

# Evidence-based Practice Center Systematic Review Protocol

## Project Title: Diagnosis and Comparative Effectiveness of Treatments for Urinary Incontinence in Adult Women

### I. Background and Objectives for the Systematic Review

Urinary incontinence (UI) affects substantial proportions of adults in different population groups.<sup>1</sup> The estimated prevalence of UI in adults is 9 to 22 percent<sup>2-8</sup> but varies widely as a result of differences in definitions and sampled population subgroups.<sup>9</sup> Recent studies have reported that 25 percent of young women,<sup>10</sup> 44 to 57 percent of middle-age and post-menopausal women,<sup>11,12</sup> and 75 percent of elderly women in nursing homes<sup>13</sup> experience some degree of involuntary urine loss. The fraction of nursing home admissions attributable to UI in the elderly women was 6 percent.<sup>14</sup> At the same time, the cost of incontinence care in the United States increased over the past decades;<sup>15</sup> in 2004 it averaged \$19.5 billion annually.<sup>16</sup> One estimate places the 2000 annualized cost of nursing home admissions because of UI at \$3.0 billion for elderly women.<sup>14</sup>

Baseline mechanisms of UI include hyperactive bladder, which may result in urgency UI and poor urethral sphincter function, which, in turn, can result in primary urethral incompetence and stress UI.<sup>17,18</sup> The differences in baseline mechanisms of UI lead to variable definitions of the condition, including stress, urgency, or mixed UI. Risk factors for the development and progression of UI differ according to the UI type, as does the effectiveness of pharmacological and nonpharmacological treatments.<sup>18-20</sup>

Population-based studies underestimate the incidence of UI because of sampling and self-selection of the survey participants.<sup>1</sup> Clinic-based studies include patients actively seeking treatment for UI who represent only a small proportion of adults with UI.<sup>21-24</sup> Moreover, only 45 percent of women with weekly UI episodes ever seek medical care.<sup>21</sup> Primary care providers diagnose UI in 21 percent of older women with UI.<sup>25</sup> Although data on poor patient adherence to prevention and early diagnosis of UI in different patient subpopulations are available from individual studies,<sup>26</sup> evidence about the most appropriate methods to diagnose different types of UI in primary care clinical settings has not been synthesized in systematic reviews.

Strategies to detect women at risk for and individuals who have UI have been systematically reviewed<sup>27,28</sup> but with no special attention given to associations with patient outcomes.<sup>1,29</sup> Which validated methods primary care doctors and nurse practitioners should apply to distinguish stress from urgency incontinence in clinical settings remains unclear.<sup>30-33</sup> Answering the question, “Do diagnostic methods help to prescribe appropriate treatments for different types of incontinence to best benefit patients?” would require a comprehensive review of published evidence. For this project we will systematically review published data to determine available strategies for diagnosing those women who currently have UI.

Clinical interventions to reduce UI in women have been extensively reviewed in recent years by the Agency for Healthcare Research and Quality (AHRQ),<sup>34,35</sup> the Cochrane Collaborative Group,<sup>36-63</sup> and the International Continence Society.<sup>1,29</sup> The comparative effectiveness of different UI treatments including pharmacological therapy and their effects on patient

morbidity<sup>64</sup> and quality of life<sup>65</sup> were beyond the scope of published evidence-based reports. The quality of life of women with UI<sup>66</sup> has great public health impact and should be systematically analyzed in association with available treatments.

Actionable information about which treatment is the most effective for the patient is the goal of comparative effectiveness reviews.<sup>67,68</sup> However, published evidence of aggregate treatment effects may not be applicable for individuals with specific characteristics.<sup>69</sup> Individualized high-quality care for women with UI should be based on evidence of treatment effects in homogeneous patient subpopulations, which was infrequently examined in the original studies.<sup>70</sup> An average treatment effect in a clinically diverse population may not reflect the assessment of a specific group.<sup>71,72</sup> The evidence of roles of clinical predictors of treatment failure and success in patient subpopulations with UI have not been systematically evaluated.

Previously published reports need to be updated with evidence from the large number of new publications related to diagnosis, treatment, and health care for women with UI.<sup>37,52,73-75</sup> The review, conducted by the Evidence-based Practice Center (EPC) analyzed more than 1,000 original studies of UI diagnosis and prevention that were published between January 1989 and July 2007; 1,127 new journal articles were added to MEDLINE® after that date, including 92 randomized controlled clinical trials.<sup>74</sup> Developing guidelines for female UI treatment requires synthesis of all current evidence of comparative effectiveness and harms of available treatments for different types of UI. Comparative effectiveness and harms of UI treatments can provide relevant evidence to clinical decisionmaking in weighting benefits and harms in patient subpopulations.<sup>16,76-78</sup>

The aim of this report is to synthesize published evidence about diagnosis and management of urinary incontinence in adult women. The EPC will conduct a systematic review of studies that examined diagnostic methods and treatment options in primary care settings.

After discussion with key informants<sup>79</sup> we decided to focus on adult women in primary care settings. We plan to evaluate comparative effectiveness of pharmacological and nonsurgical treatments for urinary incontinence in adult women following the principles from the Methods Guide for Comparative Effectiveness Reviews.<sup>80,81</sup>

The EPC will review the published evidence of efficacy and comparative effectiveness of the pharmacological agents that were approved by the Food and Drug Administration (FDA). Pharmacological classification of the drugs for UI that was used by the 4th International Consultation on Incontinence<sup>18</sup> will serve as a guide to synthesize comparative effectiveness and harms from available treatments.

### **Drug therapy for stress urinary incontinence:<sup>18</sup>**

#### **Serotonin-noradrenaline uptake inhibitors:**

Duloxetine  
Imipramine

#### **Estrogens**

Estrogen, topical

### **Drugs used in the treatment of overactive bladder<sup>18</sup>:**

#### **Antimuscarinic drugs**

Tolterodine  
Trospium

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Solifenacin  
 Darifenacin  
 Fesoterodine

**Drugs with mixed actions**

Oxybutynin  
 Propiverine  
 Flavoxate

**Toxins**

Botulinum toxin  
 Resiniferatoxin

The EPC will review published evidence of efficacy and comparative effectiveness of the following class III (premarket approval) urinary incontinence devices (Table 1).

**Table 1. Devices that have been examined in women with urinary incontinence are available here:**  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070852.htm>

Classification (21 CFR)	Class	Product Code	Description
<b>Gastroenterology-Urology Devices</b>			
876.5280 Implanted mechanical/hydraulic urinary continence device	III	LNM	Agent, bulking, injectable for gastro-urology use
	III	OCK	Transurethral occlusion insert, urinary incontinence-control, female
876.5310 Nonimplanted, peripheral electrical continence device	II	NAM	Stimulator, peripheral nerve, non-implanted, for pelvic floor dysfunction
876.5320 Nonimplanted electrical continence device	II	KPI	Stimulator, electrical, non-implanted, for incontinence
876.5920 Protective garment for incontinence	I 510(k) Exempt	EYQ	Garment, protective, for incontinence
N/A	Unclassified	MNG	External urethral occluder, urinary incontinence-control, female
<b>Obstetrical and Gynecological Devices</b>			
884.1425 Perineometer	II	HIR	Perineometer
884.3575 Vaginal pessary	II	HHW	Pessary, vaginal

The EPC will review published evidence of efficacy and comparative effectiveness of the following urinary incontinence devices that have been tested (Table 2).

**Table 2. Medical devices that have been tested in women with urinary incontinence**

Device	Manufacturer
CapSure (Re/Stor) continence shield	<i>(Bard Urological, C. R. Bard, Inc., Covington, GA)</i>
Contiform incontinence device	Contiform International EShop in Australia, Dr. Nicholas Biswas is the original designer of the device
Continence Guard	The Continence Guard (Coloplast A/S, Kokkedal, Denmark)
The Conveen Continence Guard	The Conveen Continence Guard (Coloplast AS, Espergarde, Denmark)

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Device	Manufacturer
FemAssis - non-invasive supple silicone domed cap that fits over the external urethral meatus	FemAssist, Insight Medical, Bolton, MA)
FemSoft urethral insert	FemSoft1 Urethral Insert (Rochester Medical Corp.)
Non-Invasive Continence Management System (NICMS)	Developed by the investigators
Pessaries	Mylex Products Inc., Chicago, IL, and Mentor Corp., Santa Barbara, CA; Suarez incontinence ring (Cook Urologic Inc., Spencer, IN
Pessary ring with floor	Gellhorn pessary (Milex, Chicago, Ill)
Pessary	Uresta (EastMed Inc, Halifax, Nova Scotia, Canada)
Pessary	Milex Products, Chicago, and PelvX/DesChutes Medical Products, Bend, Ore
The Reliance Urinary Control Insert	UroMed Corp. (Needham, Mass )
The Adjustable Continence Therapy (ACT®)	The Adjustable Continence Therapy (ACT®) Uromedica, Inc., Plymouth, MN
Urethral barrier device, Miniguard	Developed for the study, grant from Advanced Surgical Innovations, San Clemente, California
Urethral occlusive device (FemAssist*)	Insight Medical, Boston, MA
Reliance urinary control insert	Uromed Corp, Needham, MA
Adjustable continence device	Uromedica, Plymouth, Minnesota
Pulsegen device	Certificate of Approval for Use of GS Symbol No. 95 44 083; LGA, Equipment Safety Testing Institute, Nurnberg, Germany, 1995; Test Report No. T231-0087/9; Slovenian Institute of Quality and Metrology, EMC Laboratory, Ljubljana, Slovenia, 1997
Electrical stimulation unit	Hollister, Evanston, IL
Innova (Empi, Inc.) pelvic floor stimulator	Empi, Inc., St. Paul, Minnesota
Electrical stimulation unit	An MS 106 Twin (Vitacon AS, Trondheim, Norway)
Vaginal cones	Mabella cones (Vitacon AS, Trond-heim, Norway)

### Safety information from the FDA:

The FDA has released warnings for CYMBALTA available at (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm114966.htm>), and Botox:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm175011.htm>). We will monitor the FDA website for warnings and safety information for all eligible drugs and devices.

The FDA defines nonimplantable electrical incontinence devices as non significant risk devices.

(<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm126622.htm>).

The FDA defines implantable electrical urinary incontinence systems, injectable bulking agents for incontinence; and mechanical/hydraulic urinary incontinence devices as significant risk devices. Thus, we will monitor all databases for adverse effects from significant risk devices.

## II. Key Questions

Key Question 1: What constitutes an adequate diagnostic evaluation for women in the primary care setting on which to base treatment of urinary incontinence (UI)?

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1. What are the diagnostic values of different methods—questionnaires, checklists, scales, self-reports of UI during a clinical examination, pad tests, and ultrasound—when compared with multichannel urodynamics?
2. What are the diagnostic values of different methods—questionnaires, checklists and scales, self-reports of UI during a clinical examination, pad tests, and ultrasound—when compared with a bladder diary?
3. What are the diagnostic values of the methods listed above for different types of UI, including stress, urgency, and mixed incontinence?
4. What is the association between patient outcomes (continence, severity, and frequency of UI; quality of life) and UI diagnostic methods?

Key Question 2: How effective is the pharmacologic treatment of UI in women?

1. How do pharmacologic treatments affect continence, severity and frequency of UI, and quality of life when compared with no active treatment or to combined treatment modalities?
2. What is the comparative effectiveness of pharmacologic treatments when compared with each other or with nonpharmacologic treatments of UI?
3. What are the harms from pharmacologic treatments when compared with no active treatment?
4. What are the harms from pharmacologic treatments when compared with each other or nonpharmacologic treatments of UI?
5. Which patient characteristics, including age, type of UI, severity of UI, the baseline disease that effects UI, adherence to treatment recommendations, and comorbidities can modify the effects of the pharmacologic treatments on patient outcomes, including continence, quality of life, and harms?

Key Question 3: How effective is the nonpharmacologic treatment of UI in women?

1. How do nonpharmacologic treatments affect incontinence, UI severity and frequency, and quality of life when compared with no active treatment?
2. How do combined modalities of nonpharmacological treatments with drugs affect incontinence, UI severity and frequency, and quality of life when compared with no active treatment or with monotherapy?
3. What is the comparative effectiveness of nonpharmacologic treatments when compared with each other?
4. What are the harms from nonpharmacologic treatments when compared with no active treatment?
5. What are the harms from nonpharmacologic treatments when compared with each other?
6. Which patient characteristics including age, type of UI, severity of UI, the baseline disease that effects UI, adherence to treatment recommendations, and comorbidities can modify the effects of the nonpharmacologic treatments on patient outcomes, including continence, quality of life, and harms?

## Public Comment

The draft key questions were posted for public comment on the AHRQ Effective Health Care Program website for additional feedback March 31, 2010 through April 28, 2010.

We made the following changes in the key questions according to the public comments received as follows:

- We revised the research questions according to the recommendations of the International Continence Society to define urgency UI instead urge UI.
- We will prioritize clinical outcomes of continence and improvement of incontinence, quality of life, and patient satisfaction. We will analyze the harmful effects of drugs from all sources including efficacy, effectiveness, and safety trials, observational studies, and case reports. We will analyze harms regardless of how authors perceived causality of the study treatments.
- We will review the role of comorbidities in the effectiveness of treatments when examined by the authors.
- We separated the question about effectiveness of combined modalities.
- We will review the effects of different drug formulations (by doses and routes of administration) on patient' outcomes.
- We defined as eligible all drugs prescribed to treat UI, including those that are not FDA-approved for a UI indication but frequently examined in women with UI.

## Development of the Key Questions

The following considerations also guided the development of the final Key Questions

### Population(s)

For KQ1. Adult and elderly women with symptoms of UI.

For KQ2 and KQ3. Adult and elderly women with diagnosed UI.

### Interventions

For KQ1 about diagnostic methods, the methods that were defined as the gold standards:

Multichannel urodynamics

Bladder diary

**For KQ2 and KQ3 about treatments for urinary incontinence:**

Variable	Definition
Health education	Education that increases the awareness and favorably influences the attitudes and knowledge relating to the early detection and prevention of urinary incontinence
Behavioral therapy	The application of behavioral changes to detect and manage incontinence, including: education about urinary structure and function; development of individualized diaries of daily dietary, physical activities, urinary habits; pelvic floor muscle exercises; voiding schedules: prompted, timed, habit retraining, patterned urge response toileting

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Variable	Definition
Biofeedback	Process by which a person uses biofeedback information to gain voluntary control over the function of pelvic floor muscles and urination process
Pelvic floor muscle training for urinary incontinence	A systematic program of pelvic floor muscle exercises (Kegel exercises) designed to improve the strength and coordination of the pelvic floor muscles in order to improve urinary sphincter function and to control urgency
Vaginal cones	Insertion of vaginal cone (weighted device) into the vagina and contraction of the pelvic floor muscles in an effort to hold the device in place
Electrical stimulation	Application of electric current in treatment without the generation of perceptible heat Using low-voltage electric current to stimulate the correct group of muscles by using a vaginal probe for delivery
Urethral plugs and patches	Insertion of plastic shapes into the urethra to stop the flow of urine or placed externally at the urinary meatus to prevent urine leakage; used for female stress urinary incontinence
Pessaries	A plastic or silicone device that is inserted into the vagina to provide support to the uterus, vagina, bladder, or rectum when there is pelvic organ prolapse; special pessaries with knobs are available to treat urinary incontinence
Magnetic stimulation	Stimulation with a brief magnetic field on the pelvic floor muscles and sacral roots without insertion of an anal or vaginal probe
Urethral bulking: Transurethral or periurethral injection techniques for women	Artificially inflating the submucosal tissues of the bladder neck; FDA-approved urethral bulking agents include collagen (Contigen <sup>®</sup> ), autologous fat, and carbon bead particles (Durasphere <sup>®</sup> )

**Pharmacological interventions in women with urinary incontinence<sup>82</sup>**

Drug Name	Labeled for UI	Active Ingredients	Dose	Dosage Form/Route
DETROL		TOLTERODINE TARTRATE	1MG	TABLET; ORAL
DETROL		TOLTERODINE TARTRATE	2MG	TABLET; ORAL
DETROL LA		TOLTERODINE TARTRATE	2MG	CAPSULE, EXTENDED RELEASE; ORAL
DETROL LA		TOLTERODINE TARTRATE	4MG	CAPSULE, EXTENDED RELEASE; ORAL
OXYTROL		OXYBUTYNIN	3.9MG/24HR	FILM, EXTENDED RELEASE; TRANSDERMAL
GELNIQUE		OXYBUTYNIN CHLORIDE	10%(100MG/PACKET)	GEL; TRANSDERMAL
DITROPAN XL		OXYBUTYNIN CHLORIDE	5MG	TABLET, EXTENDED RELEASE; ORAL
DITROPAN XL		OXYBUTYNIN CHLORIDE	10MG	TABLET, EXTENDED RELEASE; ORAL
DITROPAN XL		OXYBUTYNIN CHLORIDE	15MG	TABLET, EXTENDED RELEASE; ORAL
DITROPAN		OXYBUTYNIN CHLORIDE	5MG	TABLET; ORAL
SANCTURA		TROSPIUM CHLORIDE	20MG	TABLET; ORAL
SANCTURA XR		TROSPIUM CHLORIDE	60MG	CAPSULE, EXTENDED RELEASE; ORAL
ENABLEX		DARIFENACIN HYDROBROMIDE	EQ 7.5MG BASE	TABLET, EXTENDED RELEASE; ORAL
ENABLEX		DARIFENACIN HYDROBROMIDE	EQ 15MG BASE	TABLET, EXTENDED RELEASE; ORAL

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Drug Name	Labeled for UI	Active Ingredients	Dose	Dosage Form/Route
VESICARE		SOLIFENACIN SUCCINATE	5MG	TABLET; ORAL
VESICARE		SOLIFENACIN SUCCINATE	10MG	TABLET; ORAL
TOVIAZ		FESOTERODINE FUMARATE	4MG	TABLET, EXTENDED RELEASE; ORAL
TOVIAZ		FESOTERODINE FUMARATE	8MG	TABLET, EXTENDED RELEASE; ORAL
<b>Off label use</b>				
BOTOX		Botulinum Toxin Type A	100U/VIAL	VIAL; SINGLE-USE
CYMBALTA		Duloxetine hydrochloride	EQ 20MG BASE	CAPSULE, DELAYED REL PELLETS; ORAL
CYMBALTA		Duloxetine hydrochloride	EQ 30MG BASE	CAPSULE, DELAYED REL PELLETS; ORAL
CYMBALTA		Duloxetine hydrochloride	EQ 60MG BASE	CAPSULE, DELAYED REL PELLETS; ORAL
IMIPRAMINE HYDROCHLORIDE		IMIPRAMINE HYDROCHLORIDE	50MG	TABLET; ORAL
PREMARIN		ESTROGENS, CONJUGATED	0.625MG/GM	CREAM; TOPICAL, VAGINAL
SYNTHETIC CONJUGATED ESTROGENS A		ESTROGENS, CONJUGATED SYNTHETIC A	0.625MG/GM	CREAM; VAGINAL

## Comparator

**For KQ1 about diagnostic methods, the index methods that were tested:**

- Questionnaires
- Checklists and scales
- Self-reported UI during a clinical examination
- Provocation stress test
- Frequency volume chart
- Pad tests
- Paper towel test
- Ultrasound

**For KQ2 and KQ3 about treatments:**

Efficacy	Placebo, no active treatment, or regular care
Comparative effectiveness	Active pharmacological treatment, education, behavioral therapy, biofeedback, bladder retraining (Kegel exercises), electrical stimulation, pads, and pessaries

## Outcomes

Outcomes for KQ1 about diagnostic methods:

1. True positive for any, stress, and urgency incontinence
2. True negative for any, stress, and urgency incontinence
3. False positive for any, stress, and urgency incontinence
4. False negative for any, stress, and urgency incontinence
5. Sensitivity for any, stress, and urgency incontinence
6. Specificity for any, stress, and urgency incontinence
7. Positive predictive likelihood ratio for any, stress, and urgency incontinence

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Primary outcomes after treatments (clinical outcomes):

1. Continence
2. Quality of life: measured by using a validated generic or condition-specific measure of quality of life developed to address issues related specifically to UI

Secondary outcomes:

1. Remission of continence; diminution of symptoms and signs of incontinence.
2. Contained incontinence; urine contained with pads or appliances.
3. Dependent continence; dry with toileting assistance, behavioral treatment, and/or medications.
4. Independent continence; dry and not dependent on ongoing treatment.

Symptoms of incontinence:

The subjective indicator of incontinence or changes in its severity, as perceived by the patient, caregiver, or partner, and may lead her to seek help from health-care professionals.

Signs of incontinence:

Observed by the physician, including simple means, to verify symptoms and quantify them. The subjective indicator of incontinence or changes in its severity, as perceived by the patient, caregiver, or partner, and may lead her to seek help from health-care professionals.

Urodynamic observations:

Observations made during urodynamic studies that have a number of possible underlying causes and do not represent a definitive diagnosis of a disease.

**Measures of the frequency, severity, and impact of urinary incontinence<sup>83</sup>**

1. Micturition time chart: Records of times of micturitions (day and night) for at least 24 hours.
2. Frequency volume chart (FVC): Records of volumes voided and the time of each micturition (day and night) for at least 24 hours.
3. Bladder diary: Records of times of micturitions, voided volumes, incontinence episodes, pad usage, and other information, such as fluid intake, the degree of urgency, and the degree of incontinence.
4. Daytime frequency: The number of voids recorded during waking hours, including the last void before sleep and the first void after waking and rising in the morning.
5. 24-hour frequency: The total number of daytime voids and episodes of nocturia during a specified 24-hour period.
6. 24-hour production: All urine produced during 24 hours.
7. Maximum voided volume: The largest volume of urine voided during a single micturition, as determined either from the frequency/volume chart or the bladder diary.
8. Pad testing: The amount of urine lost during incontinence episodes (comparison of a short provocative test to a 24-hour pad test).
9. Improvement in incontinence: Reduction frequency and severity of incontinence episodes and reduction in restrictions of daily activities due to incontinence.

10. Progression of incontinence: Increase in frequency and severity of incontinence episodes, increase in restrictions of daily activities because of incontinence, continence not achieved; no reduction in the frequency and severity of incontinent episodes.

Harms:

1. Adverse events resulting from drugs.
2. Adverse events resulting from nonpharmacological treatments.

**Timing**

Followup after treatments for at least 1 month

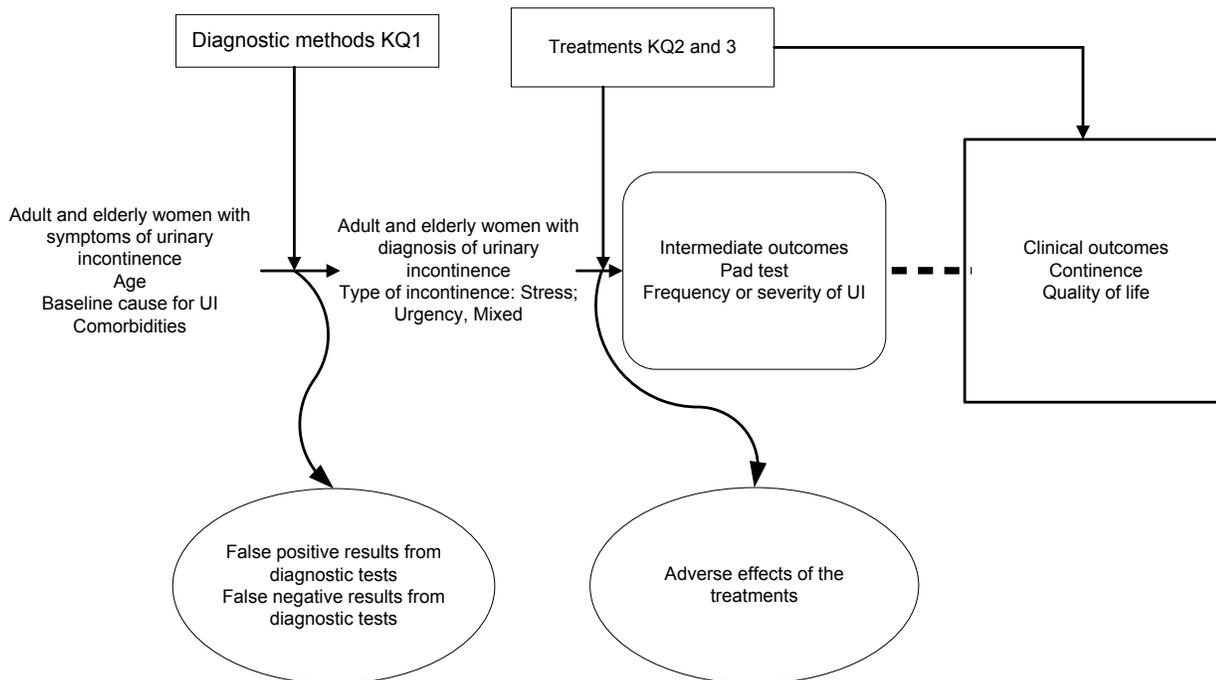
**Settings**

Primary care clinic  
 Specialized clinic (nurse practitioners)  
 Cointerventions as reported in studies

**III. Analytic Framework**

(developed following Methods Guide for Comparative Effectiveness Reviews<sup>80,81,84</sup>)

**Figure 1. Diagnosis and Comparative Effectiveness of Treatments for Urinary Incontinence in Adult Women**



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## IV. Methods

### A. Criteria for Inclusion/Exclusion of Studies

The EPC will follow the Methods Guide for Comparative Effectiveness Reviews to select evidence from controlled trials and observational studies.<sup>85</sup> Three investigators will independently decide on the eligibility of the studies according to recommendations from the Cochrane manual for systematic reviews.<sup>86</sup> The algorithm to define eligibility of the studies will be developed for each research question (Appendix 1).

#### Inclusion Criteria:

1. Original epidemiologic studies, including randomized controlled clinical trials, nonrandomized multicenter clinical trials, and observational studies that used the strategies to reduce bias (adjustment, stratification, matching, propensity scores);
2. Publication in English after 1989;
3. Target population of community dwelling adult or elderly women;
4. Eligible outcomes of urinary incontinence (total, mixed, stress, urgency), quality of life in women with UI, harms after treatment, or secondary outcomes that are listed above;
5. Eligible interventions of drug therapies or nonsurgical treatments.

For question 1, we also plan to include the studies that evaluated different methods to diagnose UI in women in primary care settings and provide the number of true and false positive, true and false negatives, sensitivity, specificity, or predictive value of the diagnostic tests. We will apply criteria for assessing whether a body of trial data is sufficient to answer the question of diagnostic methods.<sup>85</sup> We may include any observational studies that reported sensitivity and specificity of diagnostic methods for different types of female UI.

For questions 2 and 3, we will define efficacy and effectiveness trials following criteria from the Methods Guide for Comparative Effectiveness Reviews. We will apply criteria for assessing whether a body of trial data is sufficient to answer the question of treatment comparative effectiveness.<sup>85</sup> We will compare results from observational studies and RCTs on positive clinical outcomes and harms. We will focus on published randomized controlled clinical trials. We will review unpublished randomized controlled clinical trials that were included in the FDA medical and statistical reviews. We will review the abstracts of RCTs that were presented at scientific meetings if they provided data on clinical outcomes after eligible treatments that were not available in the published articles.

We plan to include RCTs that combined men and women if they reported outcomes in women separately or the women constituted more than 75 percent of all subjects.

#### Exclusion Criteria:

1. Studies that did not test the associative hypotheses and did not provide adequate information on tested hypotheses (e.g., least square means, relative risk);
2. Case series with fewer than 100 subjects;
3. Case-series that reported short-term (less than 4 weeks) crude rates of the outcomes and/or did not use strategies to reduce bias;
4. Secondary data analysis, nonsystematic reviews, letters, or comments;
5. Studies of children, adolescents, or men;

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6. Studies of surgical treatments for urinary incontinence or urogenital prolapse;
7. Studies of drugs not approved by the FDA; studies with no clinical outcomes relevant to urinary incontinence;
8. Studies that reported absolute values of the diagnostic tests in incontinent women;
9. Studies that did not report true and false positive and negative cases of diagnostic tests.

To assess harms of treatments we will follow the recommendations from the Methods Guide for Comparative Effectiveness Reviews<sup>87</sup>) and include published and unpublished evidence of the adverse effects of eligible drugs and non surgical treatments for female urinary incontinence including:

- Randomized controlled trials;
- Published non randomized trials;
- Unpublished supplemental trials data from the website  
<http://www.clinicalstudyresults.org>;
- Observational studies;
- Observational studies based on patient registries or analyses of large databases;
- Case reports and post-marketing surveillance.

We define harms as a totality of all possible adverse consequences of an intervention.<sup>87</sup> We will analyze harms regardless of how authors perceived causality of treatments.

We do not plan to contact the investigators of the primary studies. We will discuss with the TOO, Technical Expert Panel (TEP) members, and the SRC the possibility of gaining additional information from the authors or manufactures, if necessary.

## B. Literature Search Strategies

We will search several databases including MEDLINE<sup>®</sup> via OVID and via PubMed<sup>®</sup>, the Cochrane Library, SCIRUS, and Google Scholar to find published studies. We will also review grey literature packets we received from the Scientific Resource Center. This search includes regulatory documents and conducted clinical trials. The regulatory documents include medical and statistical reviews from the FDA, Health Canada - Drug Monographs, and Authorized Medicines for EU - Scientific Discussions. The following clinical trial registries have been searched for completed trials related to the key questions: ClinicalTrials.gov, Current Controlled Trials (UK), Clinical Study Results (PhRMA), and WHO Clinical Trials (International). Scopus and CSA Conference Papers Index have been searched for conference papers and abstracts related to urinary incontinence.

We will review registered ongoing studies of women with UI in [www.Clinicaltrials.gov](http://www.Clinicaltrials.gov). We will consult with the EPC librarian to define exact search strategies which will be guided by the SRC. We have developed an *a priori* search strategy based on relevant medical subject headings (MeSH) terms, text words, and weighted word frequency algorithms to identify related articles. The TEP members and peer reviewers may suggest additional sources of the evidence. We will document each recommended, included, and excluded study in the master library. We will repeat the literature search to identify studies published through September 30, 2010.

Searching the evidence will involve several steps. First, we will evaluate previously published systematic reviews.<sup>88</sup> Then we will conduct a comprehensive literature search in the databases listed above to retrieve the references that will be stored in the reference manager

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Endnote X3. We will screen the abstracts against pre-established inclusion/exclusion criteria. Finally, we will retrieve and review full articles on eligible studies to determine potential inclusion in the evidence synthesis. We will determine the eligibility of studies based on the developed *a priori* algorithm.

To ensure consistency, all evaluators will attend a training session prior to beginning the abstract review. The inclusion and exclusion criteria will be presented and discussed. In addition, the project team will meet after reviewing the first 25 abstracts to detect, discuss, and minimize disagreements, and develop a standardized reviewing approach. In addition, we will randomly select a 10 percent sample of excluded studies for re-review by the project director. We will develop a coding scheme to document and account reasons for exclusion.

### **C. Data Abstraction and Data Management**

Evaluations of the studies and data extraction will be performed independently by three researchers. The data abstraction forms are in Appendix 2. Errors in data extractions will be assessed by a comparison with the established ranges for each variable and the data charts with the original articles. Any discrepancies will be detected and discussed. We will abstract the information relevant to the PICOT framework for each question. We will abstract minimum datasets to reproduce the results that were presented by the authors. For categorical variables we will abstract a number of events among treatment groups to calculate rates, relative risk, and absolute risk differences (ARD). Means and standard deviations of continuous variables will be abstracted to calculate mean differences with a 95 percent confidence interval (CI).

For randomized controlled trials (RCTs), we will abstract the number randomized to each treatment group as the denominator to calculate estimates applying intention to treat principle. We will abstract the time when the outcomes were assessed as weeks from randomization and the time of followup post treatments. For observational studies we will extract crude rates or, preferably, relative measures of the association (relative risk, hazard ratio, odds ratio) with standard error or 95 percent CI and reported adjustments for patient age, race, methods of detection, baseline variables, and comorbidities.

### **D. Assessment of Methodological Quality of Individual Studies**

We will rate the quality of studies according to recommendations from the Methods Guide for Comparative Effectiveness Review:

#### **Stage 1. Classify the study design**

Most studies can be classified as interventions (RCT or nonrandomized controlled clinical trial or nonrandomized uncontrolled clinical trial) or observations (cohort or case-controls studies, cross-sectional studies, or case series).

#### **Stage 2. Abstract predefined criteria for quality for critical appraisal.**

We propose to evaluate quality of observational studies using criteria of internal and external validity.

We propose to evaluate quality of interventional studies using criteria from the Methods Guide for Comparative Effectiveness Reviews including randomization, adequacy of randomization and allocation concealment, masking of the treatment status, intention to treat principles, and justification of the sample size.

We will use the following ratings of quality of individual studies:

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1. *Well designed and conducted* (good- low risk of bias). These studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality include the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low dropout rate; and clear reporting of dropouts.
2. *Fair*. These studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
3. *Poor* (high risk of bias). These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Applicability of the population will be estimated by evaluating the selection of women in observational studies and clinical trials.<sup>89</sup> Studies of community dwelling adult women that were treated in primary care settings will have high applicability. Large observational cohorts based on national registries, population-based surveys, population-based effectiveness trials, and nationally representative administrative and clinical databases will have high applicability. Applicability of the intervention duration will be high for studies with followup of 1 year or more and acceptable for studies with followup of 6-12 months.

## E. Data Synthesis

We will summarize the results into evidence tables. We will analyze urinary incontinence with the definitions of signs and symptoms of UI promoted by the International Continence Society, including mixed, stress, and urgency incontinence.<sup>18,90</sup> Continence will be defined as self-reported absence of involuntary urine loss. We will also analyze urinary continence defined as negative stress and pad tests. We will use the term “urodynamic UI” to replace the older term “genuine stress incontinence.”

*Patient outcomes (clinical events).* We will synthesize prevalence of incontinence as they were used by the authors of the original studies and with calculated rates of continence, improvement, and progression if incontinence for purposes of comparison:

1. The number of incontinent women after active and control interventions.
2. The number of women who became continent after clinical interventions.
3. The number of women with improved continence.
4. The number of women with progression defined an increase in frequency and severity of incontinence.

*Continuous outcomes (surrogate outcomes of frequency or severity of UI and measures of quality of life).* We will define *subjective continuous outcomes* as the number of incontinent episodes, use of supplies, and scores from validated scales to analyze quality of life with incontinence.

We will prioritize clinical outcomes and measures of quality of life following the FDA guidelines for UI.<sup>82</sup>

In addition, we will evaluate the patients' global report of overall improvement and their overall treatment satisfaction as reported in primary studies.

We will calculate relative risk and absolute risk difference from the abstracted events using Meta-analyst<sup>91</sup> and STATA<sup>92</sup> software at 95 percent confidence level. We may calculate standard deviations when authors report standard errors:

Standard deviation = Standard Error \* Square root of the sample size in the group. We will extract medians when authors did not report means assuming normal distribution of the outcome.

We will analyze in logarithmic scale adjusted regression coefficient with standard error of association between intervention and outcome.

Consistency in the results will be tested comparing the direction and strength of the association.<sup>93</sup> Chi squared tests will be used to assess heterogeneity in study results.<sup>94,95</sup> We plan to explore heterogeneity with meta-regression and sensitivity analysis and will report the results from random effects models only.<sup>96</sup>

We plan to test the following hypotheses in pooled analysis.<sup>96</sup>

1. The urinary incontinence outcome is associated with an active treatment as a categorical variable compared to the control interventions. A random effects model will be used to incorporate heterogeneity across the studies.
2. The effect size of an active treatment can be modified by the methods of detection, type of UI, baseline subject variables, and doses/intensity of the treatment.

We will group different definitions of continence and improvement in incontinence to have an overall estimation of the interventions.

Attributable risk will be calculated as the outcome events rate in patients exposed to different clinical interventions.<sup>92,97,98</sup>

The number needed to treat to prevent one event of incontinence will be calculated as reciprocal to absolute risk differences in rates of outcomes events in the active and control groups:<sup>92,99</sup>

$$1 / (\text{control group event rate} - \text{treatment group event rate}).$$

The number of avoided or excess events (respectively) per 1000 population is the difference between the two event rates multiplied by 1000:

$$(\text{control group event rate} - \text{treatment group event rate}) * 1000$$

We will calculate diagnostic values of different tests to diagnose incontinence:

$$\text{Sensitivity} = \text{TP} / (\text{TP} + \text{FN})$$

$$\text{Specificity} = \text{TN} / (\text{FP} + \text{TN})$$

$$\text{Predictive value positive} = \text{TP} / (\text{TP} + \text{FP})$$

Positive predictive likelihood ratio:

$$\text{LR+} = \frac{\text{probability of an individual **with** the condition having a positive test}}{\text{probability of an individual **without** the condition having a positive test}}$$

$$LR+ = \frac{\text{sensitivity}}{1-\text{specificity}}$$

## F. Grading the Evidence for Each Key Question

We will assess study quality and strength of evidence following the guidelines from the Methods Guide for Comparative Effectiveness and will judge the strength of evidence according to risk of bias, consistency, directness, and precision for each major outcome.<sup>93</sup> When appropriate, dose-response association, presence of confounders that would diminish an observed effect, strength of association, and publication bias will also be included.

We will grade the quality of evidence for primary outcomes across studies as illustrated in the table below:

Grade	Definition
<b>High</b>	<b>High confidence that the evidence reflects the true effect.</b> Further research is very unlikely to change our confidence in the estimate of effect.
<b>Moderate</b>	<b>Moderate confidence that the evidence reflects the true effect.</b> Further research may change our confidence in the estimate of effect and may change the estimate.
<b>Low</b>	<b>Low confidence that the evidence reflects the true effect.</b> Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
<b>Insufficient</b>	Evidence either is unavailable or does not permit a conclusion.

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## VI. Definition of Terms

The first step is to define the term “incontinence,” which has many different implications for different groups of patients. Treating incontinence as a universal construct may impede understanding of the condition and its treatment. For example, incontinence in younger women occurs most likely because of pelvic floor failure, whereas in frail older women it is often the result of problems with mobility or intellectual performance.

### Definitions of urinary incontinence:

Variable	Definition
Symptoms of urinary incontinence <sup>83</sup>	Any involuntary leakage of urine
Signs of urinary incontinence	Urine leakage seen during physical examination; this leakage may be urethral or extraurethral
Uncategorized incontinence	Involuntary urine leakage that cannot be classified into any of the categories listed above on the basis of signs and symptoms
Transient urinary incontinence <sup>17,100</sup>	Potentially reversible incontinence resulting from conditions that may resolve if the underlying cause is managed: delirium/confusional state; urinary tract infection (symptomatic); atrophic urethritis/vaginitis; use of pharmaceuticals; psychological conditions, especially depression; excessive urine output related to another medical condition (e.g., congestive heart failure, hyperglycemia); restricted mobility; stool impaction
Established urinary incontinence <sup>17,100</sup>	Urinary incontinence that is attributed to bladder or urethral dysfunction, such as: detrusor overactivity; detrusor underactivity; urethral incompetence
Stress urinary incontinence	Involuntary urine leakage on physical exertion or effort or with sneezing or coughing
Urgency urinary incontinence	Involuntary leakage accompanied by or immediately preceded by urgency
Overflow incontinence <sup>101</sup>	Urinary incontinence associated with: bladder overdilatation; a contractile detrusor; hypotonic or underactive detrusor, occurring secondarily to drugs, fecal impaction, diabetes, lower spinal cord injury, or disruption of the motor innervation of the detrusor muscle
Mixed urinary incontinence <sup>1,83</sup>	Involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing
Situational urinary incontinence	Incontinence during sexual intercourse or when giggling

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<b>Variable</b>	<b>Definition</b>
Continuous urinary leakage	Continuous urinary leakage
Acute incontinence <sup>102</sup>	Sudden onset of symptoms related to an illness, treatment, or medication
Chronic incontinence	Persistent urinary incontinence, including disorders of storage (stress and urgency) and of emptying (overflow) and functional and mixed incontinence
Severity of incontinence	Measured as incontinent episodes/unit time; pad changes/unit time; pad weight/unit time; number of micturitions/unit time; urine loss on a pad test. Also indicated by urodynamically diagnosed detrusor overactivity; urodynamic stress incontinence
Sandvik's severity index <sup>103</sup>	Multiplied reported frequency (4 levels) by the amount of leakage (2 levels).
Slight incontinence	Leakage of drops a few times a month (~6 g/24 hours, 95% confidence interval 2–9)
Moderate incontinence	Daily leakage or drops (~17 g/24 hours, 95% confidence interval 13–22)
Severe incontinence	Leakage of large amount of urine at least once a week (~56 g/24 hours, 95% confidence interval 44–67)

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## VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

**NOTE: The following protocol elements are standard procedures for all protocols.**

### VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments.

### IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report, and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

### X. Peer Review (*Standard Language*)

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports, such as reports requested by the Office of Medical Applications of Research, National Institutes of Health, there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.