Project reference: 15/09/06

The Effectiveness and cost-effectiveness of Surgical Treatments for womEn with stRess urinary incontinence: An evidence synthesis (ESTER)

Protocol v1.0 4th July 2016

The Effectiveness and cost-effectiveness of Surgical Treatments for womEn with stRess urinary incontinence: An evidence synthesis (ESTER)

Summary of research

Aim: The aim of this research is to evaluate the clinical effectiveness, safety and cost-effectiveness of surgical treatment for stress and stress-predominant mixed urinary incontinence in women.

Background: Urinary incontinence in women is a distressing and common condition which restricts quality of life and results in a large economic burden in terms of both use of NHS resources and to women themselves. The prevalence of urinary incontinence varies during life but is greater in women who have had children and in older women (20 to 50%). It is estimated that women have a 10% life-time risk of having continence surgery and the number of women having surgery is rising as the older population increases. The choice of operation has changed over the last decade as more minimally invasive techniques have been pioneered. Consequently, the majority of women now have minimally-invasive mid-urethral sling surgery and, because of its perceived safety and efficacy, there has been a substantial increase in the total number of women having continence surgery.

There are several types of urinary incontinence. The precise economic burden of these in totality has proved difficult to calculate: however estimates for stress urinary incontinence alone (the main focus of this proposal) range from £818 million for combined health, personal and societal expenditure, to £117 million per year for health care costs alone.

The aim of surgery is to support or partially obstruct the bladder neck and/or urethra, thus blocking the leakage of urine on exertion or coughing. There are several surgical treatment options, with a number of variations of most techniques. Essentially they fall into nine distinct categories, each of which will be evaluated in this research.

Recent concerns regarding supposed long-term severe adverse effects from common mesh procedures have caused anxiety in women and uncertainty for clinicians and decision-makers. There is, however, no clear evidence to support or reduce this uncertainty. Further research may be required to fully address this uncertainty: however as a first step a comprehensive evidence synthesis is needed to ensure that there is clarity regarding the totality of the evidence and to ensure that any further research is optimally designed to reduce the uncertainty faced by decision-makers.

Methods: A systematic review of clinical effectiveness and safety will be undertaken following well established, robust methodology. Network meta-analysis methodology will be used to combine direct and indirect evidence, where a network of trials exists, to allow an estimate of treatment effects for interventions where no direct head-to-head clinical trials have been conducted. This analysis will provide relative treatment effects for all comparisons. In addition, an economic model of the alternative surgical techniques will be developed. The model will be used to estimate the cost-effectiveness of the alternative techniques and to undertake a value of information analysis. The model will be parameterised using data from the systematic review, network meta-analysis and appropriate cost sources.

Results: The results obtained will enable decision-makers to identify which type of surgery is most clinically effective, safest for the patient and most cost-effective for the NHS. The value of information analysis will allow us to quantify both the main uncertainties facing decision-makers and quantify the value of undertaking further research.

The Effectiveness and cost-effectiveness of Surgical Treatments for womEn with stRess urinary incontinence: An evidence synthesis (ESTER)

1. Aim

To evaluate the clinical effectiveness, safety and cost-effectiveness of surgical treatment for stress and stress-predominant mixed urinary incontinence in women.

2. Objectives

We will meet our aim by undertaking a comprehensive evidence synthesis to assess the clinical effectiveness, safety and cost-effectiveness of surgical interventions for the treatment of stress and stress-predominant mixed urinary incontinence in women. This will include meeting the following objectives:

- An evidence synthesis including a network meta-analysis to estimate the relative clinical effectiveness of the different types of surgery and to inform key clinical parameters for a decision model.
- A review of safety/adverse effects associated with each type of surgical intervention.
- The development of a decision model to estimate the cost-effectiveness of surgical treatments for stress and stress-predominant mixed urinary incontinence and undertake a value of information (VOI) analysis to assess the need for further primary research.

3. Background

Urinary incontinence (UI) in women is a distressing and common condition which restricts quality of life and results in a large economic burden in terms of both use of NHS resources (surgery, physiotherapy, drugs and containment products), admission to residential care, and consequent high dependency on staff/carers, and to women in terms of use of containment products, loss of ability to work and engage in social and physical activity, dependence on family, friends and carers, sexual dysfunction and loss of self-esteem. The precise economic burden has proved difficult to calculate. One published UK study, however, suggests an estimated total figure for combined health, personal and societal expenditure of £818 million for stress urinary incontinence;(1) whilst another suggested a health care cost to the UK NHS (stress urinary incontinence only) of £117 million per year.(2)

The prevalence of UI varies during life but is greater in women who have had children and in older women (20 to 50%).(3) Conservative treatment with physiotherapy to deliver pelvic floor exercises and bladder training is accessed initially by many women but when this fails, surgery is the mainstay of treatment. It is estimated that women have a 10% life-time risk of having continence surgery.

The aim of surgery is to support or partially obstruct the bladder neck and/or urethra, thus blocking the leakage of urine on exertion or coughing (SUI). Women with mixed urinary incontinence (MUI), who also have urgency urinary incontinence (UUI), may also be helped because they are better able to defer voiding and leakage. However, urinary urgency and UUI can be caused by or made worse by stress incontinence surgery.(3)

There are several different types of urinary incontinence, which are defined according to the International Continence Society as:(4)

- Urinary incontinence (UI): involuntary loss of urine.
- Stress urinary incontinence (SUI): involuntary loss of urine on effort or physical exertion e.g. sporting activities, or on sneezing or coughing. (N.B. ‘‘activity-related incontinence’’ is an alternative which avoids confusion with psychological stress).
- Urgency urinary incontinence (UUI): involuntary loss of urine associated with urgency.
- Mixed urinary incontinence (MUI): involuntary loss of urine associated with urgency (UUI) and also with effort or physical exertion or on sneezing or coughing (SUI).
- Postural urinary incontinence (PUI): involuntary loss of urine associated with change of body position, for example, rising from a seated or lying position.
- Nocturnal enuresis (NE): involuntary loss of urine which occurs during sleep.
- Continuous urinary incontinence (CUI): continuous involuntary loss of urine.
- Insensible urinary incontinence (ISI): urinary incontinence where the woman has been unaware of how it occurred.
- Coital incontinence: involuntary loss of urine with coitus. This symptom can be further divided into that occurring with penetration or intromission, and that occurring at orgasm.

This proposal will focus specifically on women with stress urinary incontinence (SUI) and stress-predominant mixed incontinence (MUI) who require a surgical treatment. There are several surgical treatment options for the management of these women. Further, there are a number of variations on most techniques, but essentially they fall into nine distinct categories, each of which has been previously evaluated in a Cochrane systematic review:

- anterior vaginal repair (anterior colporrhaphy)(5)
- bladder neck needle suspensions(6)
- open abdominal retropubic colposuspension(7)
- laparoscopic retropubic colposuspension(8)
- traditional suburethral retropubic sling procedures;(9)
- mid-urethral sling (MUS) procedures (two distinct categories):(10)
    - retropubic MUS and
    - transobturator MUS
- single incision sling procedures (‘mini-slings’)(11)
- peri-urethral injections (injectable bulking agents)(12)

One of the earliest operations described for SUI was anterior repair with urethral buttressing sutures (Kelly sutures). While curing over half of women, the high failure rate (and that of another operation, bladder neck needle suspension) led to the development of colposuspension, which is an open abdominal method of elevating the bladder neck. The evidence base suggested this was more effective but with greater morbidity and a longer recovery time than the previous options. Laparoscopic colposuspension, while being a minimally invasive variation of colposuspension, was slightly less effective than the open surgery. These issues led to the development of traditional suburethral slings, where a piece of material which could be biological (such as a rectus sheath graft) or synthetic (such as a polypropylene mesh sling) is placed under the urethra and the free ends secured in a number of different ways. The advent of a new minimally invasive technique which enabled the sling to be placed without tension ushered in a new era of simpler, effective and also cheaper treatment. This brief summary of the evidence concurs with the conclusions of the Cochrane reviews which have collated the relevant evidence for these types of procedures.(5-12)

The Effectiveness and cost-effectiveness of Surgical Treatments for womEn with stRess urinary incontinence: An evidence synthesis (ESTER)

The number of women having surgery is rising, and the choice of operation has changed over the last decade. In 2013-14, HES data for England show that around 12,000 women had a mid-urethral sling (MUS) operation, with around 500 having another type of continence procedure (colposuspension ~300 and traditional slings ~200), and just over 700 having periurethral injections. In contrast, 10 years earlier, just under 7000 had a MUS while ~1400 had a colposuspension and ~250 had a traditional sling. Thus, the majority of women now have a minimally-invasive MUS; and because of its perceived safety and efficacy, there has been a substantial increase in the total number of women having continence surgery.

In 2011 AUGS (American Urogynaecologic Society) and SUFU (Society of Urodynamics, Female pelvic medicine and Urogenital reconstruction) published a position statement, '*The polypropylene mesh mid-urethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women.'* However, subsequent international media publicity regarding supposed long-term severe adverse effects from mesh procedures has caused anxiety in women, many of whom have decided due to high levels of uncertainty to avoid any type of surgery involving synthetic material, including MUS, despite the lack of any new evidence to support this view.

In response to women's concerns about adverse effects, recently at least two Government enquiries (one in England and another in Scotland) have been commissioned to look into the safety of MUS, which use a synthetic non-absorbable mesh (tape / sling) to support the mid-urethra. These enquiries have been rapid and as such are only able to access some published information about the procedures. As a result, they can only provide a broad summary of the evidence. Nevertheless, prior to the publication of the findings of these two enquiries, the Scottish Government Health Minister asked all Scottish hospitals to consider suspending the use of MUS procedures. Many hospitals followed this advice and consequently few women in Scotland currently have access to continence surgery because many surgeons can no longer carry out the older operations or have no training in them. Should this ban be imposed throughout the UK, it will impact on the choices available to the many women who require surgical treatment for their debilitating UI. The impact on their quality of life is therefore currently uncertain.

Currently there is no clear evidence to indicate whether the alternative operations that were previously available (such as anterior repair or colposuspension) really result in equivalent or better outcomes than the polypropylene MUS. However, the feeling of our clinical experts who used to offer colposuspension and traditional slings is that these techniques had more frequent and severe associated complications and returning to them may be detrimental to women. In order to enable women to make an evidence-based choice and inform practice guidelines, it is therefore essential to collect reliable evidence in a transparent, concise manner to allow impartial counselling of women regarding the benefits and risks of MUS and the alternative non-mesh surgical operations for the management of stress urinary incontinence.

The wide range of surgical operations available, the different techniques used to perform these operations and the lack of a consensus among surgeons, make it challenging to establish which procedure is the most effective. The existing evidence base, including the Cochrane systematic

reviews, has focused on discrete two-way comparisons with no attempt being made to collate all of the evidence on the surgical options available and rank them in terms of clinical effectiveness, safety and cost-effectiveness. This has resulted in a piecemeal evidence base that is difficult for women and clinicians to interpret.

By drawing together all of the relevant evidence, one of the main purposes of the proposed research will be accomplished by conducting a network meta-analysis (NMA) of all the evidence from RCTs. This will allow all the available surgical treatments, for what we believe to be the first time, to be compared with each other in order to determine which treatments should be offered in clinical practice on the basis of being the most clinically effective, safest and most cost-effective.

4. Adverse effects/Quality of life

All types of UI profoundly impact on women's quality of life. UI is often associated with reduced ability to work, reduced social interactions and physical activity, loss of self-esteem and sexual problems mainly related to the fear of leakage during intercourse.(13, 14)

Complications and adverse effects associated with continence surgery can be divided into those which are common to all surgical operations, such as bleeding, haematoma, infection, thrombosis, damage to organs or nerves, chronic pain, dyspareunia, and anaesthetic complications; and those associated with particular types of surgery (e.g. mesh-related exposure and extrusion; bladder perforation which is more common during retropubic rather than transobturator procedures; while pain attributed to nerve damage is more common after the latter). The rates of complications and adverse events after surgery vary, some are more amenable to resolution than others, and may impact in different ways on women's quality of life. Arguably, those which have the most profound and long-term impact on quality of life are regarded as more important.

There is therefore a balance to be struck between the chance, type and impact of complications and adverse effects and the undoubted ability of continence surgery to improve quality of life by reducing incontinence.(15)

5. Why research is needed now

The current proposal is particularly pertinent due to the high level of uncertainty facing women in light of the ongoing 'mesh debate'. The controversy surrounding the use of mesh has hit the headlines both in the UK and internationally. The debate has resulted in a virtual ban on mesh continence surgery in Scotland pending the outcome of an Independent Review of the evidence commissioned by the Scottish Health Minister. However, other countries, including England, continue to deliver this treatment option whilst undertaking their own independent assessment. These independent reviews, whilst necessary, are opportunistic and unlikely to be able to produce comparative or comprehensive recommendations based on the most up to date information.

While they are likely to provide some interim guidance, clearly a thorough comprehensive synthesis of the current evidence base on the clinical effectiveness, safety and cost-effectiveness of all surgical interventions for the management of SUI and stress-predominant MUI is essential to inform future policy, as well as future research. The work that we are proposing will achieve that goal.

6. Research methods

6.1 Effectiveness and Safety Review

The Cochrane Incontinence group has published eight systematic reviews which are relevant to this proposal on the nine distinct surgical categories of procedures for the treatment of stress urinary incontinence in women. We will use these existing Cochrane systematic reviews to identify studies that meet our inclusion criteria. We will then utilise the existing data extraction and risk of bias assessments undertaken as part of these Cochrane reviews as the foundation for our evidence synthesis. Further, we will undertake additional searching to identify relevant studies that have been published or updated subsequent to the searches conducted for these reviews as well as studies that meet our inclusion criteria but not necessarily those of the published Cochrane reviews.

An initial scoping exercise has indicated that there are approximately 200 relevant RCTs already included in the relevant Cochrane systematic reviews, and approximately 60 new studies. This project will combine this body of evidence within a NMA, in order to estimate the relative effectiveness of each surgical intervention.

To ensure a consistent methodology across all studies included in our assessment (both those included in the published Cochrane systematic reviews and those identified with additional literature searches), we will assess all the relevant studies by means of the same review process, which includes screening/selection of studies, data extraction and risk of bias assessment. The review process will be conducted according to current methodological standards and recommendations.

Details of the relevant review stages are outlined below.

Inclusion criteria

Study design

We will include randomised or quasi-randomised controlled trials (RCTs) evaluating the effects of treatment for stress incontinence and stress-predominant MUI in women, where at least two management arms compared one of the distinct categories of surgical procedures of interest listed above.

Populations

Our population of interest will be adult women with urinary incontinence, diagnosed as having stress urinary incontinence (SUI) or stress-predominant mixed urinary incontinence (MUI). Either a clinical or urodynamic diagnosis of SUI will be accepted. We will include: women having continence surgery as primary or repeat procedures; and women having a continence procedure alone or with concomitant prolapse or other gynaecological surgery.

Outcomes

The primary outcome of interest is urinary incontinence as reported by women at one year (subjective UI) as a marker of short term treatment failure. If a trial does not report this outcome, we will use an objective measure of UI (clinician-observed or composite) as a surrogate for subjective UI. The secondary outcomes of interest are: the number of women having repeat continence surgery as a marker of long term treatment failure; and the number of women suffering clinically important complications and adverse events (such as voiding dysfunction or pain). Patient satisfaction, quality of life and cost data will also be extracted if available; these data will be utilised in the economic modelling.

Types of interventions

We will include all RCTs or quasi-RCTs which compare any one of the nine distinct categories of surgery with another one (or more than one e.g. in a three-arm trial). The use of a NMA approach will allow us to estimate the relative effects of each of these nine operations with each other. We will not include RCTs comparing specific variations of the relevant surgical techniques (e.g. inside-out transobturator MUS versus outside-in transobturator, or one injectable versus another), as our question is focused on which type of surgery rather than a comparison of approaches within each category type.

Search methods

The main source of relevant RCTs and quasi-RCTs will be the lists of included, excluded, and ongoing studies in the relevant Cochrane reviews. To bring the searches fully up to date, since the last search performed prior to publication for each Cochrane review, the following sources will be searched: the Cochrane Incontinence Group Specialised Register which includes searches of MEDLINE, MEDLINE in process, CENTRAL (Cochrane Central Register of Controlled Trials), ClinicalTrials.gov, and WHO ICTRP; and Scopus for in press publications. Searches will be performed during the first two months of this project and a further updated search will be performed during months 9 and 10 to ensure the review of effectiveness is as up to date as possible at the time of submission of the report.

For the cost effectiveness analysis the following sources will be searched: MEDLINE, MEDLINE in process, Embase, HMIC, NHS EED, Health Management Information Consortium (via Ovid) and the cost-effectiveness analysis registry (https://research.tufts-nemc.org/cear4/default.aspx)

Additional searches for quality of life information may be required in which case the following sources will be searched: MEDLINE, MEDLINE in process, Embase, and Research Papers in Economics: http://ideas.repec.org/

In addition to the usual sources of peer review literature feeding into systematic reviews of effectiveness, the review of safety and adverse effects will need to draw more widely on multiple evidence sources outside the peer reviewed literature (e.g. commissioned, narrative reviews, safety reviews, grey literature sources, patient experience evidence). Given the likely heterogeneity of this evidence base, a critical feature will be a consideration of the evidential limits associated with differing evidence sources.

Study selection

All relevant Cochrane reviews will be examined and relevant studies identified. Where applicable, duplicates (e.g. trials included in more than one Cochrane review) will be removed. Concurrently, results from the additional searches (e.g. titles and abstracts) will be independently assessed for inclusion by two reviewers using a screening form designed for the purpose of this assessment.

Disagreements will be resolved through discussion and, where necessary, consultation with a third reviewer.

For those searches undertaken for the economic component of this research, results will be screened by the two health economists. Whilst the health economists will be transparent in the approach taken when reviewing these studies, the studies identified and selected for use in the economic component of this research will be reviewed separately to those included in the clinical effectiveness review.

Data extraction

For those studies already included in a Cochrane review the original data extraction will be used as a baseline and, if required, verified or augmented with relevant additional information (such as papers reporting updated information for already-included RCTs). Based on the scoping exercise we anticipate that this work will be minimal.

For newly identified studies a data extraction form will be developed, based on that used in the relevant Cochrane reviews. For each trial, details of the study methods, characteristics of patients, characteristics of interventions and comparators, outcome measures and other results will be recorded. Data extraction will be undertaken by one reviewer and duplicated independently or checked by a second reviewer. Discrepancies will be resolved by consensus, or consultation with a third reviewer. When necessary, authors of trials will be contacted for clarification and missing data. Data from trials with multiple publications will be extracted and reported as a single trial.

Quality assessment

For studies already included in a Cochrane review the previously undertaken risk of bias assessment will be used and updated if necessary.

For each newly identified study, risk of bias assessment will be performed using the Cochrane Risk of Bias tool, which addresses six specific domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'). Further questions specific to this assessment will be added if necessary during the course of the systematic review process.

We will adopt the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessing the overall quality of evidence. The overall quality of evidence refers to the level of confidence that can be placed on the estimates of treatment effect that have been derived from a particular study. The quality of evidence is classified as one of four levels: high, moderate,

low and very low. Evidence from randomised controlled trials is initially rated as “high quality”. However, it can be downgraded for five factors including: risk of bias assessment; inconsistency of results; indirectness of evidence; imprecision of result; and publication bias. The quality of evidence will be assessed for all primary outcomes.(16, 17)

Analysis

Prior to undertaking the main quantitative analysis, a number of data consistency checks will be required. Due to the independent nature of each of the Cochrane reviews, it is possible that the methods used to deal with data could have varied across the reviews. It will therefore be important and necessary to ascertain the strategy of the reviews for dealing with drop-outs, cross-overs, standardisation of outcomes, outcome time points, etc. and ensure that we select an appropriate strategy based on the previous work and best practice methodology.

Synthesis of results

A detailed plan for quantitative data synthesis will be developed during the protocol stage of the review. Briefly, we will provide a description of the included studies based on important clinical and methodological variables. For example the mean age of included women; the proportion of women with stress-predominant MUI; the method used to assess incontinence (subjective versus objective or composite); risk of bias; and the number of arms randomised. The primary and secondary outcomes will be summarised using the odds ratio and 95% confidence intervals. In the first instance, a random effects pair-wise meta-analysis model will be used to compare direct evidence from trials that evaluate the same interventions. Heterogeneity between studies will be assessed on clinical criteria, by visual inspection of data plots, and from the chi square test for heterogeneity, and the I^2 statistic.

We will then use network meta-analysis (NMA) to combine direct and indirect evidence, where a network of trials exists, to allow an estimate of treatment effects for interventions where no direct head-to-head clinical trials have been conducted. Multi-arm trials will be included with an adjustment for potential correlation between arms within these trials. The key assumptions of NMA models will be assessed using the appropriate methods, i.e. assessing consistency within each closed loop and then further in the whole network using the design-by-treatment interaction proposed by White et al.(18) Treatments will be ranked and sensitivity of rankings will be tested in light of inconsistency if required. Analyses will be done in Stata and WinBUGs.(19)

The primary outcome of urinary incontinence at one year is dichotomous. We will model this within a generalised linear modelling framework that has been described by many authors but comprehensively and succinctly in Dias et al’s 2013 Medical Decision Making paper.(20) Briefly, we’ll establish the number of incontinent women out of the total number of women randomised in each arm in each trial. We will then model the probability of outcome on the log-odds scale (using a logit link function) to estimate relative treatment effects, most likely using a random effects model given the points below and what we know from the existing reviews. Treatment effects will be estimated relative to a “baseline” treatment which will be anterior vaginal repair. To estimate probabilities for the economic modelling we’ll apply the relative treatment effects to a baseline history model. The exact form of the baseline history model is to be decided, but will be developed between the clinical,

health economics and statistical teams in jointly, drawing on suitable data from the search strategy and other available sources. Data fit will be assessed using residual deviance and standard diagnostic plots and statistics monitored to identify problems with models. These models are easily extended to include multi-arm trials if any meet inclusion criteria, and also to include covariates if heterogeneity is suspected and/or evident. We will use a Bayesian MCMC approach in WinBUGS.

Heterogeneity of interventions: by this we assume the board mean heterogeneity within each of the nine broad categories we defined on page three of our detailed project description. The initial starting point will be that each category of intervention will be suitably homogenous to include in the NMA as one lumped node in the network. Before we start the NMA modelling though we will carry out a thorough assessment of heterogeneity of treatment effects within each data set from the updated Cochrane reviews. The first step will be an assessment of new and existing trials from a clinical aspect to (re)assess the combining of subtle variations of treatments under one category. We then propose to follow the general guidance of Dias and colleagues comprehensive NICE DSU Technical Support Document 3. Specific types of intervention within each Cochrane review will be considered as categorical trial-level covariates and a model using treatment by subgroup interaction term.

A similar approach will be taken to the patient groups included. In theory all women eligible for one treatment are eligible for all the treatments to be included in the review. However, in reality it is likely that inclusion and exclusion criteria will differ from trial to trial. The first stage will include an in-depth assessment of these inclusions and exclusion criteria across all included trials when assembling the dataset. Secondly we'll abstract trial level patient characteristics on potential treatment effect modifiers, describe these and assess potential impact on treatment effects using meta-regression. For categorical covariates the approach will be similar to above in most cases. For continuous covariates we will centre the covariate and use a common interaction term. We compare models to assess impact of including covariates using the deviance information criterion.

Meta-regression, sensitivity analysis and subgroups

Potential sources of heterogeneity and/or inconsistency will be investigated using meta-regression or sensitivity analysis to assess any impact on derived treatment effect estimates. Effect modifiers may include: type of incontinence; repeat surgery; concomitant surgery; number of randomised arms; and the method of outcome assessment. Where data allow, secondary analysis of the following sub-groups will be undertaken:

- women with stress-predominant MUI versus women with SUI alone
- repeat surgery (after failed previous continence surgery) versus primary procedures
- women with and without co-existing vaginal prolapse/having concomitant prolapse surgery

Long-term adverse effect data

At present, data collection on long-term safety of MESH implants is not routinely performed. There are, however, a number of recent high-level evidence sources, which have gathered literature on adverse effects to inform practice, including the CSO independent review of safety and efficacy of mesh and tapes for prolapse and continence surgery (link to draft report (http://www.gov.scot/About/Review/Transvaginal-Mesh-Implants) and a recent European Scientific Committee report (http://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scenihr_consultation_27_en.htm)

In addition, primary research has been conducted into the use of ISD and HES data to provide more detail on medium and long-term serious consequences of continence surgery. These data sources, alongside other high-level relevant sources will be considered to inform the assessment of long-term adverse effects.

Systematic review protocol development

A key first stage of the proposed work will be to develop a full research protocol for the systematic review to fully define elements of the work (e.g. the data extraction tool, the risk of bias criteria, etc.). The evidence synthesis of clinical effectiveness will be conducted according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions(21) and the general principles of the CRD's guidance for undertaking reviews in health care,(22) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). (21-23) Further, the protocol will be written in accordance with the new PRISMA-P initiative and registered on the international prospective register of systematic reviews (PROSPERO). (24)

7. Economics

An economic model will be developed in a suitable software package to compare the cost-effectiveness of the various surgical interventions for treatment of women with SUI or stress-predominant MUI. The model will be informed by a review of published economic evaluations and the findings of the review of clinical effectiveness being proposed.

Model structure

The Markov model structure will be developed by the research team based on the aforementioned literature, in conjunction with relevant clinical expert co-applicants. The structure will also be presented and agreed at the project advisory group meeting. The time horizon of the model will be the lifetime of the women. Shorter time horizons will be incorporated into the model if they are considered meaningful and useful to the decision-makers. The model will be based on a hypothetical cohort of women undergoing surgical interventions for SUI/stress-predominant MUI. The relevant surgical interventions are those described earlier in section 4.

Model inputs

A review of relevant economic evaluations will be undertaken to help inform the model development. This will follow the same methods as the clinical effectiveness review described previously. All full economic evaluations of relevance will be included. A full economic evaluation will be defined as a comparative study which includes both costs and effects for two or more surgical interventions for the treatment of urinary incontinence. The focus of the review will be to identify modelling methodology pertinent to the development of a *de novo* model to address the decision question addressed by this proposal. The results of the clinical effectiveness systematic review and network meta-analysis and the safety review described above will also be used to inform the economic model. The primary and secondary clinical outcomes (e.g. incontinence rates) within the model will be derived from these sources.

Quality of life data

The impact of incontinence for patients can only really be captured through its impact on the patient's health-related quality-of-life. Quality of life outcomes can be measured using a variety of tools: disease specific, discipline specific, general health or utility. These outcomes will be captured through the systematic review element of this research ensuring that the best available outcome data are used to inform the model. Decision analytic modelling and VOI analyses depend heavily on the use of appropriate outcome measures for fully capturing the effects of any treatment. However, there is a clear lack of understanding regarding women's preferences for the different characteristics and outcomes of these surgeries.

A Discrete Choice Experiment (DCE) be undertaken to allow us to fully understand the relative importance of the different attributes of the surgical techniques and the trade-off women are willing to make e.g. what incidence of adverse effects are they willing to tolerate for an increase in the post-operative time to recurrence when making decisions about surgery. In addition to providing important stand-alone results, the findings from the DCE will be used to inform exploratory analysis on the impact that women's preferences may have on the cost-effectiveness results produced by the economic model. Further, rather than only evaluating the model using a cost-utility framework, by incorporating cost as an attribute within the discrete choice experiment we will be in a position to evaluate our decision model using a cost-benefit framework with willingness-to-pay as the main outcome measure.

Discrete Choice Experiment

We propose to conduct a discrete choice experiment (DCE) amongst women who have had or are waiting to have surgical interventions for urinary incontinence.

The outcome(s) from the DCE will be:

- a ranking of the relative importance of the different attributes;
- an understanding of the trade-off women are willing to make, e.g. what incidence of adverse effects are women willing to tolerate for an increase in the post-operative time to recurrence when making decisions about surgery; and
- the willingness-to-pay for different attributes.

DCEs are an economic technique used to explore preferences for different types of service, policy or intervention and have been used extensively to explore patient, provider and policy maker preferences for different characteristics of goods and services in health care.(25, 26) In the DCE the surgical interventions for urinary incontinence will be described in terms of a number of characteristics or 'attributes' e.g. post-operative pain, length of stay, risk of recurrence, risk of adverse event, recovery time and cost to the NHS, etc. The extent to which an individual values the intervention/procedure would depend on the 'level' of those attributes. For example for the attribute length of stay, the levels might be 1, 2 or 3 days. We will include cost as one of the attributes, as this will allow us to determine willingness to pay for different attributes and evaluate the proposed decision model using a cost-benefit framework.

The design of the DCE will follow well established guidelines.(27) Results of the existing Cochrane systematic reviews and qualitative research methods, such as focus groups will be used to determine attributes and attribute levels to be included in the DCE.(5-12) Focus group participants will be drawn from relevant consumer groups and societies, including the Cochrane Consumer Group and the Bladder and Bowel Foundation.

We propose a minimum sample size of 100 respondents, who we anticipate will be recruited with the assistance of the two aforementioned groups. However, a final sample size calculation will be made after the focus group work, once attributes and levels are finalised. The DCE will be a self-administered paper based questionnaire that should take no longer than 30 minutes to complete. Data will be analysed using a random utility framework and appropriate logistic regression techniques used to analyse the data.

This work would be undertaken by researchers from the health economics team at Newcastle University.

Decision model cost inputs

The economic decision model will take the perspective of the NHS and the Personal Social Services. The resources relating to direct health service costs, such as theatre costs, inpatient costs and outpatient costs will be included. Resources will be measured through primary data, reviewed literature and experts. Unit costs for these resource use estimates which will be extracted from the literature or obtained through other relevant sources such as NHS reference costs and manufacturer price lists. Costs will be discounted at 3.5% per annum, where appropriate.

Results/sensitivity analysis/value of information analysis.

The cost per quality-adjusted life-year (QALY) gained will be the main outcome used to characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this parameter uncertainty is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision – that is, decision uncertainty. This is presented using cost-effectiveness

acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.

Further, expected value of information analysis will be undertaken to identify whether further research is worthwhile and also what type of additional evidence would be most valuable (expected value of perfect information for parameters).

8. Dissemination and project outputs

The planned outputs from this research will be a detailed final report, at least two peer reviewed academic journal articles, two conference presentations at relevant international society meetings, such as the International Continence Society or the International Urogynecological Association, and a summary article aimed at patients and a more general audience, with a target distribution list.

In order to disseminate the findings of our research to patients and other interested parties we will set up and maintain a Facebook page and linked Twitter account. Also as part of our final Advisory Group meeting we will present our findings and agree with the representatives from support groups and our patient advisors a dissemination plan that will ensure that the results are made accessible to patients and carers as well as health professionals and their professional bodies.

9. Plan of investigation and timetable

The project will take place over a 14 month period, with a start date of 1st August 2016. The key milestones are as follows:

TASK	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Systematic reviews														
Protocol development														
Literature searches														
Screening and study selection														
Data extraction, quality assessment, checking														
Synthesis (network meta-analysis)														
DCE														
Value of information analysis														
Additional searches														
Screening and study selection														
Data extraction, quality assessment, checking														
Model development														
Model results														
Value of information analysis – EVPI														
Value of information analysis – EVSI														
Report														
Report writing														

Project management

Dawn Craig will co-ordinate and supervise all aspects of the research project. The project will be managed through a steering group comprising all co-applicants, which will be responsible for strategic leadership and to ensure the project will be delivered according to plan; and day-to-day management via the Project team, which involves senior and junior staff at both institutions. The steering group will meet (in person or via phone conference) on a monthly basis. The day to day running of the project will be the responsibility of Dawn Craig in Newcastle and Miriam Brazzelli in Aberdeen to reflect the clear division of responsibility between the two institutions (Aberdeen: systematic review of clinical effectiveness, statistical analysis including NMA and content expertise; Newcastle: discrete choice experiment, modelling and economic evaluation). Administrative support will be provided at both institutions and has been included in the costings. It is worth noting that the two renowned institutions have a track record of similar collaborative projects, which have been delivered successfully.

Patient and public involvement (PPI)

- Isobel Montgomery, who has experience both as a patient and as a patient representative on RCTs of surgery for prolapse and incontinence, will be a member of the Advisory Group for this project. She has been involved in putting together this application and will help guide the research to ensure that the patient's perspective is considered throughout.
- We will also recruit at least two patient advisors. These individuals will be recruited via the Cochrane Consumer Network and/or the Bowel and Bladder Foundation; both entities have been approached and have agreed in principle that they are happy to be involved should funding be secured.
- As part of the first Advisory Group meeting and throughout the project we will consult Isobel Montgomery and the other patient representatives on the development of the structure of the decision model so that it captures the key elements of the condition and has face validity.
- At a later Advisory Group meeting we will present our final results and agree with Isobel Montgomery and our other patient advisors a final dissemination plan so that the results are accessible to patients. In addition to academic outputs, results will be disseminated in a patient accessible format via the Bowel and Bladder Foundation.

Patient advisors will be recompensed for their time in accordance with INVOLVE rates. Advice and support for PPI elements of the project will also be available from the wider research teams at both Aberdeen and Newcastle Universities.

10. Expertise and advisory group

The research project team is a multi-disciplinary partnership between Newcastle and Aberdeen Universities, in collaboration with NHS Grampian, University Hospital Southampton and the Scottish Public Health Network / NHS Health Scotland.

The Effectiveness and cost-effectiveness of Surgical Treatments for womEn with stRess urinary incontinence: An evidence synthesis (ESTER)

The Evidence Synthesis and Health Economics Groups within the Institute of Health & Society (IHS), Newcastle University, have extensive experience in the design and conduct of model based economic evaluations, including the use of value of information techniques. IHS has an established track record of securing funding (annual award income > £10 million) and successfully hosts teams and units including: FUSE, the Centre for Translational Research in Public Health; the UK CRC registered Newcastle Clinical Trials Unit; and the NIHR Research Design Service (RDS) in the North East.

The University of Aberdeen hosts the editorial base for the Cochrane Incontinence Group. The University of Aberdeen's Health Services Research Unit (HSRU, www.abdn.ac.uk/hsru) is an internationally recognised centre of research excellence with a long and distinguished record in conducting evidence syntheses including health technology assessments and modelling (including the NICE TAR contract). HSRU also hosts the Centre for Healthcare Randomised Trials (CHaRT) a UK Clinical Research Collaboration registered clinical trials unit.

The multidisciplinary project team has the right expertise to cover all components of the proposed research (i.e. clinical expertise, systematic reviewing, meta-analysis, preference elicitation, decision-modelling and health technology assessment). Our advisory group will provide additional clinical expertise and patients' perspective on surgical interventions for the treatment of urinary incontinence. The group membership will have strong links with relevant professional and patient organisations such as the Bowel and Bladder Foundation. Two clinical co-applicants have already been involved in this proposal and are appropriately costed in our proposal to ensure their continued involvement. We feel it is crucial to the success of this project that a range of expertise and perspectives are considered and reflected, particularly in the development of the structure of the economic model, its parameterisation and the interpretation of results.

Dawn Craig (Newcastle) leads the Evidence Group within the Institute of Health & Society at Newcastle University. She is an experienced health economist with considerable expertise in both decision modelling and evidence synthesis. In addition to overall day-to-day project management, she will lead the decision modelling and VOI analysis. She also has experience in systematic reviews/evidence synthesis and will contribute to all aspects of the project.

Miriam Brazzelli (Aberdeen) has substantial experience in systematic reviews and health technology assessments, and is one of the leads for the HSRU NICE TAR contract. She is an editor of the Cochrane Stroke Group and a member of the Cochrane Diagnostic Test Accuracy Editorial Team. She will contribute to the review of clinical effectiveness evidence, drafting of the final report and subsequent relevant publications.

Graeme MacLennan (Aberdeen), Senior Statistician: has experience in design, conduct and analysis of surgical RCTs in urology and incontinence; provides statistical support for Health Technology Assessments commissioned by NICE; has experience of systematic reviewing, network meta-analysis and evidence synthesis in urology and incontinence. He will contribute to the statistical analysis by leading the NMA, drafting of the final report and subsequent publications.

Laura Ternent (Newcastle), Senior Lecturer in Health Economics, has a strong research background in economic evaluations alongside randomised controlled trials and health outcome valuation, particularly the use of discrete choice experiments and contingent valuation. She will contribute by leading the DCE component, drafting of the final report and subsequent publications.

Frauke Becker (Newcastle) has experience of both economic evaluation and preference elicitation by means of discrete choice experiments. She will contribute to the conduct of the DCE, drafting of the final report and any subsequent publications.

Eoin Moloney (Newcastle) has experience in both economic evaluation and economic modelling. He will contribute to both the economic model and VOI analysis, drafting of the final report and subsequent publications.

Sheila Wallace (Aberdeen) has extensive experience in literature searching and systematic review methodology within the incontinence field and has successfully contributed to a number of NIHR HTA reports, as well as Cochrane reviews. She will contribute to the literature searching, the drafting of the final report and any subsequent publications.

Lucky Saraswat (Aberdeen) is a recently-appointed Consultant Gynaecologist who has an interest in Cochrane reviews and health services research. She conceived the idea for the study, and will contribute to the design, conduct and interpretation of the review from a clinical perspective. She is also a review author on one of the contributory Cochrane reviews. She will contribute to the review, drafting of the final report and any subsequent publications.

Phil Mackie (Edinburgh) is Lead Consultant in Public Health, Scottish Public Health Network & Head of Knowledge and Research Services, NHS Health Scotland. He has experience in public health/health service effectiveness research. He also has experience in human judgement and decision making research in the context of professional decision -making. He will contribute to the cost-effectiveness and service effectiveness work, as well as the review of safety from secondary sources.

Ash Monga (Southampton) is a Consultant Gynaecologist and subspecialist Urogynaecologist with extensive experience in managing women with incontinence and is widely published in this field. He is currently Chairman of the British Society of Urogynaecology. He will contribute to the review of the clinical data looking at effectiveness and particularly complications, and to drafting the final report and any subsequent publications.

Muhammad Imran Omar (Aberdeen) is the Managing Editor of the Cochrane Incontinence Review Group and member of the GRADE Working Group, the Cochrane Bias Methods Group and the Cochrane Statistical Network. He has contributed to several Cochrane systematic reviews. He will provide expertise in the application of the GRADE approach.

Further to the applicants named above the research will also be informed by the views of an

Advisory Group which will comprise:

Isobel Montgomery, who has undergone prolapse surgery as a patient and is a patient representative on several RCTs for surgery and incontinence, as a grant applicant, member of the TSC or an advisory panel. She has also been co-opted to the Scottish Office Short Life Working Group which is looking at providing support for women having surgery for pelvic floor problems, and is a member of the Scottish Office Independent Review Committee evaluating effectiveness and safety of mesh and tapes. She also has extensive business experience.

Chantal Dumoulin a physiotherapist, professor Faculty of Medicine, University of Montreal, holds a Canadian Research Chair on Urogynecological Health and Aging at the Montreal Geriatric Institute. She is also an Editor for the Cochrane Incontinence Review Group. She has extensive experience is this field and will provide advice throughout all stages of the work.

Luke Vale currently holds the Health Foundation Chair in Health Economics at Newcastle University where he leads the Health Economics Group. He has extensive experience in health technology assessments and has led several pieces of work in the field of incontinence. He will provide advice and guidance throughout all stages of the work.
It is also our intention to recruit patient representation through both the Cochrane Consumer Group and/or the Bladder and Bowel Society to join our advisory group.

Four members of the project group are also members of the Scottish Office Independent Review Committee evaluating effectiveness and safety of mesh and tapes (, LS, AM, PM, IM). AM is also Chair of the equivalent English Enquiry Committee.

We plan at least two full advisory group meetings over the duration of the project. The expectation will be that all Advisory Group members provide advice throughout the project and comment/guide the final report and other project outputs.