Adjustable Anchored Single-Incision Mini-Slings Versus Standard Tension-Free Mid-Urethral Slings in the Surgical Management Of Female Stress Urinary Incontinence; A Pragmatic Multicentre Non–Inferiority Randomised Controlled Trial

HEALTH ECONOMICS ANALYSIS PLAN

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1.0 Background

Urinary incontinence (UI) is a common and distressing condition for women especially those over 40 years [1]. It is estimated that 6 million (40%) of this age group in the UK have clinically significant UI symptoms, 1 million (6.2%) are bothered by symptoms and 0.33 million (2.2%) find them socially disabling. UI has a negative impact on women's quality of life as it affects their social, physical and psychological wellbeing. UI has significant cost implications to the both the individual and the health service. Costs borne by women in terms of out of pocket expenses were £230 million[2] or £290 per woman per year [3]. All values reported are inflated to 2009 values. The total annual cost to the UK NHS for the management of women over the age of 40 with UI was £301 million or 0.3% of the NHS budget [4]. UI in women is a major issue for the NHS and for society, with the number affected and cost of treatment posing a significant burden for healthcare both now, and in the future with an ageing population.

Of the surgical treatments available, tension-free standard mid urethral slings (SMUS; RP-TVT & TO-TVT) are the most commonly performed procedures for SUI resulting in 11,000 finished consultant episodes in England in 2009-10, with estimated costs of £2,044 per procedure i.e. a total of £22.5 million/year.

1.1 Objective of the study

The aim of the main study (a pragmatic multicentre RCT) is to determine the clinical effectiveness and cost- effectiveness of adjustable anchored Single Incision Mini-Slings (SIMS) compared to tension-free Standard Mid-urethral Slings (SMUS) in the surgical management of female stress urinary incontinence (SUI). The primary objective is to compare SUI outcomes in terms of patient-reported success rates as measured by the PGI-I at 12 months. The secondary objectives are to compare objective success rates (24 hour pad test/ home cough stress test), other patient-reported outcomes including: postoperative pain scores

and health related QoL using the ICIQ-LUTSqol, impact on other urinary symptoms (ICIQ-FLUTS), impact on sexual function (ICIQFLUT- Sex/ PISQ-IR), complication rates and disease recurrence.

The primary economic objective is to compare cost-effectiveness measured in terms of quality adjusted life years (QALYs) derived from responses to the EQ-5D and the ICIQ-LUTSqol over the follow up period. The primary outcome for the economic evaluation is the incremental cost-effectiveness ratio (ICER) of SIMS and SMUS. The secondary economic objectives are costs to the NHS and patients. Incremental net benefit will also be reported.

1.2 Study design

The main economic evaluation will be based on data collected alongside a pragmatic multicentre non–inferiority randomised controlled trial comparing adjustable anchored single-incision mini-slings (SIMS) with tension-free standard mid-urethral slings (SMUS) in surgical management of stress urinary incontinence (SUI) in women. Cost benefit analysis will be conducted using the results of a discrete choice experiment (DCE).

1.3 Study population

Women aged 18 years or over with SUI who have been referred to the collaborating surgical gynaecology, urology and urogynaecology units from across the UK for treatment of SUI for whom surgery has been indicated. The setting of the study is secondary and tertiary care acute hospital settings across the UK.

1.4 Study perspective

The analysis will assess the costs and cost-effectiveness of the interventions compared from the perspectives of the NHS. The within trial analysis will also include a societal perspective that will consider the cost to the participants and their families.

1.5 Study interventions

1. Adjustable Anchored single-incision mini-slings (SIMS) which fulfil the following criteria of robust anchorage and post-insertion adjustability:

- SIMS is made of Type I polypropylene Mesh: monofilament & macro-porous (pore size =75 um).
- Robustly anchored to Obturator Complex (Robust insertion is defined as: Immediate pull-out force = 12 Newtons (N) and/ or four weeks pull out force = 30N).
- Fully adjustable sling post insertion.
- Proven feasibility to be done under local anaesthetic (LA).
- Minimum of level 2 evidence showing their safety and short term (minimum 3-month) patient reported outcome.

2. Standard tension-free mid-urethral slings (SMUS) including retropubic tension free vaginal tapes (RP-TVT) and transobturator vaginal tapes (TO-TVT).
Retropubic Tension Free Vaginal Tape (RP-TVT):

- RP-TVT will be Type-1 polypropylene Mesh (monofilament and macro-porous - pore size ≥75 um). The Tension Free Vaginal Tape (TVT®) procedure was developed by Ulmsten and Petros [(5)].
- Transobturator Tension Free Vaginal Tape (TO-TVT):
- TO-TVT will be Type-1 polypropylene mesh (monofilament and macro-porous - pore size ≥75 um).

1.6 Follow-up period

Resource utilisation and quality of life will be measured over six time points (baseline, four weeks, three, 15, 24, and 36 months), over the 36 months follow-up period using two sources (CRFs and patient reported questionnaires).

1.7 Discounting

The costs and benefits incurred in the second and third years will be discounted at the NICE recommended rate of 3.5% [(6)].

2. Data collection

2.1 Resource use

Intervention resource use will be captured through the operation case review form (CRF). This form will specify the grade of surgeon performing the procedure and whether they were supervised, type of procedure performed (RP-TVT/TO-TVT/SIMS), type of anaesthesia (general/spinal/local with IV sedation/LA with oral sedation/LA only),

analgesics/anxiolytic/sedative (several specified) received from procedure time (from anaesthetic start time to leaving operating room time) till discharge. Post-operative resource use will include the number of inpatient days and whether the patient received a catheter patient during or after their procedure. Information on the type of catheter and details of any return to theatre before hospital discharge will also be collected.

Further post-operative resource use will be recorded retrospectively for every woman within the study using CRFs and patient reported questionnaires completed at several time points (Table 1). This recourse use will include visits to the outpatient department, inpatient stay, further interventions such as SIMS/SMUS, partial /full tape removal among others. Primary care resource use will be collected as various time points from the patient reported questionnaires. Resource use incurred at personal cost to the participants (over the counter medication and visits to private healthcare providers) will be collected using questionnaires. Resource-use data collected will include the use of primary (GP services) and secondary (hospital inpatient stay, surgical interventions for their incontinence) NHS services by the participants, including further referral for subsequent additional specialist management. Health service refers to those incurred directly by the NHS due to any surgery, subsequent appointments and procedures.

Table 1: Resource use data

	Resource	**Unit**	**Source**
Intervention resource use	Surgeon	Type	CRF
	Procedure	Type	CRF
	Type of anaesthesia	Type	CRF
	Medications analgesics/anxiolytic/sedative	Type	CRF
	Inpatient Stay	Number	CRF
	Other Staff (anaesthetist, theatre nurses)	Number	Experts
	Operation time	Minutes	CRF
	Return to theatre	Minutes	CRF
Secondary care	Outpatient visit	Number	CRF
	Further interventions	Type and number	CRF
	Inpatient readmissions	Number	CRF
Primary care	Practice nurse visit	Number	PR Questionnaire
	GP visit	Number	PR Questionnaire

	Resource	Unit	Source
	Visit to other providers	Number	PR Questionnaire
Participant resource use	Medications	Number	PR Questionnaire
	Pads/catheters	Number	PR Questionnaire
	Visits to non-NHS providers	Number	PR Questionnaire

PR patient reported CRF case review forms

2.2 Unit costs

The unit costs will be applied in British Pound Sterling £. Unit costs/prices will be obtained using published estimates BNF[7] Reference costs[8], PSSRU Unit Costs of Health and Social Care[9], Information Services Division Scotland (ISD)[10] and the Electronic drug tariff [11], as outlined in Table 2.

Table 2: Average unit costs

Area of resource use	Resource	Unit cost £	Source
Intervention	Surgeon		PSSRU
	Anaesthetist		PSSRU
	Other staff		PSSRU
	Device		Manufacturer
	Type of anaesthesia		Various
	Medications analgesics/anxiolytic/sedative		BNF
	Catheter indwelling/supra-pubic		Electronic Drug Tariff
	Theatre overheads		ISD
	Return to theatre		ISD
	Inpatient Stay		Reference costs
Primary care	NHS doctor visit		PSSRU
	NHS nurse visit/physiotherapist		PSSRU
	Secondary care		
Secondary care	Outpatient department visit		
	Overnight stay in hospital		Reference costs
	Further intervention		Reference costs
Participant	Medications		BNF
	Pads		Reference costs
	Catheters Permanent/disposable		Electronic Drug tariff

Area of resource use	Resource	Unit cost £	Source
	Visits to non-NHS healthcare providers		Participants
	Nurse		Participants
	Physiotherapist		Participants

Participant resource use and cost estimation

Participant resource utilisation will comprise three main elements: self-purchased healthcare; travel costs for making return visit(s) to NHS health care; and time costs of travelling and attending NHS health care. Estimation of travel costs requires information from participants about the number of visits to, for example, their GP or physiotherapist (estimated from the health care utilisation questions) and the unit cost of making a return journey to each type of health care provider (from the Participant Time and Travel Cost Questionnaire). The cost of participant time will be estimated in a similar manner.

The participant will be asked, in the Participant Time and Travel Cost Questionnaire, how long they spent travelling to and attending their last visit to each type of health care provider. Participants will also be asked what activity they would have been undertaking (e.g. paid work, leisure, housework) had they not attended the health care provider. These data will be presented in their natural units, e.g. hours, and also costed using standard economic conventions, e.g. the Department of Transport estimates for the value of leisure time. They are further asked if they were accompanied by a friend or a relative and their time and travel costs will also be incorporated into the analysis. These unit time costs will then be combined with the number of health-care contacts derived from the health-care utilisation questions to elicit a total time and travel cost from a patient perspective. Details of unit costs applied to the various activities are included below.

Data collected through the patient reported questionnaire will be used to estimate the costs of self-purchased health care including pads bought by the participant, prescription costs and over the counter medications. All self-purchased health care relates to treatment purchased for the management or treatment of urinary incontinence. Medications will be costed using the British national formulary (most up to date version at time of analysis) and other direct patient costs will be sourced from the patient administered questionnaires (e.g. cost of over the counter medications and products related to the women's urinary incontinence). The source of private costs will come mainly from the participants and the rest will be the HMRC Expenses

and benefits[12], hospital car service [13], the annual survey of hours and earnings[14] and the transport analysis guidance data book [15]. Details of the unit costs are reported in (Table 3).

Table 31: Participant time and travel cost

Activity	Unit cost (£)	Source and notes
Unit costs applied to participant and companion travel		
Cost per mile travelled by car		HMRC
Car parking charges	Various	As reported by participants
Cost of public transport (bus, train, taxi)	Various	As reported by participants
Cost of return journey by hospital car	Per trip	Torbay and South Devon NHS Foundation Trust
Cost of non-emergency patient transport service (via ambulance)	Per trip	NHS reference costs
Unit costs applied to participant and companion time		
Paid work	Per hour	ONS annual survey of hours and earnings
Housework	Per hour	ONS annual survey of hours and earnings
Child-care	Per hour	ONS annual survey of hours and earnings
Caring for a friend/family member	Per hour	ONS annual survey of hours and earnings
Voluntary work	Per hour	ONS annual survey of hours and earnings
Retired	Per hour	TAG data book
Leisure	Per hour	TAG data book
Unemployed	Per hour	TAG data book
Ill/disabled (long term, unrelated to incontinence)	Per hour	TAG data book

2.3 Estimation of cost per patient and average cost per patient by elements of resource use and total cost per patient

For each area of resource use, estimates of resource utilisation (Table 4) will be combined with unit costs (Table 3) to derive total costs for each item of resource use and each patient. These data will be averaged to provide estimates of the average cost per patient for each item of resource use.

Table 4: Average resource use per arm of treatment and difference

	SIMS N Mean SD	**SMUS N Mean SD**	**Difference [95% CI]**
Surgeon			
Procedure			
Type of anaesthesia			
Medications analgesics/anxiolytic/sedative			
Catheter indwelling/supra-pubic			
Return to theatre			
Inpatient Stay			
Post-operative resource utilisation			
NHS doctor visit			
NHS nurse visit/physiotherapist			
Outpatient department visit			
Overnight stay in hospital			
Further interventions			
Medications			
Pads			
Catheters Permanent/disposable			
Visits to non-NHS healthcare providers			
Nurse			
Physiotherapist			

*Number

The costs for each item of resource use for each patient will be summed to produce a total cost for each patient and an average total cost per patient (Table 5) in each intervention arm.

Table 5: Average cost per arm of treatment and difference in cost

	SIMS N Mean SD	**SMUS N Mean SD**	**Difference [95% CI]**
Surgeon			
Procedure			
Type of anaesthesia			

	SIMS N Mean SD	SMUS N Mean SD	Difference [95% CI]
Medications analgesics/anxiolytic/sedative			
Catheter indwelling/supra-pubic			
Inpatient Stay			
Operation time			
Return to theatre			
Outpatient department visit			
NHS doctor visit			
NHS nurse visit/physiotherapist			
Overnight stay in hospital			
Further intervention			
Medications			
Pads			
Catheters			
Visits to non-NHS healthcare providers			
Nurse			
Physiotherapist			

*Number

2.5 Derivation of quality of life

A generic instrument EQ-5D-3L will be used to measure the quality of life. Trial participants will be asked to complete the EQ-5D-3L at baseline and at 4 weeks, three months, 12, 24 and 36 months after their intervention. This instrument will provide the quality of life weights to compute the QALYs. The responses to the EQ-5D-3L questionnaire will be valued using UK general population tariffs, based on the time trade-off technique to generate a utility score for every participant within the trial [16]. QALYs (Table 6) will be calculated based on these assumptions, using an area beneath the curve approach, assuming linear extrapolation of utility between time points. Quality of life data is collected using items from the condition specific tool (ICIQ urinary incontinence short form questionnaire) for comparison. ICIQ-UI SF data are collected at baseline, three, 12, 24 and 36 months. These data will be converted into a utility index using a published algorithm [17].

Table 2: Quality of life measures

Score	SIMS N Mean SD	SMUS N Mean SD	Difference [95% CI]
Baseline EQ-5D-3L			
4 weeks EQ-5D-3L			
3 months EQ-5D-3L			
12 months EQ-5D-3L			
24 months EQ-5D-3L			
36 months EQ-5D-3L			
Total QALYs EQ-5D-3L			
Baseline ICIQ-LUTSqol			
3 months ICIQ-LUTSqol			
12 months ICIQ-LUTSqol			
24 months ICIQ-LUTSqol			
36 months ICIQ-LUTSqol			
Total QALYs ICIQ-LUTSqol			
Baseline EQ VAS			
4 weeks EQ VAS			
3 months EQ VAS			
12 months EQ VAS			
24 months EQ VAS			
36 months EQ VAS			

3.0 Data analysis

The economic analysis will be undertaken using the intention to treat principle. All components of costs will be described with the appropriate descriptive statistics where relevant: mean and SD for continuous and count outcomes; numbers and percentages for dichotomous and categorical outcomes (e.g. numbers reporting problems on EQ-5D-3L). All analyses will be conducted using Stata® version 14.1 software (StataCorp LP, College Station, TX, USA). Depending on the results, investigations will be carried out for skewed cost data (i.e. a small proportion of participants incurring very high costs), using GLMs to test alternative model specifications for appropriate fit to the data. The GLM models allow for heteroscedasticity by selecting and specifying an appropriate distributional family for the data. This family offers alternative specifications to reflect the relationship between the mean and variance of the estimates under consideration [18,19]. Two diagnostic actions will be performed to identify the

most appropriate distributional family: (1) a modified Park test (2) the Akaike information criterion (AIC) will be consulted.

Both cost and QALY difference analyses will be adjusted for:

- Centre number
- Previous supervised Pelvic Floor Muscle Training within the last two years [PFMT: Yes/No]
- Age
- Baseline EQ-5D-3L

The first two factors are in line with the clinical effectiveness analyses and the baseline EQ5D will be included for the economic analysis. We will carry out standard parametric tests for differences in costs, with the robustness of the parametric tests confirmed using bias-corrected, nonparametric bootstrapping [20].

3.1 Incremental cost per and QALYs gained

Incremental cost-effectiveness ratios will be computed comparing the cost of the interventions. The difference in effectiveness will be expressed in terms of quality adjusted life years. These data will be based on responses to EQ-5D-3L and questions from the ICIQ-LUTSqol, retrieved from the participant questionnaire. Incremental cost-utility ratios will be computed comparing the interventions. The difference in utility will be expressed in terms of QALYs at 36 months. The point estimate of the incremental cost-effectiveness ratio (ICER) will be calculated as:

$$ICER = \frac{Ci - Cj}{Ei - Ej} = \frac{\Delta C}{\Delta E}$$

where Ci and Cj are the mean costs among women in the SIMS arm and SMUS arm respectively. Similarly, Ei and Ej are the mean quality-adjusted life years in the SIMS arm and SMUS arm. The ICER will be assessed against the NICE recommended cost-effectiveness threshold £20,000-30,000 per QALY gained.

Measures of variance for NHS costs, incontinent participants and QALYs will be derived using bootstrapping. From the results of the bootstrapping cost-effectiveness acceptability curves (CEACs) will be created (Table 7). Cost-effectiveness acceptability curves will be used to display the inherent uncertainty surrounding cost-effectiveness at various threshold values for society's willingness to pay for r additional QALY. CEACs present results when the analysis

follows a net benefit approach. This approach utilises a straightforward re-arrangement of the cost-effectiveness decision rule used when calculating ICERs (see below) to create the net monetary benefit for each bootstrapped iteration at increasing values of WTP per QALY:

$$NMB = \lambda.\Delta E - \Delta C > 0$$

Where λ is represents a decision maker's willingness to pay for incontinence avoided or a QALY gained. If the above expression holds true for a given iteration and threshold WTP value (λ), then the intervention is considered cost-effective for that iteration. As society's willingness to pay is unknown, the NMB will be calculated for a number of possible λ values including the usual £20-£30K range often adopted by policymakers within the NHS [21]. Table 7 shows the data that will be collected in relation to cost-effectiveness in order to calculate ICERs and, following on from this, the NMB of the interventions.

Table 7 Cost effectiveness (replicated for all analyses)

	Cost	**Effect**	**Δ Cost**	**Δ Effect**	**ICER (ΔC/ΔE)**	**Probability cost effective £20,000**
Most costly trial arm						
Least costly trial arm						

Incremental cost effectiveness analysis will also be conducted combine the NHS and societal costs.

Missing data

Missing data are a frequent problem in economic evaluations undertaken within a randomised controlled trial setting. There are several possible methods that can be employed to account for such missing data: mean or multiple imputation. Imputation analysis will be conducted if more than 5% of the data needed is missing for the primary analysis. The handling of missing data will be dependent on the pattern of missing data. If the data is "Missing at Random (MAR)", multiple imputation will be used. Components of cost data will be imputed, based on linear regression models that were adjusted for minimisation variables, baseline utility and

treatment allocation group. Missing utility values will be imputed using predictive mean matching. Chained equations will be used for the imputations.

4.0 Sensitivity and sub-group analyses

4.1 Sensitivity analyses

Sensitivity analysis will be performed to gauge the impact of varying key assumptions and/or parameter values in the base-case analysis.

1) Depending on the amount of missing data (if greater than 5%) the base case analysis will be conducted using on multiply imputed data. Sensitivity analysis will be undertaken using complete case data.
2) Sensitivity analyses in relation to the estimation of costs. The base-case analysis will be based on the assumption that women who did not get surgery did not incur any further hospitalisations and therefore had zero costs. The first sensitivity analysis will be performed assuming that these data were missing.
3) The base-case analysis in terms of utilities will be adjusted for baseline values to account for variability that may be present amongst the intervention groups. An unadjusted analysis will also be performed as a sensitivity analysis to highlight the importance of this base-case assumption.
4) Sensitivity analysis will also be conducted using utilities estimated using a condition specific tool (ICIQ-LUTSqol).
5) Analysis exploring the impact of changing the discount rate used for second-year costs and QALYs in accordance with NICE best practice recommendations, varying the discount rate from 0% to 6% per annum will be undertaken.

4.2 Subgroup analysis

Depending on the availability of data, subgroup analysis similar to that described in the statistical analysis plan will be undertaken. This will be based on

- Type of incontinence (SUI or MUI)
- Diagnosis of stress urinary incontinence Urodynamic versus Clinical
- Adjustable Anchored SIMS vs. each type of SMUS (i.e. RP-TVT and TO-TVT separately)
- Comparison of the main types of SIMS
- We will also include an exploratory subgroup analysis comparing those above and below the observed median age of the recruited women using a formal test of interaction.

- Responses to 2 validated sexual function questionnaire: ICIQ-FLUTsex vs. PISQ-IR

5.0 Discrete choice experiment

A discrete choice experiment (DCE) will be conducted to elicit preference for the process, patient experience and health outcomes. The attributes and levels for the DCE will be informed by systematic literature searching and advice sought from clinical experts. The questionnaire will be administered to the trial participants at the end of the 3yr follow-up. Experimental design techniques will be used generate an efficient set of choices from which preferences will be estimated. Logistic regression techniques will be used to analyse the response data. A cost attribute will be included so that willingness to pay (WTP) can be estimated.

The results of the DCE information will be combined with the clinical outcomes estimated from the trial to provide an estimate of mean willingness to pay for each of the two interventions. Results of the WTP aspect of the DCE will be presented as incremental Net Benefits (NB) between groups where NB will be measured as WTP less mean cost for each intervention. The intervention with the greatest net benefit will be deemed the most efficient. The results of this analysis will be compared and contrasted with the cost/QALY outcomes and will yield some information regarding the applicability of traditional QALY measurement to conducting economic evaluation in urinary incontinence.

6.0 References

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