**Supplementary Material 2: Health Economics Analysis Plan**

# Male synthetic sling versus Artificial urinary Sphincter Trial:


## Evaluation by Randomised controlled trial

Male synthetic sling versus Artificial urinary Sphincter Trial for men with urodynamic Stress incontinence after prostate surgery: Evaluation by Randomised controlled trial

## (MASTER)

## MASTER HEALTH ECONOMICS ANALYSIS PLAN

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This purpose of this analysis plan is to describe the analysis and reporting procedure for the planned health economics analysis. This health economics analysis plan should be read in conjunction with then study protocol as well as the statistical analysis plan.

## 1.0 Objective of the study

The principal research question being addressed in the economic analysis is what is the cost effectiveness of a policy of primary implantation of the male sling compared with AUS, measured by incremental cost per quality-adjusted life-year (QALY) at 24 months?

## 1.1 Study design and perspective

The main economic evaluation will be based on data collected alongside the RCT. An additional modelling analysis which considers a longer time horizon will also be conducted to provide additional information for policy makers. Both analyses will assess the costs and cost-effectiveness of the interventions compared from the perspectives of the NHS. The within trial analysis will also estimate the cost of the participants and their families. The methods for within trial and the modelling analyses are described below.

## 1.2 Study population

Men with urinary stress incontinence (USI) after prostate surgery (radical prostatectomy or TURP), for whom surgery is judged appropriate, are the target population. For the purposes of the trial people with mild incontinence were defined as mild and therefore not requiring surgery.

## 1.3 Study interventions

Patients that consent to participate in the study are randomised into one of two groups.

1. Male Sling
2. Artificial Urinary Sphincter (AUS)

## 1.4 Follow-up period

Questionnaires will be administered at baseline when they are consented, and at six, 12- and 24-months post randomisation. Resource-use data collected will include the cost of the intervention and the use of primary and secondary NHS services by the participants, including further referral for subsequent additional specialist management. Health service costs refer to those incurred directly by the NHS due to the surgery and subsequent appointments and procedures. Personal costs to the participants (such as costs of travelling to appointments and work/social restrictions) will also be investigated.

### 1.5 Discounting

The costs and benefits incurred in the second year will be discounted at the NICE recommended rate of 3.5%.[1]

## 2 Within Trial Analysis

### 2.0 Resource use data collection

Intervention resource use will be recorded prospectively for every participant within the study (Table 1). For the surgical interventions, operative details will be recorded in a CRF at the time of surgery (e.g. time the surgery takes, grade of surgeon and assistant, grade of anaesthetist). A parallel exercise will establish resources used immediately before, during and after (i.e. in recovery) the operation e.g. other staff, consumables (surgical requisites), and capital (costs associated with using the theatre facilities, costs of using reusable equipment). Resource use incurred at personal cost to the participants (such as purchase of pads, medication) will also be collected using a questionnaire.

**Table 1 Resource use data**

| | **Resource** | **Unit** | **Source** |
|---|---|---|---|
| **Intervention resource use** | Operation time | Minutes | CRF |
| | Anaesthetic use | Type | CRF |
| | Staff | Type and grade | CRF |
| | Antibiotic use | Type | CRF |
| | Catheter | Type and number | CRF |
| | Length of stay | Number | CRF |
| Other secondary care resource use | Outpatient visit | Number | Questionnaire |
| | Inpatient readmissions | Number | Questionnaire |
| Primary care resource use | Practice nurse visit | Number | Questionnaire |
| | GP visit | Number | Questionnaire |
| | Visit to other providers | Number | Questionnaire |
| Participant resource use | Medications | Number | Questionnaire |
| | Pads/catheters | Number | Questionnaire |
| | Visits to non-NHS providers | Number | Questionnaire |

### 2.1 Unit costs

Unit costs/prices will be obtained using published estimates for health care services and/or interventions as outlined in Table 2.

**Table 2 Average NHS unit costs**

| Area of resource use | Resource | Unit cost | Source | Notes |
|---|---|---|---|---|
| Intervention resource use | Slings | | Manufacturer | |
| | AUS | | Manufacturer | |
| Other secondary care resource use | Cost per day in hospital | | Reference costs | |
| | Antibiotics | | BNF | |
| | Outpatient visit | | Reference costs | |
| Primary care resource use | Practice nurse visit | | PSSRU | |
| | GP visit | | PSSRU | |
| | Cost of visit to other health care professionals | | Patient reported/PSSRU /Ref Costs | |
| Participant resource use | Medications | | Patient reported | |
| | Visits to non-NHS providers | | Patient reported | |

### 2.3 Estimation of resource use per patient and average resource in treatment arm

Summaries for each area of resource use estimates of resource utilisation (Table 1) will be reported in Table 3.

**Table 3 Average resource use for each treatment arm and difference in resource use**

| | Slings N Mean SD | AUS N Mean SD | Difference [95% CI] |
|---|---|---|---|
| Year 1 costs (This will be replicated for Year 2 and discounted) | | | |
| Operation time | | | |
| Anaesthetic use | | | |
| Staff | | | |
| Antibiotic use | | | |
| Catheter | | | |

| |
|---|
| Length of stay |
| Outpatient visit |
| Inpatient readmissions |
| Practice nurse visit |
| GP visit |
| Visit to other providers |
| Medications |
| Pads/catheters |
| Visits to non-NHS providers |

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

For each area of resource use estimates of resource utilisation (Table 3) will be combined with unit costs (Table 2) 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. 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 4 Average cost for each treatment arm and difference in cost for each item of resource**

| | **Slings** | **AUS** | **Difference** |
|---|---|---|---|
| | **N Mean SD** | **N Mean SD** | **[95% CI]** |
| Year 1 costs (This will be replicated for Year 2 and discounted) | | | |
| Operation time | | | |
| Anaesthetic use | | | |
| Staff | | | |
| Antibiotic use | | | |
| Catheter | | | |
| Length of stay | | | |
| Outpatient visit | | | |
| Inpatient readmissions | | | |
| Practice nurse visit | | | |
| GP visit | | | |
| Visit to other providers | | | |

| | |
|---|---|
| Medications | |
| Pads/catheters | |
| Visits to non-NHS providers | |

### 2.4 Estimation of quality of life

A generic instrument (the 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 six, 12 and 24 months after their operation. This instrument will provide the quality of life weights to compute the QALYs.

**Table 5 Quality of life measures**

| Score | Slings N Mean SD | AUS N Mean SD | Difference [95% CI] |
|---|---|---|---|
| Baseline EQ-5D-3L | | | |
| 6 months EQ-5D-3L | | | |
| 12 months EQ-5D-3L | | | |
| 24 months EQ-5D-3L | | | |
| Total QALYs (EQ-5D-3L) | | | |
| Adjusted QALYs (EQ-5D-3L) | | | |
| | | | |
| Baseline SF-6D | | | |
| 6 months SF-6D | | | |
| 12 months SF-6D | | | |
| 24 months SF-6D | | | |
| Total QALYs (SF-6D) | | | |
| Adjusted QALYs (SF-6D) | | | |

Quality of life data will also be collected using the SF-36 questionnaire for comparison. SF-36 data were collected at baseline, six, 12 and 24 months. These data will be converted into a SF-6D utility index using a published algorithm.[2]

## 3 Data analysis

### 3.1 Incremental cost per QALYs gained

Incremental cost-effectiveness ratios will be computed comparing the cost of the interventions. The difference in effectiveness will be expressed in terms quality adjusted life years. Incremental cost-utility ratios will be computed comparing the interventions. The difference in

utility will be expressed in terms of QALYs at 24 months. Where appropriate, the analysis of incremental costs, effectiveness and cost-effectiveness will be based on similar statistical models as those outlined in the statistical analysis plan.

### 3.2 Net Benefits

Measures of variance for these costs, incontinent participants and QALYs will be derived using bootstrapping. From the results of the bootstrapping cost-effectiveness acceptability curves (CEACs) will be created. CEACs will be used to represent whether the various interventions are cost-effective at various threshold values for society's willingness to pay for an infection avoided or 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. The net monetary benefit (NMB) of the interventions in question is equal to:

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

Where λ is represents a decision maker's willingness to pay for incontinence avoided or a QALY. If the above expression holds true, the intervention is considered cost-effective. 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 for a QALY values which is a threshold often adopted by policymakers within the NHS.[1] Table 6 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 6 Incremental cost effectiveness (replicated for both the QALY based analyses and for the number of participants who are incontinent)**

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

### 3.3 Missing data

Missing data are a frequent problem in cost effectiveness analysis (CEA) within a randomised controlled trial. There are several possible methods that can be employed to account for such missing data mean or multiple imputation. The handling of missing data will be dependent on the pattern of missing data. The exact method to be employed, therefore, will be finalised when the nature of the missing data is known.

### 3.4 Sensitivity and sub-group analysis

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

1) Sensitivity analyses in relation to the sources used for unit costs will be performed. The base-case analysis will utilise cost estimation based on the resource utilisation. The first sensitivity analysis will be performed costs from published sources e.g. NHS Reference costs.[3] Further to this, if it is possible to obtain costs from a leading trial centre, a further analysis which utilises these costs will be performed. These analyses will serve to highlight the differences to results when using national and centre-specific tariffs.
2) The base-case analysis in terms of utilities will be adjusted for patient outcomes at baseline 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. The methods for conducting the adjusted analysis will be described and the syntax to be used maybe included.

### 3.5 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

1. Type of prostate surgery that the men had, radical prostactectomy or transurethral resection of prostrate
2. Amount of urine leaked per 24 hours at baseline, above 250ml compared to equal or below 250ml.

## 3 Modelling analysis

### 3.1 Extrapolation of within trial results

An economic model which considers a longer time horizon will also be developed to provide additional information for policy makers.

### 3.2 Model type

A long-term Markov model with annual circle will be used to evaluate effects of intervention on costs, health gains and cost effectiveness over the patient's lifetime.

### 3.3 Model structure

The structure of the model will be developed in collaboration with the expert panel of service users, patients, clinicians and trial collaborators. The model will describe care pathways that people may follow and will include the initial surgery AUS or male sling and any subsequent treatments.

### 3.4 Identification of model parameters

Parameter estimates for relative effectiveness up to two years, costs and utilities will be derived from the trial data. Data from the trial will be supplemented with data from other sources (e.g. Cochrane review, other future RCTs). The model will require 4 main sets of parameters: a) Transition probabilities between health states b) Treatment effect of the interventions c) Quality of life data d) Health care costs. These data will be assembled systematically and will follow guidelines for good practice.[4]

### 3.5 Model uncertainty

Outcomes in the model will be expressed in terms of an incremental cost per QALY. Parameter uncertainty will be integrated by the incorporation of probability distributions into the model and involve Monte Carlo simulation. Other forms of uncertainty such as that associated with choices made about the structure of the model, discount rate, etc. will be addressed through sensitivity analysis. The base case and sensitivity analyses will be presented as cost effectiveness acceptability curves. The model will also be used to identify priorities for further research by investigating the expected value of information.

### References

1. National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal.* London: NICE; 2013.

2. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care*. 2004;42:851-859.

3. NHS Improvement. NHS Reference costs 2017-2018. https://improvement.nhs.uk/resources/reference-costs/. Updated 2018. Accessed 01/20, 2020

4. Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technology Assessment*. 2004(Sep;8(36):iii-iv, ix-xi):1-158.