medical devices inserted into the vagina, most commonly ring shaped, to compress the urethra against the symphysis pubis (the bone behind the vagina) and to elevate the bladder neck.

Stress Urinary Incontinence: UI that occurs with episodes of increased intraabdominal pressure, such as when coughing, sneezing, or laughing. Stress UI is caused primarily by poor support of the urethra which results in leakage when the urethra is forced downward.

Urethral bulking: Bulking agents injected around the urethra to give structural support to the urethra.

Urethral plugs/patches: Disposable or reusable adhesive plugs or patches to temporarily seal the urethral opening and thus prevent urinary leakage.

Urge urinary Incontinence: UI associated with a frequent feeling of the need to urinate with loss of bladder control (i.e., with UI); associated with overactive bladder.

Urinary Incontinence (UI): Leakage of urine, by definition involuntary.

Vaginal cones/weights: Weighted cones inserted into the vagina that are used to exercise the pelvic floor muscles.

VII. Summary of Protocol Amendments

No protocol amendments to date.

If we need to amend this protocol, we will give the date of each amendment, describe the change, and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Example table

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol.	Specify where the change would be found in the protocol.	Describe the language of the original protocol.	Describe the change in the protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as "because the AE/TOO/TEP/Peer reviewer told us to" but explain what the change hopes to accomplish.

VIII. Key Informants/Technical Experts and Review of Key Questions

Key Informants are the end users of research and include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions.

Technical Experts constitute a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, and outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development.

Key Informants and Technical Experts were included in a multi-stakeholder virtual workshop by PCORI in December 2016. The workshop reviewed scoping for the updated review, prioritization of key questions, and a discussion of where the evidence base has accumulated since the prior review and emerging issues in UI. This UI protocol was developed based upon the findings of the multi-stakeholder virtual workshop. Key Informants and Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer- or public-review mechanism.

IX. Peer Reviewers

Peer Reviewers, representing the diversity of perspectives included in the definition of "Key Informants" and "Technical Experts" above, are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer Reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer Reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

X. EPC Team Disclosures

No team members have financial conflicts of interest.

XI. Role of the Funder

This project was completed under Contract No. HHSA 290-2015-00002-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services, through funds provided by a partnership with the Patient-Centered Outcomes Research Institute (PCORI). The AHRQ TOO reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by PCORI, the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XII. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A: Literature Search Strategy

("Urinary Bladder, Overactive"[Mesh]
OR "Urinary Incontinence"[Mesh]
OR "Enuresis"[Mesh]
OR overactive bladder
OR ((bladder or urine) AND incontinen*)
OR enuresis
OR nocturia
OR "Nocturia"[Mesh]
OR ((bladder or urine) and (overactive or incontinence or urgent or urgency or frequent or frequency or detrusor or leak*))
OR detrusor instability
OR "Urinary Bladder, Neurogenic"[Mesh]
OR (bladder AND (neurogen* or neurologic*))
OR "Urinary Incontinence, Urge"[Mesh]
OR "Urinary Incontinence, Stress"[Mesh]
OR ((urine OR urina* or bladder*) and urge*))

AND

Interventions
("Urinary Incontinence/Radiotherapy"[Mesh]
OR "Urinary Incontinence/Rehabilitation"[Mesh]
OR "Urinary Incontinence/Surgery"[Mesh]
OR "Urinary Incontinence/Therapy"[Mesh]
OR "Urinary Incontinence/Diet Therapy"[Mesh]
OR "Urinary Incontinence/Nursing"[Mesh]
OR "Urinary Incontinence/Drug"[Mesh]
OR ((non pharmacologic* or nonpharmacologic*) AND "Treatment Outcome"[Mesh])
OR mirabegron
OR "Adrenergic beta-3 Receptor Agonists"[Mesh]
OR Resiniferatoxin
OR "Botulinum Toxins"[Mesh]
OR "Botulinum Toxins, Type A"[Mesh]
OR botulinum
OR botox
OR estrogen*
OR "Estrogens"[Mesh]

OR Antimuscarinics
OR oxybutynin chloride
OR trospium chloride
OR darifenacin
OR solifenacin succinate
OR fesoterodine
OR tolterodine
OR propiverine
OR "Calcium Channel Blockers"[Mesh]
OR Calcium Channel Blocker*
OR nimodipine
OR TRPV1 antagonists
OR resiniferatoxin
OR Tricyclic antidepressants
OR "Antidepressive Agents, Tricyclic"[Mesh]
OR imipramine
OR Beta 3 adeno-receptor agonists
OR mirabegron
OR "Neuromuscular Agents"[Mesh]
OR neuromuscular agents
OR ((pelvic floor or bladder) AND (train* or exercise or physical therapy))
OR kegel
OR "Physical Therapy Modalities"[Mesh]
OR physiotherapy
OR biofeedback
OR "Biofeedback, Psychology"[Mesh]
OR electric* stimulation
OR “Electric Stimulation"[Mesh]
OR nerve stimulation
OR “Transcutaneous Electric Nerve Stimulation"[Mesh]
OR stoller
OR “Electrodes, Implanted"[Mesh]
OR (vesical pacing or interstim)
OR “fluid therapy"[Mesh]
OR (fluid AND (therapy or manage*))
OR urge suppression
OR “Behavior Therapy”[Mesh]
OR ((behavior* or behaviour*) AND (therapy or modif* or treat*))
OR “hypnosis”[Mesh]

OR (hypnosis or hypnotherapy)
OR “Drinking Behavior”[Mesh]
OR “Complementary Therapies”[Mesh]
OR ((alternative or complementary) AND (therapy or treatment))
OR “diet”[Mesh]
OR diet
OR “Quality of Life”[Mesh]
OR biofeedback
OR Vaginal cone*
OR bladder support*
OR impressa
OR (Urethra* AND (Plug or patch))
OR Magnetic stimulation
OR "Magnetic Field Therapy"[Mesh]
OR Urethral bulking
OR ((transurethral or periurethral) AND injection*)
OR Intravaginal electrical stimulation
OR Magnetic stimulation
OR Pessar*
OR (Urethral AND (plug* OR patch*)
OR Posterior tibial nerve stimulation
OR neuromodulation
OR Coaptite
OR (Vaginal AND (cone* OR weight*)
OR Impressa
OR Macroplastique implants
OR Milnacipran OR Savella
OR Trospium OR Sanctura
OR Onabotulinum toxin A OR Botox
OR Paroxetine OR Paxil
OR Mirabegron OR Myrbetriq
OR solifenacin succinate OR vesicare
OR Amitriptyline OR Elavil
OR Rimabotulinum toxin B OR Myobloc
OR Fluoxetine OR Prozac
OR Duloxetine OR Cymbalta
OR Citalopram OR Celexa
OR Escitalopram OR Lexapro
OR Levomilnacipran OR Fetzima

OR AbobotulinumtoxinA OR Dysport
OR oxybutynin chloride OR Ditropan
OR Fluvoxamine OR Luvox CR
OR Imipramine OR Tofranil
OR Nortriptyline OR Pamelorl
OR Clomipramine OR Anafranil
OR IncobotulinumtoxinA OR Xeomin
OR Doxepin OR Silenor
OR Protriptyline OR Vivactil
OR Trimipramine OR Surmontil OR 5-HT2 receptor antagonist
OR Doxepin OR Silenor
OR Sertraline OR Zoloft
OR Tolterodine OR Detrol
OR Desipramine OR Pertofrane
OR Desipramine OR Norpramin
OR Darifenacin OR Enablex
OR Desvenlafaxine OR Pristiq
OR Topical estrogen OR premarin OR synthetic conjugated estrogens

AND

Study types
"Cohort Studies"[Mesh] OR cohort OR "Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR (follow-up or followup) OR longitudinal OR "Placebos"[Mesh] OR placebo* OR "Research Design"[Mesh] OR "Evaluation Studies" [Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Comparative Study" [Publication Type] OR ((comparative or Intervention) AND study) OR Intervention Stud* OR pretest* OR pre test* OR posttest* OR post test* OR prepost* OR pre post* OR “before and after” OR interrupted time* OR time serie* OR intervention* OR (("quasi-experiment*" OR quasiexperiment* OR quasi or experimental) and (method or study or trial or design*)) OR "Case-Control Studies"[Mesh] OR (case and control) OR "Random Allocation"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR random* OR "Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Placebos"[Mesh] OR placebo OR ((clinical OR controlled) and trial*) OR ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)) OR rct OR crossover OR cross-over OR cross-over

NOT

(“addresses”[pt] or “autobiography”[pt] or “bibliography”[pt] or “biography”[pt] or “case reports”[pt] or “comment”[pt] or “congresses”[pt] or “dictionary”[pt] or “directory”[pt] or “editorial”[pt] or “festschrift”[pt] or “government publications”[pt] or “historical article”[pt] or “interview”[pt] or “lectures”[pt] or “legal cases”[pt] or “legislation”[pt] or “letter”[pt] or “news”[pt] or “newspaper article”[pt] or “patient education handout”[pt] or “periodical index”[pt] or "comment on" or ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] or cow[tw] or cows[tw] or chicken*[tw] or horse[tw] or horses[tw] or mice[tw] or mouse[tw] or bovine[tw] or sheep or ovine or murinae or ("Men"[Mesh] NOT "Women"[Mesh]) OR "Pregnant Women"[Mesh])

Limit:
2011-2017