NCCHTA

07 July 2008

Version 6, 29/01/2008

Draft protocol for a (HTA) systematic review and economic modelling of the effectiveness and efficiency of non-surgical treatment for women with stress urinary incontinence (SUI)

1. Background to SUI

Urinary incontinence is a symptom defined as the complaint of any involuntary leakage of urine (Abrams, Cardozo, Fall et al. 2002). Clinically, it is classified as: (a) stress urinary incontinence (SUI), which is the symptom of urine loss on effort, exertion, coughing or sneezing; (b) urgency urinary incontinence (UUI), which is the symptom of urine loss accompanied by or immediately preceded by urinary urgency; and (c) mixed urinary incontinence (MUI), which is a combination of stress and urgency urinary incontinence. A further classification takes into account findings from urodynamic investigations (particularly cystometry): urodynamic stress incontinence (USI), which is urine loss due to increased abdominal pressure during filling cystometry, in the absence of a detrusor contraction; and detrusor overactivity incontinence (DOI), which is urine loss due to a urodynamically observed detrusor contraction.

SUI is the most common type of incontinence, especially in middle-aged women (Hunskaar et al. 2004). SUI can result from damage to the nerve supply to the bladder sphincter or the pelvic floor muscles, or from direct mechanical trauma to the pelvic floor. Normally, the urethral sphincter mechanisms at the bladder outlet respond to the challenge of increased abdominal pressure by a reflex increase in closure pressure thus preventing a leak. Failure of these mechanisms represents the predominant underlying cause of SUI and is often aggravated by conditions that result in chronically raised intra-abdominal pressure such as obesity and chronic obstructive pulmonary disease.

The risk of urinary incontinence is increased by vaginal delivery, increasing age and parity, obesity and the menopause (Thom, van den Eeeden and Brown 1997;

MacArthur et al. 2006; MacLennan et al. 2000). With respect to SUI, childbearing is considered to be the main predisposing factor, although the exact mechanism of pelvic floor injury or contribution made by pregnancy and parturition in the development of SUI remains debatable (MacLennan et al. 2000; Rortveit et al. 2003). Longitudinal studies have reported that two thirds of women with SUI during their first pregnancy continue to have symptoms at a follow up of 15 years, and having antenatal SUI doubles its risk (Dolan et al. 2003). In a large population-based cross sectional study of premenopausal women, high body mass index (BMI >30), diabetes mellitus, previous urinary incontinence surgery, parity and first delivery under the age of 22 years were reported as significant risk factors for severe SUI (Fritel et al. 2005). A history of gynaecological surgery for prolapse increases the risk of developing SUI over two-fold, while hysterectomy and other gynaecological procedures increase the risk of SUI about 1.5-fold (Hampel et al. 2004).

Studies investigating the prevalence of SUI in women are hampered by differing definitions of SUI, and social factors such as poor help-seeking due to embarrassment. Although the reported prevalence of urinary incontinence ranges between 14 and 57% in the UK (Hunskaar et al. 2004), only 15% of the women identified as suffering from SUI consult a health professional (Shaw et al. 2006; Shaw et al. 2001). Embarrassment associated with urinary incontinence may cause withdrawal from social situations and reduces quality of life (Hunskaar and Vinsnes 1991). Many women with SUI show symptoms of depression and introverted behaviour, together with dysfunctional interpersonal relationships (Norton et al. 1988). Furthermore, SUI may lead to withdrawal from regular physical activities and thus impair women's general health (Nygaard 1990).

Various surgical and non-surgical therapies have been developed with the aim of increasing urethral closure pressure in order to alleviate the symptoms of SUI, improve quality of life and patient satisfaction. The wide range of proposed treatments and the rather disappointing reviews of efficacy suggest that none of the options yet provide the ideal combination of clinical efficacy, high safety, patient satisfaction and low cost (Black et al. 1998).

2. Objectives

This HTA review aims to assess the literature of the effects of the non-surgical treatment of women with SUI. The objectives are:

- To determine the clinical effectiveness of the different conservative treatments for SUI.
- To determine the safety in terms of the magnitude of any risks or side effects of treatments for SUI.
- To estimate the cost-effectiveness of the alternative management pathways.
- To rank the treatments in terms of benefits, risks and cost-effectiveness
- To assess whether treatment or management pathways should differ between women presenting with (a) SUI postpartum or at any other time; (b) SUI alone or mixed urinary incontinence; and (c) SUI with or without the presence of a co-existing anterior vaginal wall prolapse.
- To identify areas for future research

Much of the evidence on clinical effectiveness has already been included in the systematic reviews conducted by the Cochrane Incontinence Group, which has a broader remit of examining treatment for adults (men and women) with all types of urinary incontinence (see Appendix 1). For treatments under study for which Cochrane reviews are available, this HTA review will utilise data reported in the existing Cochrane reviews as the first point of reference. It will also assist in the update of these reviews. For treatments for which Cochrane reviews are not available, we will undertake new systematic reviews using the Cochrane format. Literature searching for these new and updated reviews will be performed within 12 months of submission of the draft final report for HTA (November, 2008)

3. Criteria for considering studies for this review

3.1. Types of studies

The review includes all randomised or quasi-randomised controlled trials of treatment for women with predominantly stress urinary incontinence in which at

least one management arm involves a non-surgical treatment regardless of the length of follow-up. Trial data reported in conference abstracts as well as full-text papers are included. For abstracts, solely those from the Cochrane Incontinence Group Specialised Register of trials will be used – there will be no additional searching performed to identify other potentially relevant conference abstracts from other sources.

3.2. Types of participants

Adult women with any of the following will be included:

- stress urinary incontinence, diagnosed clinically (SUI), or by urodynamics (urodynamic stress incontinence or USI)
- mixed (stress and urge) urinary incontinence (MUI), with stress as predominant pattern
- Undiagnosed, uncategorised or not characterised urinary incontinence, if being given treatment for stress urinary incontinence in a given trial

Classification of diagnoses will be accepted as defined by the trialists.

Studies that primarily focus on patients with urgency urinary incontinence (UUI), overactive bladder syndrome (OAB) or detrusor overactivity (DO) with or without incontinence will be excluded. Studies of women with MUI or undiagnosed urinary incontinence where interventions are designed predominantly for the treatment of UUI (e.g. bladder training) will also be excluded.

Studies of women with urinary incontinence whose symptoms might be due to significant factors outside the urinary tract will be excluded, e.g. neurological disorders, cognitive impairment, lack of independent mobility. Studies investigating nocturnal enuresis in women will also be excluded.

Studies that recruit men and women are eligible for inclusion, providing demographic and outcome data are reported separately for women.

Studies that investigate treatment of SUI specifically for antenatal or postnatal women (up to three months from delivery) and postpartum women (12 months from delivery) will be included. Data from these childbearing women will be subjected to subgroup analysis (see section 5.3), on the assumption that the effect of PFMT might differ in this group due to the physiological changes of pregnancy and in the postpartum period. Studies investigating prevention of incontinence among childbearing women will be excluded.

3.3 Types of interventions

The primary focus will be on non-surgical (conservative) treatments. We define non-surgical treatment as that which could be undertaken in a physician's office, clinic or home. The non-surgical treatments can be classified into the five main groups as shown in Table 1.

Table 1: Type of interventions included in the review

Include	Exclude
Lifestyle interventions	
• Dietary factors • Caffeine • Fluid intake (volume and type, e.g. carbonated drinks) • Smoking • Weight • Physical exercise • Alcohol consumption • Limiting heavy activity • Constipation	
Physical therapy	
• Pelvic floor muscle training (PFMT) alone • PFMT + adjuncts (e.g. biofeedback, perineometer, exercisers, vaginal cones) • Vaginal cones • Electrical stimulation (non-implanted, local stimulation of pelvic floor muscles) • Electromagnetic stimulation	• Electrical nerve stimulation, e.g. transcutaneous electrical nerve stimulation (TENS); and percutaneous electrical stimulation, such as posterior tibial nerve stimulation, percutaneous nerve evaluation
Behavioural therapy	
• Bladder training (if given for SUI patients) • Multi-component therapy, which can include PFMT with other non-specific interventions such as the use of bladder training	• Prompted voiding • Timed voiding
Pharmacotherapy	
• Serotonin and norepinephrine reuptake inhibitors (SNRI) • Local administration (in form of cream or pessaries) of intravaginal low dose oestrogens, given as an adjunct to other therapy (e.g. PFMT) in post-menopausal women	• Adrenergic agonists • Hormonal treatment (oestrogens) given alone • Injectable agents (usual agents such as collagen, as well as upcoming technologies such as myoblasts and stem cells) though it is recognised that these procedures would not be necessarily performed in an operating theatre.
Non-therapeutic interventions	
• Mechanical devices designed to control urinary leakage by being inserted within the urethra or vagina or applied to the external surface of the urethra, e.g. pessaries or tampons • Containment/absorbent pads • Catheters and simple collecting devices (their main roles are diversion and hygienic collection of the urinary stream)	

Trials comparing methods of delivering services (e.g. nurse-led care) are also considered for inclusion, if they involve one of the included interventions listed above.

A valid comparator is one of the included interventions or no treatment. Studies will be excluded if the comparator is an excluded intervention (e.g. PFMT vs. adrenergic agonists). However, where non-surgical interventions have been compared with surgical interventions, a surgical intervention may be included as a comparison in order to enable the performance of indirect comparisons of non-surgical treatment.

The use of non-surgical therapies for prevention of incontinence is excluded. Complementary therapies such as acupuncture, hypnosis and herbal medicines are also excluded.

3.4 Types of outcome measures

One of the problems with the assessment of incontinence is that there is no standard method of measurement. Outcomes measures to be used in this review are therefore guided by the Standardisation Committee of the International Continence Society's recommendations on the outcome domains of research investigating the effect of therapeutic interventions for women with urinary incontinence (Lose 1998). These outcomes domains include:

(1) the women's observation (symptoms, e.g. frequency, quantity or magnitude)
(2) quantification of symptoms (e.g. diary, pad-weighing test)
(3) the clinician's observations (anatomical and functional, e.g. pelvic muscle activity, cystometry)
(4) quality of life
(5) socioeconomic measures.

The principal measures of effectiveness are the proportion of women whose symptoms are 'cured' (continent or dry) or 'improved' following treatment. Using this definition usually implies the patient self-report of the presence or absence of

incontinence. However, objective measures that may provide an estimate for cure rates will also be sought. Other data that may reflect women's quality of life after treatment will also be important.

Data for the following outcome measures will be sought:

A. Women's observations

- Number not cured (worse/unchanged/improved versus cured)
  - Within first year
  - After first year
- Number not improved (worse/unchanged versus improved/cured)
  - Within first year
  - After first year
- Participant satisfaction/Desire for further treatment
  - Within first year
  - After first year

B. Quantification of symptoms (using urinary diary, bladder chart, visual analogue score, etc.)

- Number of incontinent episodes over 24 hours
- Number of pad changes over 24 hours
- Mean volume or weight of urine loss on pad test (short-term office tests performed under standardised conditions or long-term tests usually performed by the patient at home during 24-28 hours)
- Number of micturitions over 24 hours

C. Clinicians' observations

- Number not cured (objective test, e.g. urodynamics, visual confirmation)
  - Within first year
  - After first year
- Long-term outcomes (12 months or more)
  - Number having incontinence surgery
  - Return of symptoms (recurrence)

D. Quality of life

- General health status measures, e.g. Short Form 36 (Ware 1993)
  - Within first year
  - After first year
- Condition-specific health measures (specific instruments designed to assess urinary incontinence)
  - Within first year
  - After first year

E. Socioeconomic measures

- Health economic measures, e.g.
  - GP/hospital visits (number)
  - Additional medications/interventions received (type and number)
  - Number of inpatient visits (LOS)
- Process of care outcomes:
  - Description of consumables (type and number)
  - Description of equipment (type and number)
  - Staff (grade, number and time)
  - Sessions of treatment (number and duration)
  - Care provider (type and number)
  - Number of contractions per day (PFMT)
  - Frequency and pulse duration (electrical stimulation)
  - Dose (drugs)

F. Adverse effects

- Number experiencing adverse effects (total, any)
- Number experiencing adverse effects causing withdrawal from treatment (i.e. treatment adherence)
- Rare serious adverse effects (if reported in trial reports; no additional search will be performed for the effectiveness review)

H. Other intermediate or explanatory outcomes

- Treatment-specific outcomes

- *Measure of pelvic floor muscle function, e.g. electromyography, vaginal squeeze pressure*
- Volume and type of fluid intake
- Change in BMI

- Other non pre-specified outcomes judged important when performing the review

4. Search strategy for identification of studies

An extensive electronic search will be carried out to identify reports of relevant published and ongoing studies as well as grey literature and recent meeting abstracts included in the Cochrane Incontinence Group Specialised Register. A highly sensitive search strategy based upon the one developed for the Cochrane Incontinence Review Group will be adopted (Grant et al. 2000). Searches will be performed for any RCTs (and quasi-RCTs) required to update existing relevant Cochrane Reviews and for RCTs relevant to comparisons for which Cochrane Reviews are not currently available. For relevant reviews of active non-surgical management, searches will be performed within 12 months of submission of the draft final report for this study (November 2008). For non-active management (mechanical devices, absorbent products and catheters), the Cochrane Reviews will be accepted as published with no updates or extra searches.

Relevant trials will be identified from the Cochrane Incontinence Group's Specialised Register of controlled trials of interventions for urinary incontinence. The register contains trials identified from: MEDLINE (covering January 1966 onwards), the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (covering January 1982 to December 2000) and from hand searching relevant journals and conference proceedings. Searches of MEDLINE, MEDLINE Extra and CENTRAL are updated on a regular basis.

Highly sensitive search strategies will also be developed that use controlled vocabulary and text word terms that reflect the clinical condition, interventional procedures and study designs that are also considered within the scope of this

project, for use in bibliographic databases not currently covered by the Specialised Register. The following additional databases will be searched:

- CINAHL (January 1982 onwards)
- EMBASE (1980 onwards)
- BIOSIS (1985 onwards)
- Science Citation Index (1981 onwards)
- HTA database
- the National Research Register
- Current Controlled Trials
- ClinicalTrials.gov

In addition:

- the Health Management Information Consortium (1983 onwards) and
- NHS Economic Evaluations Database

will be searched for the economic evaluation component.

An Internet search will include the websites of relevant professional organisations, manufacturers and any additional relevant conference proceedings that have not been covered by the Specialised Register hand searching or the database searches. There will be no language or date restriction.

Plan of Action

Seven main searches are planned:

Intervention	**Planned search**
Lifestyles for SUI + MUI	No published Cochrane Review – substantial searching may be required
PFMT (+ vaginal cones) for SUI + MUI	One published and two ongoing Cochrane reviews, 2 more required -- substantial searching may be required
Electrical stimulation (non-implanted) for SUI + MUI	No published Cochrane Review – substantial searching may be required
Electromagnetic stimulation for SUI + MUI	Cochrane protocol recently published – liaise with Cochrane reviewers. This treatment is not available on the NHS accordingly will rely on the Cochrane review authors to produce this – no extra searching required.

Behavioural therapy for SUI + MUI	Cochrane Review on bladder training recently updated – searching to update this review will be required
SNRI for SUI + MUI	Cochrane Review recently updated – searching to update this review will be required
Injectables for SUI + MUI	Cochrane Review recently updated. Some debate about classification of this intervention as surgical or non-surgical – decided to use the published Cochrane Review with no extra searching required.

No extra specific searches for oestrogens will be performed, as they are only included if given as an adjunct to one of the seven included interventions.

There will be no additional searching performed to identify trials comparing methods of delivering care, as again they are only included if they involve one of the included interventions.

The Specialised Register searches of MEDLINE, MEDLINE Extra and CENTRAL will be updated and lists (with abstracts) of any new trials (listed by intervention) that may be eligible for the above reviews will be assessed.

Searches will be run for each of the intervention areas listed above on each of the databases listed. The main searches will be run during September/October/November with updates in December 2007/January-February 2008 (this is in line with the timelines sheet). A set of urinary incontinence terms will be combined with a set of terms to cover the five main interventions listed above. These terms will be combined with a study design filter as appropriate for each database – InterTasc website design filters will be assessed and used if suitable (http://www.york.ac.uk/inst/crd/intertasc/).

Database	Lifestyles	PFMT	Electric stimulation	Vaginal cones	SNRI	Delivery of care (only in relation to one of the included interventions	Behavioural including bladder training
CINAHL (January 1982 onwards)							
EMBASE (1980 onwards)							
BIOSIS (1985 onwards)							
Science Citation Index (1981 onward)							
HTA database							
National Research Register							
Current Controlled Trials							
ClinicalTrials.gov							
Health Management Information Consortium (1983 onwards)							
NHS Economic Evaluations Database							

5. Methods of the review

5.1. Data extraction

	Method (1) Data extraction from individual studies	**Method (2) Data extraction from Cochrane Reviews**
(A) Interventions for which Cochrane Reviews are not currently available	YES	
(B) Interventions for which Cochrane Reviews exist but require minor update	YES (for minor update)	YES
(C) Interventions for which Cochrane Reviews exist		YES

(1) Data extraction from individual studies

Two reviewers will independently screen the titles and abstracts of all items identified by the search strategy. Full-text copies of all potentially relevant reports will be obtained and independently assessed by two reviewers, to determine whether they meet the inclusion criteria. Any disagreements will be resolved by consensus or arbitration by a third person. Two reviewers will independently extract details of study design, methods, participants, interventions, and outcomes onto data extraction forms developed for the review (One reviewer will check all papers, and the second reviewers vary depending on the topic).

(2) Data extraction from existing Cochrane Reviews

Two reviewers will screen the individual studies included in the relevant Cochrane Reviews to determine whether they meet the inclusion criteria of the present (HTA) review. Any disagreements will be resolved by consensus or arbitration by a third person. Provided that any data published in the Cochrane reviews have already been scrutinised by multiple reviewers (double data extraction), one reviewer will extract the summary data reported in the published Cochrane reviews wherever possible. The same reviewer will then check

extracted data against the original articles and extract additional data, if necessary, using the same data extraction forms as described above.

5.2. Quality assessment

All included randomised and quasi-randomised studies that have been included in the existing Cochrane reviews have already been assessed independently by two reviewers in terms of their methodological quality, using the Cochrane Incontinence Group's assessment criteria (Grant et al. 2000). Given this, for the present (HTA) review, only one reviewer will extract assessment details from the published reviews using an adapted version of the same checklist.

For individual studies that have not been included in any of the existing Cochrane reviews, two reviewers will independently assess the quality of all included studies using the same checklist as described above.

To enable subgroup analysis, the following patients' characteristics will be sought:

- Age
- Nature of the incontinence (SUI or USI versus MUI)
- % postpartum women (within 12 months of childbirth)
- % women with a co-existing vaginal wall prolapse

To assess baseline comparability of the intervention and control groups in each of the included studies and to identify potential prognostic factors, data on the following patients' baseline characteristics will also be sought, provided that these are routinely recorded in the existing Cochrane reviews:

- Ethnicity
- BMI
- Education
- Employment status
- Parity
- Severity of symptoms, e.g. mild/moderate/severe

- % postmenopausal women
- Previous incontinence (urogynecological) surgery

5.3. Data analysis

Data analysis will be performed in two stages:

(1) Pair-wise (head-to-head) comparisons, using direct evidence, with subgroup analysis, if appropriate;

(2) Multiple treatments comparison (if possible).

(1) Pair-wise (head-to-head) comparisons

Each treatment comparison will be considered in turn, using direct evidence only. All data will be tabulated. Trial data will be grouped by type of incontinence: either (1) stress urinary incontinence (SUI or USI) or (2) Mixed or any urinary incontinence. A fixed effect model will be used to derive summary estimates with 95% confidence intervals of relative risk for dichotomous variables and weighted mean difference for continuous variables. Where an alternative summary measure is used reasoning will be given. Heterogeneity between studies will be assessed by visual inspection of plots of the data, the χ^2 test for heterogeneity and the I^2 statistic. Possible reasons for heterogeneity will be explored, such as differences in the populations studied, the treatment given, or the way in which the outcomes were assessed. Where there is no clear reason for any heterogeneity observed a random effects models will be used, if appropriate. Where a quantitative synthesis is considered to be inappropriate or not feasible, then a narrative synthesis of the results will be provided. Initial analysis will be performed in STATA due to its greater flexibility and ease of data manipulation.

Subgroup analysis

If sufficient data are available, subgroup analysis will be performed. The subgroups of interest may include:

- Nature of presentation: postpartum (within 12 months of childbirth) versus at any other time.
- Nature of the incontinence: SUI alone versus mixed/any urinary incontinence.
- Presence or absence of a co-existing anterior vaginal wall prolapse.

Subgroup analysis will be performed using STATA.

(2) Multiple Treatment Comparison

Although the review aims to assess the effectiveness of several treatments for SUI, the direct head-to-head comparisons for some of the treatments are likely to be limited. Evidence that does exist from direct comparisons of treatments, however, does not always allow us to identify which treatment is 'best' on selected outcomes. Therefore, within the data available from our systematic review, we will seek to analyse the data with a multiple treatment comparison model which incorporates indirect evidence of all eligible treatments (Caldwell, Ades and Higgins, 2005).

The objective of this model is to assess which treatment may be 'best' on the selected outcomes. The advantages of using this type of model are that the data are supplemented with an indirect estimate of the benefit of a particular treatment where no direct evidence exists and that a single analysis is performed, simultaneously comparing all eligible treatments by incorporating direct and indirect evidence.

This method will be used for key treatments and outcomes (e.g. cure rates) selected on the basis of data quality and availability as well as clinical relevance. A Bayesian model will be used (Caldwell, Ades and Higgins 2005). Differences between interventions will be assessed by the corresponding odds ratios and 95% credible intervals. WinBUGS software (Lunn et al., 2000) will be used to perform the analysis.

The multiple treatment comparison analysis will be performed in three stages:

a) Set up a database,

b) Perform multiple treatment comparison,

c) Undertake checks for consistency of direct and indirect evidence.

We would then attempt to derive results in the format shown in Table 3 (adapted from Caldwell, Ades and Higgins (2005), Table 2), although this would depend on the quality and availability of data gathered in our systematic review.

Table 3: Provisional results table template

	Fixed effect		**Random effect**	
Treatment comparisons	**Direct comparisons**	**Multiple comparison**	**Direct comparisons**	**Multiple comparison**
PFMT-1 vs.	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Lifestyle-1				
ES-1				
Drug-1				
PFMT+Drug				
Surgery-1				
Lifestyle-1 vs.				
ES-1				
Drug-1				
PFMT+Drug				
Surgery-1				
ES-1 vs.				
Drug-1				
PFMT+Drug				
Surgery-1				
Drug vs.				
PFMT+Drug				
Surgery-1				
PFMT+Drug				
Surgery-1				

Note: PFMT = pelvic floor muscle training; ES = electrical stimulation

6. Report methods for synthesising evidence of cost-effectiveness

The economic model described in section 6.2 below will compare alternative strategies in terms of treatment of women with SUI. Some of the data required for this will be obtained from the systematic review of clinical effectiveness

described above. Other data will be obtained from a structured review of the non-surgical management of people with SUI with associated costs and outcomes. Further data will be obtained from a review of evidence-based guidelines for the management of SUI that are relevant to the UK. The review is structured rather than systematic, as it will attempt to identify data relevant to the UK in a transparent and reproducible manner. Costs of treatment will be estimated by combining estimates of the use of care with appropriate unit costs. The methods used to obtain these unit costs are briefly described in the following section.

6.1 Identifying and systematically reviewing published cost-effectiveness studies

Given the number of relevant comparators, a formal systematic review of existing economic evaluations will not be attempted, as it is highly unlikely that any economic evaluations will have been conducted that will have considered all comparators from the perspective of the UK NHS. Also a quick search of the NHS EED databases indicated that, although there was one cost-effectiveness study performed on the non-surgical treatment and management of SUI, it may not be generalisable to the UK setting.

6.2 Evaluation of costs and cost-effectiveness

Economic modelling will be performed to estimate the cost-effectiveness of the strategies developed from the care pathways developed using the methods described above**.** This model will display the temporal and logical sequence of the clinical decision problem by describing the pathway of individuals covering the period of first and second line non-surgical treatment, the costs and consequences of any subsequent outcomes including further follow-up and surgical treatment. The structure of the economic model will be based upon the consideration of the strengths and weaknesses of the previously conducted evaluations based on modelling exercises conducted in this area. The economic model represents a further level of evidence synthesis that will integrate information on the relative effectiveness of the treatments derived from the

systematic review of clinical effectiveness along with other published information derived using the methods described above.

The modelling exercise will consist of a long-term Markov state transition model that will be developed to reflect the consequences of each strategy in terms of follow-up of patients with SUI and subsequent costs and outcomes. The data required for this model are likely to relate to the primary outcome which is subjective (self reported) cure or improvement and objective cure (using methods of measuring urine loss such as pad weights) as a secondary outcome as well as the effectiveness of treatment in the follow-up of women with SUI. These data will be derived from the systematic review of clinical effectiveness and the structured review of guidelines and other evidence. The model will be based on a hypothetical cohort of patients presenting with SUI. This cohort of people will be followed up in the model for the remainder of their lives, although cumulative costs and outcomes may also be presented for shorter time horizons, depending upon the nature of the available data. Depending on the availability of data, sub-group analysis may be performed.

With respect to the cost data required for the model the primary perspective for the costing will be the NHS and Personal Social Services. Cost data, therefore, will include the direct health service costs associated with each treatment strategy and the costs of treatment and subsequent follow-up. The following resource use data will be required to estimate costs incurred by the NHS for treatment: care provider, primary or secondary care, type of staff, consumables, length of treatment/number of visits, relevant overheads and capital charges associated with each treatment, and all the resources associated with any subsequent patient follow-up and management. The quantity of resources utilised will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. We anticipate that unit cost data will be extracted from the literature or obtained from other relevant sources (e.g. manufacturer price lists, NHS reference costs).

The results of the model will be presented in terms of a cost-consequence analysis (e.g. number of people who get cured of SUI). Depending on the availability of data, cost-effectiveness analysis may also be conducted, where the results are presented in terms of an incremental cost per unit change in a natural or clinical measure of outcome such as incremental cost per case correctly treated. Where appropriate, costs and outcomes will be discounted at 3.5%. An attempt will be made to identify quality of life weights associated with the different outcomes of treatments in order to extend the economic evaluation into a cost-utility analysis. A focused search of the literature and other relevant sources (e.g. the Harvard Database of Cost-utility Analyses) will be performed to identify if there are any quality of life data relevant to a UK setting. If sufficient data are available, different outcomes will be ascribed utility values and quality adjusted life years (QALYs) will be estimated.

Probabilistic and deterministic sensitivity analysis will be applied to the model in order to assess the robustness of the results to realistic variations in the levels of the underlying data. Cost per unit of case cured and cost per QALY data will be presented in terms of cost-effectiveness acceptability curves (CEACs). Where the overall results are sensitive to a particular variable, the sensitivity analysis will be reported. Such analysis may involve changes to the structure and the parameter inputs (cure rates, resource use, unit costs, utilities) used in the economic model. Finally, the results of the evaluation will be used to estimate the cost implications to the NHS of using the method which the review of clinical effectiveness finds to be the optimal intervention.

7. Timescale (16.5 months)

Jul-Sep 2007	Develop the protocol, conduct and analyse the survey of members of Incontact, build the initial structure of the model, develop and run literature searches, agree tools for data extraction and quality assessment
Oct 2007-Feb 2008	Systematic review of the effects of the treatments under consideration (Data collection)

Mar 2008 - mid-Sep 2008 Data analyses using the meta-analysis and the economic model, including sensitivity analyses

Mid-Sep 2008 - 15 Nov 2008 Interpretation of data, report writing and delivery of the report to NCCHTA

Key dates:

- Start of project 01/07/2007
- 1st collaborators meeting 14/09/2007
- Progress report (HTA) 01/03/2008
- ICI meeting in Paris 5-8 July 2008
- 2nd collaborators meeting September 2008
- Final HTA report due 15/11/2008

8. Alphabetical list of review team members

Abrams, Paul
Bain, Christine
Buckley, Brian
Cardozo, Linda
Cody, June
Cook, Jonathan
Eustice, Sharon
Glazener, Cathryn
Grant, Adrian
Hay-Smith, Jean
Hislop, Jennifer
Imamura, Mari
Jenkinson, David
Kilonzo, Mary
Mowatt, Graham

Nabi, Ghulam

N'Dow, James

Pickard, Robert

Vale, Luke

Wallace, Sheila

Wardle, Judith

Zhu, Shihua,

9. Competing interests of authors

10. References

Abrams P, Cardozo L, Fall M. *et al*. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Am J Obstet Gynecol, 2002 187: 116.

Black N, Bowling A, Griffiths J, *et al*. Impact of surgery for stress incontinence on the social lives of women. Br J Obstet Gynaecol, 1998. 105: 605.

Caldwell D, Ades A, Higgins J. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005;331:897-900.

Dolan L, Hosker G, Mallett V, *et al*. Stress incontinence and pelvic floor neurophysiology 15 years after the first delivery. Br J Obstet Gynaecol, 2003. 110: 1107.

Fritel X, Ringa V, Varnoux N, *et al*. Mode of delivery and severe stress incontinence. A cross-sectional study among 2,625 perimenopausal women. Br J Obstet Gynaecol, 2005. 112: 1646.

Grant AM, Cody DJ, Glazener CMA, Hay-Smith J, Herbison P, Lapitan MC, Moore KN, Norton C, Wallace SA, Wilson PD (eds). Cochrane Incontinence Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2000, Issue 4. Art. No.: INCONT

Hampel C, Artibani W, Espuna Pons M, *et al*. Understanding the burden of stress urinary incontinence in Europe: a qualitative review of the literature. Eur Urol, 2004. 46: 15.

Hunskaar S, Lose G, Sykes D. *et al*. The prevalence of urinary incontinence in women in four European countries. Br J Urol Int, 2004. 93: 324.

Hunskaar S, Vinsnes A. The quality of life in women with urinary incontinence as measured by the sickness impact profile. J Am Geriatr Soc, 1991. 39: 378.

Lose G, Fantl JA, Victor A, Walter S, Wells TL, Wyman J, et al. Outcome measures for research in adult women with symptoms of lower urinary tract dysfunction. Neurourology andUrodynamics 1998; 17(3):255-62.

Lunn DJ, Thomas A, Best N, and Spiegelhalter D. WinBUGS – a Bayesian modelling framework: concepts, structure, and extensibility. Statistics and Computing 2000; 10:325-337

MacArthur C, Glazener C, Wilson P, Lancashire R, Herbison G, Grant A. Persistent urinary incontinence and delivery mode history: a six year longitudinal study. Br J Obstet Gynaecol 2006. 113 (2):218-224.

MacLennan A, Taylor A, Wilson D, Wilson D. The prevalence of pelvic floor disorders and their relationship to gender, age, parity and mode of delivery. Br J Obstet Gynaecol 2000. 107 (12):1460-1470.

Norton P, MacDonald L, Sedgwick P *et al*. Distress and delay associated with urinary incontinence, frequency, and urgency in women. BMJ 1988. 297: 1187.

Nygaard, I., DeLancey, J. O., Arnsdorf, L. *et al*.: Exercise and incontinence. Obstet Gynecol, 1990. 75: 848.

Rortveit G, Daltveit A, Hannestad Y, *et al*. Urinary incontinence after vaginal delivery or cesarean section. N Engl J Med, 2003. 348: 900.

Shaw C, Das Gupta R, Williams K, *et al*. A survey of help-seeking and treatment provision in women with stress urinary incontinence. Br J Urol Int, 2006. 97: 752.

Shaw C, Tansey R, Jackson C, *et al*. Barriers to help seeking in people with urinary symptoms. Fam Pract, 2001. 18: 48.

Thom D, van den Eeden S, Brown J. Evaluation of parturition and other reproductive variables as risk factors for urinary incontinence in later life. Obstet & Gynecol 1997. 90 (6):983-989.

Appendix 1: Status of existing Cochrane reviews of non-surgical treatment for women with urinary incontinence

Relevance to HTA report				*Intervention*	*Existing Cochrane review (last search date)*	*Inclusion criteria for Cochrane reviews (Types of participants)*	*Notes*
Substantial	*Minor update*	*No update*	*Not relevant*				
				Lifestyle			
√				Lifestyle	Nygaard, 2002 (protocol) 6 trials (last search Aug 2003?)	Adults (men and women) with urinary incontinence OR Women with urinary incontinence, or urinary frequency and urgency (i.e. OAB, overactive bladder)	Mandy Wells to act as a co-reviewer.
				Physical			
	√			PFMT (pelvic floor muscle training) ± biofeedback (BF) vs. no treatment	Issue 1, 2006 (searched Dec 2004). 13 trials, N=714	Women with SUI, UUI or MUI Exclusion (1) antenatal or postnatal women (<3 months of delivery), (2) incontinence due to factors outside the urinary tract, e.g. neurological disorders, cognitive impairment and lack of independent mobility; (3) studies on nocturnal enuresis in women	Update due end 2007 by Chantale Dumoulin (lead) and Jean Hay-Smith
	√			One type of PFMT vs. another PFMT	No published review		Ongoing: due end 2007 by Jean Hay-Smith, Rebecca George and Chantale Dumoulin
√				PFMT (±BF) vs. other single treatment	No published review		Reviewers: Anand Patel (Sheffield, lead), Sam Datta, Elias Kovoor. Draft protocol received.
√				PFMT (±BF) + OTHER vs. PFMT	No published review		NO REVIEWERS
			√	PFMT (±BF) + OTHER vs. OTHER	No published review		Reviewers: Kovoor ET, Datta SN, Patel AK. Draft protocol received.

Relevance to HTA report							
Substantial	*Minor update*	*No update*	*Not relevant*	*Intervention*	*Existing Cochrane review (last search date)*	*Inclusion criteria for Cochrane reviews (Types of participants)*	*Notes*
	√			PFMT (±BF) for childbearing women (treatment, not prevention)	No published review		Ongoing (review drafted) by Hay-Smith.
	√			Electric stimulation	Berghmans, in editorial process (last search Aug 2006). 26 trials	Men and women with SUI, DO with UI, UUI or MUI; **full-text papers only**	Data extraction and analysis may be required. Revised draft received
?				Electro-magnetic simulation	Khazali. Protocol published.	Men and women with urinary incontinence regardless of type of incontinence or criteria for diagnosis.	Cochrane author contacted
	√			Vaginal cones	Herbison. Issue 2, 2006 (searched Oct 2005). 16 trials, N=1246	Women whose predominant complaint is SUI.	Update due 2, 2008 (April) May be considered as one type of muscle training
				Behavioural			
	√			Bladder training	Wallace, Issue 1, 2007 (searched March 2006) 12 trials, N = 1473	Men and women with any type of urinary incontinence	

Relevance to HTA report							
Substantial	*Minor update*	*No update*	*Not relevant*	*Intervention*	*Existing Cochrane review (last search date)*	*Inclusion criteria for Cochrane reviews (Types of participants)*	*Notes*
				Phamacotherapy			
	√			Serotonin and noradrenaline reuptake inhibitors (SNRI)	Mariappan. Issue 3, 2005 (Searched Dec 2004). 9 trials, N=3327 (5 comparisons)	Men and women with SUI, USI (urodynamic stress incontinence) or MUI	Update submitted for publication in Issue 4, 2007 (October) of the Cochrane Library.
	√ ?		?	Injectables	Keegan, Issue 3, 2007 (searched Feb 2007) 12 trials, N = 1318	Women with urinary incontinence	
			√	Adrenergic agonists	Alhasso. Issue 3, 2005 (Mar 2005). 22 trials, N=1099	Men and women with urinary incontinence	Update due 3, 2007 by Ammar & Charis.
			√	Oestrogens	Moehrer. Issue 2, 2003 (searched Nov 2002). 28 trials, N=2926	Women with SUI, UUI or MUI	Update due 2, 2008 by Charis.
				Non-therapeutic			

Relevance to HTA report							
Substantial	*Minor update*	*No update*	*Not relevant*	*Intervention*	*Existing Cochrane review (last search date)*	*Inclusion criteria for Cochrane reviews (Types of participants)*	*Notes*
		√		Containment/ absorbent products for light incontinence	Fader, Issue 2, 2007 (searched Mar 2005) 1 study, N = 85	Women with light urinary incontinence (urine loss that can be contained within a small absorbent pad, typically 50 g to 500 g; ISO 1996)	Fader (2007) assesses the effectiveness of different types of absorbent product. The included trial had no 'no treatment' arm.
		√		Containment/ absorbent products for heavy incontinence	Under revision. Due 3, 2007?		
		√		Mechanical devices	Shaikh. Issue 2, 2006 (searched Dec 2005). 6 trials (1 with 3 arms), N=286	Women with SUI, UUI or other incontinence	Update due 2, 2008 (April). May not need further update. Probably a sub-group for those not fit or willing to undergo surgery. The review by Shaikh (2006) found 2 small trials comparing a device with no treatment, with data available from one trial on one outcome only (pad weight test), and 5 trials comparing different types of device. There were no trials comparing a mechanical device with another type of treatment.
		√		Tampons	Part of published mechanical devices review	See above	See above

Relevance to HTA report							
Substantial	*Minor update*	*No update*	*Not relevant*	*Intervention*	*Existing Cochrane review (last search date)*	*Inclusion criteria for Cochrane reviews (Types of participants)*	*Notes*
		√		Catheters (long-term)	Jahn, Issue 3, 2007 (searched Dec 2004) 3 trials, N = 102	Adults with indwelling urethral or suprapubic catheters for more than thirty days, irrespective of primary disease and care setting	Types of indwelling urinary catheters for long-term bladder drainage in adults
		√		Catheters (long-term)	Niël-Weise, Issue 2, 2006 (searched Jan 2006) 7 trials, N = 328	All patients requiring long-term (>14 days) catheterisation for urinary incontinence or retention that cannot be managed by another method, e.g. people suffering from SUI, UUI and MUI, dementia, prostatic hypertrophy unsuitable for other management, stroke, neurological problems, spinal cord injury and spina bifida. They may receive this care at home, in residential homes or in hospital.	Urinary catheter policies for long-term bladder drainage Other Catheter reviews are either short-term or include neurogenic bladder disorders so not relevant