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Abstract:

Introduction:

Single incision mini-slings(SIMS) represent the 3rd generation of mid urethral slings(MUS). They have been developed with the aim of offering a true ambulatory procedure for treatment of female stress urinary incontinence(SUI) with reduced morbidity and earlier recovery while maintaining similar efficacy to Standard mid-urethral slings(SMUS). The aim of this study is to determine the clinical and cost- effectiveness of adjustable anchored SIMS compared to tension-free SMUS in the surgical management of female SUI, with 3-years follow-up.

Methods and analysis:
A pragmatic multicentre non–inferiority randomised controlled trial

The primary outcome measure is the patient-reported success rate measured by the Patient Global Impression of Improvement(PGI-I) at 12-months. The primary economic outcome will be incremental cost per QALY gained at 12-months.

Secondary outcome measures include: Adverse events; Objective success rates; Impact on other lower urinary tract symptoms; Health-related quality of life (QoL) profile and sexual function; and re-operation rates for SUI.. **Secondary economic outcomes include:** NHS and patient primary and secondary care resource use and costs; Incremental cost-effectiveness; and Incremental net benefit.

The statistical analysis of the primary outcome will be by intention-to-treat (ITT) and also a per protocol (PP) analysis. Results will be displayed as estimates and 95% confidence intervals. Confidence intervals around observed differences will then be compared to the pre-specified non-inferiority margin. Secondary outcomes will be analysed similarly.

Ethics and dissemination:
The North of Scotland Research Ethics Committee has approved this study(13/NS/0143).

The dissemination plans include HTA monograph; presentation at international scientific meetings; and publications in high-impact open access journals; the results will be included in the updates of NICE and EAU (European Association of Urology) guidelines; these two specific guidelines directly influence practice in the UK and worldwide specialists respectively. In-addition, plain English language summary of the main findings/results will be presented for relevant patient organisations.

Registration details: ISRCTN93264234

Strengths and limitations of this study:

Strengths:

- The study design as a multicentre randomised controlled trial; the gold standard study design to assess surgical interventions.
- The pragmatic nature of the study (with few inclusion or exclusion criteria) ensures the generalisability of the results (i.e. the findings will be applicable to most women and most surgeons in the NHS).
- The study protocol ensures surgeons' experience in both study arms prior to participation. This avoids the potential bias associated with limited surgical experience with relatively new surgical techniques.
- Primary outcome is the patient-reported success rate obtained by a validated instrument. Patient-reported outcomes are recognised as the most relevant clinical trial outcomes in this field.
- Outcomes are obtained by postal questionnaires; this eliminates the assessor bias.
- An integrated health economic analysis is a major strength
- The analysis plan for this non-inferiority design randomised trial includes both Intention to treat and per-protocol analysis
  Similar protocol was used in other similar trials worldwide allowing comparison of the results and relevant meta-analysis.

Limitations:

- The lack of an objective assessment post-intervention can be seen by some as a limitation.

INTRODUCTION

1.1. Background

Urinary incontinence (UI) is a common and distressing condition for women particularly over the age of 40 years.[1] In the UK, it is estimated that 6 million (40%) of this age group have clinically significant UI symptoms, 1 million (6.2%) are bothered by symptoms and 0.33 million (2.2%) find them socially disabling.[2] UI has a negative impact on a woman's social, physical and psychological wellbeing; leading to embarrassment, low self-esteem and social isolation. UI is associated with negative effects on the productivity of working women, with some avoiding employment because of fear of embarrassing situations.[3] UI has significant cost implications to the individual and the health service. 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] Costs borne by women in terms of out of pocket expenses were £230 million[5] or £290 per woman per year.[6] All values reported are inflated to 2009 values. It is therefore clear that 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.

SUI is the most common type of UI in premenopausal women, accounting for almost 50% of cases.[7] It is defined as involuntary leakage of urine on effort, or exertion, or on sneezing or coughing. Initial management of SUI includes conservative therapy such as pelvic floor muscle training (PFMT), biofeedback, electrical stimulation or drugs. When conservative therapy fails, in about one third of cases, surgery is the next option.[7] 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/ procedure[8] i.e. a total of £22.5 million/year. The Cochrane review of minimally invasive MUS[9] concluded that there was no evidence of significant differences in patient-reported outcomes between RP-TVT & TO-TVT and therefore the control arm for the proposed RCT is a pragmatic combination of these 2 types of SMUS. Analysis of BSUG database showed that the vast majority of SMUS in UK are done under GA or deep intra-venous patient sedation.[10]

SIMS represent the 3rd generation of mid urethral slings (MUS); they have been developed with the aim to offer a true ambulatory procedure for treatment of SUI with reduced morbidity, earlier recovery while maintaining similar efficacy to SMUS. NICE undertook an Interventional Procedure overview of SIMS[1] for the management of SUI in women in July 2007 (NICE guidance/ IP398): there was no RCT evidence and only small case series data were available. The report concluded that the current evidence on the safety and efficacy of SIMS was inadequate in quality and quantity, and recommended that SIMS should only be performed in the context of research. Similarly, the Cochrane review of minimally invasive MUS found no randomised evidence evaluating SIMS.[9]

1.2. Rationale for the study

The European guidelines[11] on the management of urinary incontinence describe two concepts of MUS for the surgical treatment of SUI in women: (1) Tension-free MUS that include all MUS that depend on their post-insertion fixation mechanism on friction to nearby tissues within their relatively long trajectory of insertion such as SMUS (both RP-TVT and TO-TVT); one type of non-anchored SIMS (Contasure-Needleless) also fits into this group. (2) Anchored MUS that include all other SIMS and other anchored slings such as Remeex TRT; the latter is mainly used in women with recurrent SUI.[12,13] SIMS fundamentally differs from SMUS because they have a shorter trajectory of insertion and therefore need a robust anchoring mechanism to the obturator complex with a strong post-insertion pull-out force. All currently available SIMS share the same tape material (type 1 polypropylene) and the insertion technique through a single vaginal incision; however, they differ in the type/robustness of the anchorage mechanism used.[14,15] A number of recently developed

SIMS, such as Ajust, Altis, and TFS, have an added advantage that allow post-anchorage adjustment of the sling tension and have been shown in independent animal studies, assessing their immediate and delayed extraction forces, to be associated with the strongest and most robust anchoring mechanism to the obturator complex.[14,15]

A multicentre prospective cohort study of adjustable anchored SIMS- Ajust® in 100 women has shown its acceptability (75%) and feasibility (97%) to be done under local anaesthesia (LA).[16] We recently concluded our multicentre prospective pilot RCT[17] where 137 women were randomised to adjustable anchored SIMS-Ajust® (n=69), performed under LA, vs. SMUS (TVT- O™; n=68). At a minimum of 12 months follow-up (FU); there were no significant differences in the patient-reported success rate (OR 0.895; 95% CI 0.344, 2.330; p= 1.000), objectives success rate (OR 0.929; 95%CI 0.382, 2.258; p=1.00) and re-operation rates (OR 0.591; 95% CI 0.136, 2.576; p=0.721) between both groups. Comparable number of women reported significant improvement in their QOL (quality of life) (p=0.190) and sexual function (p=0.699) in both groups. Similar results were recently reached by a Deutsch group in similar small RCT, Similarly, a number of observational studies assessing adjustable anchored SIMS, from various countries (UK, France, Italy, USA and Israel), with varying cohort sizes, and length of FU (6-12 month) have shown similar patient-reported and objective success rates of 85% - 91%.[18-21]

A recent updated systematic review and meta-analysis[22] comparing the effectiveness and complications of SIMS versus SMUS for the surgical management of female SUI; included a total of 26 RCTs (n = 3308 women). The results showed that, after excluding RCTs evaluating TVT-Secur which was clinically irrelevant having been excluded from clinical practice, that there was no evidence of significant differences between SIMS and SMUS in patient-reported cure rates (risk ratio [RR]: 0.94; 95% confidence interval [CI], 0.88–1.00) and objective cure rates (RR: 0.98; 95% CI, 0.94–1.01) at a mean follow-up of 18.6 months. These results pertained on comparing SIMS versus TO-TVT and RP-TVT separately. SIMS had significantly lower postoperative pain scores (weighted means difference [WMD]: -2.94; 95% CI, -4.16 to -1.73) and earlier return to normal activities and to work (WMD: -5.08; 95% CI, -9.59 to -0.56 and WMD: -7.20; 95% CI, -12.43 to -1.98, respectively). SIMS had a non-significant trend towards higher rates of repeat continence surgery (RR: 2.00; 95% CI, 0.93–4.31). The authors performed an exploratory subgroup analysis of four RCTs evaluating adjustable anchored SIMS (Ajust and TFS) versus TO-TVT and found no evidence of significant differences in patient- reported or objective cure rates. However, it is important to note that they found no RCTs evaluating Altis.[22] The authors concluded that on excluding TVT-Secur, there was no evidence of significant differences in patient-reported and objective cure between currently used SIMS and SMUS at midterm follow-up while associated with more favourable recovery time. The authors urged caution in interpretation of results due to the heterogeneity of the small trials included, lack of blinding of the assessors which can be source of bias, level of incomplete data leading to attrition bias, and the relatively short term of follow-up.

Evidence of longer term outcomes for adjustable anchored SIMS are now emerging. In July 2012, Sivaslioglu et al,[23] reported the 5-year follow up for their RCT (n=80) comparing adjustable anchored SIMS-TFS® vs. SMUS. The results showed objective and patient-reported success rates of 83% & 89% in the SIMS-TFS® group compared to 75% & 78% in the SMUS group; the difference was not statistically significant (p=0.16). Most recently, Naumann et al[24] reported their prospective observational study of 51 women who underwent SIMS-Ajust® with 20-29 month follow- up; the patient-reported success rate was 86%.

The cost-effectiveness of any new technology is a pre-requisite for its adoption in clinical practice and therefore we have conducted the first health economic analysis of adjustable anchored SIMS - Ajust® versus SMUS-TVT-O™ [25] which was performed alongside our pilot RCT (n=137).[17] The health economic outcome measures were incremental costs to

the health services, patient QALYs and incremental cost per QALY. Results have shown an incremental total cost savings to the health service of £142/procedure with adjustable anchored SIMS, not counting the further potential economic gain of earlier return to work in these women. There were no significant differences in QALYs generated compared to SMUS; 95%CI -0.008 to 0.002. Assuming these results were generalisable to all currently performed MUS procedures in England and Wales (approximately 11,000 in 2010),[10] our analyses suggest the potential for substantial cost savings to the NHS in the UK of about £1.5 million per year. However, these results have to be confirmed in the definitive RCT.

The above evidence has led to a consensus amongst urologists and urogynaecologists that an adequately powered RCT with clinical effectiveness as the primary end point is now timely and required to inform surgeons, patients and decision makers with the most clinically-effective, cost- effective surgical treatment for primary SUI, that is associated with the least burden on patients QoL and NHS resources.

1.3 STUDY OBJECTIVES

The aim of this 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 hypothesis being tested is that patient-reported success rate following surgical treatment with adjustable anchored SIMS procedures is non-inferior to tension–free SMUS while the former is associated with less post-operative pain, shorter hospital stay, earlier recovery and consequently earlier return to usual activities/ work and is more cost-effective than SMUS.

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 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-LUTS qol) over the follow up period.

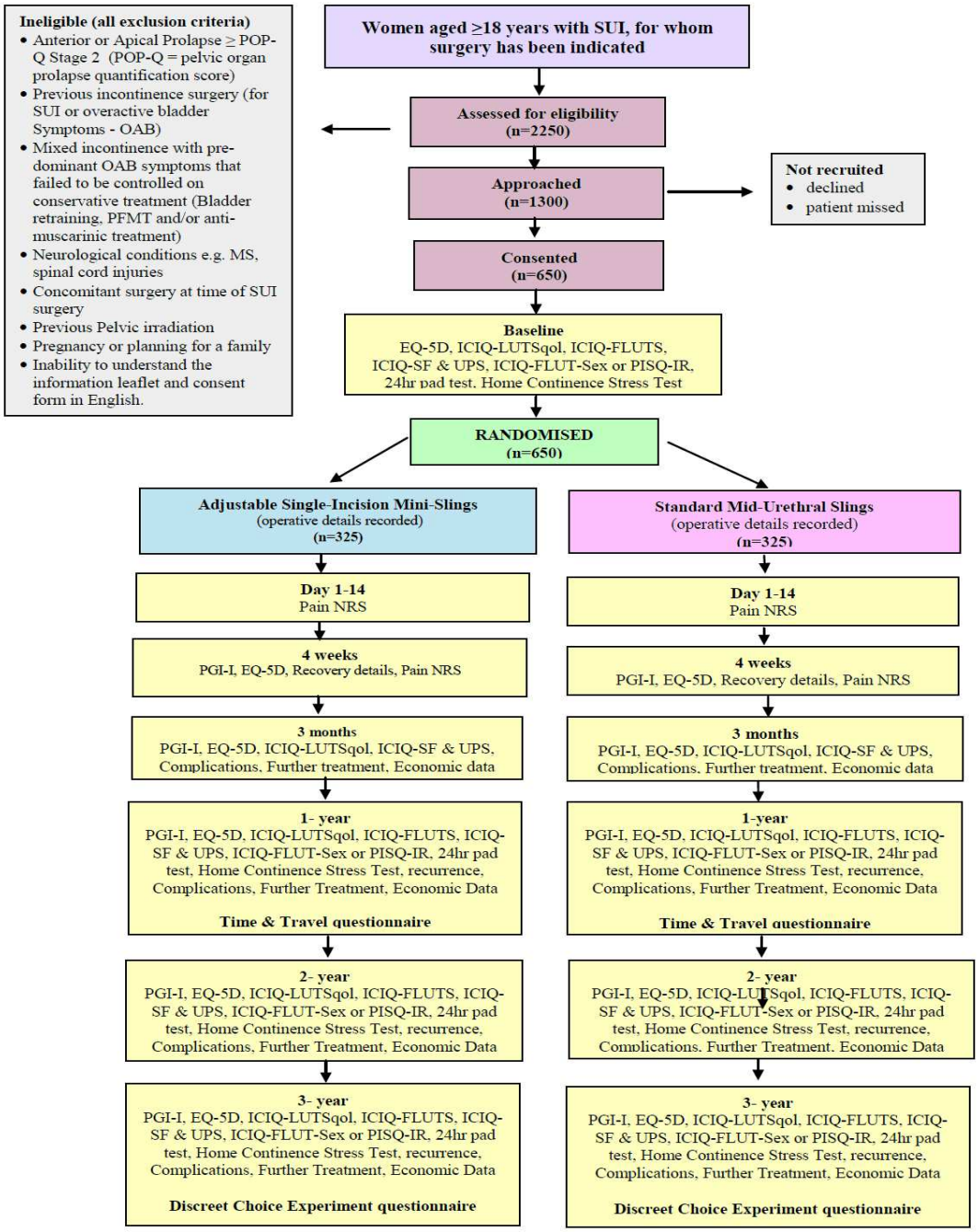
The secondary objectives are to compare objective success rates (24 hour pad test/ home cough stress test), other patient-reported outcomes including: postoperative pain scores and health related QoL using the ICIQ-LUTSqol, impact on other urinary symptoms (ICIQ-FLUTS), impact on sexual function (ICIQ-FLUT- Sex/ PISQ-IR), complication rates, disease recurrence and costs to the NHS and patients.

2. Methods:

2.1. Study Design

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. The trial structure is presented below (Figure 1).

Figure 1 Flow diagram



2.2. Intervention to be evaluated

The interventions being compared are: 1) tension-free standard mid-urethral slings (SMUS) including RP-TVT & TO-TVT and 2) 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: mono-filament & 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 outcomes.

SMUS will be performed under general anaesthetic (GA) or deep intravenous sedation while adjustable anchored SIMS will be done under local anaesthetic (LA) as an opt-out policy (i.e. LA will be the standard type of anaesthesia for adjustable anchored SIMS unless specifically declined by a participant requesting GA). Furthermore, participant's requests for conversion to GA will be respected at any stage of the procedure. A standard LA protocol, which we have previously published and successfully used in two previous studies[16,17] will be used as a guidance (Appendix 1).

All participants, in both arms, will receive pre-operative analgesia (30-60 minutes prior to the operation): Paracetamol and Non-steroidal anti-inflammatory drug NSAID (Diclofenac Sodium or Ibuprofen); a vaginal application of EMLA cream (a 5% emulsion preparation, containing 2.5% each of lidocaine/prilocaine) and optional 10ml of intra-urethral Instillagel (anaesthetic, antiseptic lubricant). All participants would receive preoperative/ intra-operative prophylactic broad spectrum antibiotics. A cystoscopy (rigid or flexible) will be performed in all women following insertion of the sling, regardless of the study arm. It is worth noting that rigid cystoscopy was well tolerated by all women under LA in the pilot RCT. No vaginal packs or catheters would be routinely inserted. Postoperatively all participants will undergo voiding assessment including assessment for post-voiding residual urine volume (PVR) using a bedside bladder-scanner (Appendix 2, guidance protocol & flowchart for postoperative voiding assessment).

2.1.1 Adjustable anchored single-incision mini-slings (SIMS)

A standard combination of fast and delayed action LA (dose dependant on participant's body weight) will be infiltrated vaginally into either side of the urethra, the vaginal angles (sulci) and behind the inferior pubic ramus into the obturator complex (e.g. using a curved black spinal needle and/or pudendal block needle). Women will be accompanied by a nurse for support. All participating surgeons will use an adjustable anchored SIMS that meet the pre-specified criteria described below. A standardised insertion technique will be used by all surgeons following the original description of the particular SIMS used. Most adjustable anchored SIMS, however, have a fairly similar procedure of insertion. We describe below the standard insertion steps for the adjustable anchored SIMS (Ajust®-CR Bard and Altis®-Coloplast): women will be positioned in Lithotomy position with hips flexed at 90-100 degree. LA infiltration as above; a sub-urethral vertical vaginal incision (~1.5 cm) will be made; bilateral para-urethral tunnels created reaching to the posterior margin of the inferior pubic ramus but without piercing the obturator membrane. Further infiltration of LA into the obturator membrane; SIMS, with the 'fixed anchor' end mounted on the applicator, would be introduced through the pre-dissected para-urethral tunnel until reaching behind the inferior pubic ramus. The applicator would then pivot slowly behind the ramus and through the obturator complex allowing the fixed anchor to maintain its position in the obturator membrane and muscles at points equivalent to 10 & 2 O'clock in relation to the

urethral orifice. The insertion steps would be repeated on to the other side allowing the 'adjustable anchor' to be fixed in the contra-lateral obturator complex. The SIMS is now robustly anchored and the tension would then be adjusted as required to achieve continence whilst avoiding voiding difficulty. Performing the cough stress test can prove very helpful in this adjustment process and is recommended .The adjustable anchor would then be locked in case of the Ajust (not required with Altis), a cystoscopy will be performed to exclude perforation and the vaginal incision closed.

2.1.2 Standard tension-free mid-urethral slings (SMUS):

The choice of SMUS whether retropubic or transobturator will depend on surgeons' experience. We expect a 50% representation of each type of SMUS in the control arm.

2.1.3 Retropubic Tension Free Vaginal Tape (RP-TVT):

RP-TVT will be Type-1 polypropylene Mesh (mono-filament and macro-porous - pore size ≥75 um). The Tension Free Vaginal Tape (TVT®) procedure was developed by Ulmsten and Petros.[26] The procedure will be done under GA or intravenous sedation as per the standard practice of each surgeon. The bladder will be emptied with a Foley catheter. Close to the superior rim of the pubic bone, two 1-cm long transverse incisions 3cm either side of the midline will be made after injection of LA into the abdominal skin just above the symphysis pubis, down along the back of the pubic bone to the retropubic space and vaginally into the peri- urethral area. An incision ~1.5 cm long will be made in the midline of the suburethral vaginal wall; followed by dissection of the peri-uretheral tunnels to allow introduction of the TVT® needle. A stent will be inserted into the Foley catheter to deviate the urethra-vesical junction away from the path of the needle. The TVT® needle perforates the urogenital diaphragm and will be brought up to the abdominal incision 'shaving' the back of the pubic bone. The procedure will then be repeated on the other side, and a cystoscopy will be performed to exclude perforation. The cough stress test may then be performed, according to surgeon's standard technique, and the sling adjusted in a tension-free fashion and the incisions are closed.

2.1.4 Transobturator Tension Free Vaginal Tape (TO-TVT):

TO-TVT will be Type-1 polypropylene Mesh (mono-filament and macro-porous - pore size ≥75 um). All procedures will be performed under GA as originally described by Delrome[72] and de-Leval[28] for the outside-in and inside-out routes respectively. Women are positioned in Lithotomy position with hips flexed at 100-110 degrees and LA may be infiltrated into the vaginal angles; the latter is not a standard practice however is recommended in a similar regime to the one used in the adjustable SIMS insertion (above). ~1.5 cm sub-urethral longitudinal vaginal incision will be made and bilateral para-urethral tunnels created reaching to the posterior margin of the inferior pubic ramus. Bilateral groin incisions are made 1-2cm lateral to the labio-femoral fold and 2 cm above level of urethra. The transobturator trocar is inserted from groin incisions at 90 degree to pierce the obturator muscles and membranes and then guided by the surgeon's finger to the vaginal incision. TO-TVT is then mounted on the trocar and the trocar is withdrawn in reverse order. The previous 2 steps are repeated on the contra-lateral side achieving TO-TVT sub-urethral placement and the TO-TVT is then adjusted tension-free. For the inside-out technique of insertion, TO-TVT would be introduced in the reverse route from the vaginal incision towards the groin using the winged guide to protect the lower urinary tract (LUT). A cystoscopy will be performed to exclude LUT injury. Vaginal and skin incisions will then be closed.

2.3. 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.

Setting: Secondary and tertiary care acute hospital settings across the UK. NHS Grampian will be the clinical co-ordinating centre and house the Chief Investigator (CI).

Each unit will have at least one participating surgeon who is competent in performing SIMS under LA prior to enrolling in the RCT. Ideally, the surgeon will have performed 20 adjustable anchored SIMS procedures (with 10 performed under LA); within prospective audit and results submitted to a national surgical database. The CI, or a delegated expert in SIMS, will provide training in SIMS under LA for enrolling surgeons as necessary and will ensure adequate expertise of surgeons in both arms. Surgeons will be experienced in at least one type of SMUS (RP-TVT or TO-TVT) and will have performed an adequate workload in the preceding 2 years.

2.3.1. Selection of participants

As standard practice, clinicians will assess patients likely to require surgery for SUI. A log will be taken of all potentially eligible patients assessed in order to document the reasons for non-inclusion in the study (e.g. reason they were ineligible, or declined to participate) to inform the CONSORT diagram.

Brief details of potentially eligible patients will be recorded in the screening logs at each site (these will be an aid to monitoring potential participant inclusion).

2.3.2. Planned inclusion and exclusion criteria

Inclusion criteria:

Women aged 18 years or over with SUI, who have been referred to one of the collaborating units from across the UK, and for whom surgery has been indicated. Women will have completed their families, failed or declined conservative treatment (supervised pelvic floor muscle training - PFMT). All women will have urodynamic stress incontinence, or urodynamic mixed urinary incontinence with predominant SUI bothering symptoms. The small group of women with pure symptoms & signs of SUI ***and*** no symptoms of overactive bladder (OAB) or voiding dysfunction (VD) can be included without urodynamic investigations as per the updated NICE guidelines.

Pre-operative urodynamic investigations include: free uroflowmetry, post-voiding residual urine volume assessment and subtracted filling cystometry. Other tests such as Urethral pressure profile and Leak point pressure pressures are not mandatory however are welcome as they will inform a number of the pre-planned secondary outcomes.

Exclusion criteria:

Women will be excluded if they have one or more of the following:

- Anterior or Apical Prolapse ≥ POP-Q Stage 2 (POP-Q = pelvic organ prolapse quantification score)
- Previous incontinence surgery (for SUI)
- Mixed incontinence with pre-dominant OAB symptoms (defined as OAB failed to be controlled on conservative treatment such as Bladder retraining, PFMT and/or anti-muscarinic treatment)
- Neurological conditions e.g. MS, spinal cord injuries.
- Concomitant surgery at time of SUI surgery.
- Previous Pelvic irradiation
- Pregnancy or planning for a family.
- Inability to understand the information leaflet and consent form in English

2.4. Recruitment and Study Procedures

2.4.1. Identifying participants

Local procedures at the participating hospitals are different and the timing and mode of approach to patients and the consent process will vary to accommodate both the variability at the sites and the needs of the patients. Where possible, the Patient Information Sheet will be sent to patients together with their clinic appointments ensuring that they have ample time (>24 hours) for consideration before being approached by the research team at the clinic.

Patients likely to require surgery for SUI and who meet the eligibility criteria will be identified at the pre-assessment clinics, urodynamic clinics and outpatient urology/ gynaecology clinics by the consultant, research nurse (RN) or a designated team member. The consultant/ research nurse (RN) will introduce the study to the patient and provide her with the Patient Information Sheet as appropriate; answer any queries and if appropriate the participant may sign the consent form; receive the baseline assessment pack for completion at home and bring back on the day of surgery or send back to the site using pre-paid post.

Patients whose first approach is at the clinic will be given as much time as they require to consider participation; patients may make a decision to participate at this time or may agree to be contacted at home by the local RN. If a patient agrees to be contacted at home she will receive a telephone call from the local RN to discuss any queries. If a patient agrees to the study at that stage, then arrangements will be made for baseline assessment and consenting; this could be done as a separate appointment or at a pre-admission clinic. As above, participants can complete the baseline assessment pack at home and bring back on the day of surgery or send back to the site using pre-paid post. These arrangements can be individualised for each centre.

2.4.2. Informed consent

The patient information leaflet explains that the trial is investigating the use of either adjustable single-incision mini-slings (SIMS) or standard tension-free mid-urethral slings (SMUS) for the surgical management of stress urinary incontinence (SUI) in women. Signed informed consent forms will be obtained from the participants in all centres. Participants who cannot give informed consent (e.g. due to incapacity) will be not be eligible for participation. The participant's permission will be sought to inform their general practitioner that they are taking part in this trial.

2.4.3. Randomisation and allocation

Eligible and consenting participants will be randomised to one of the two study groups in a 1:1 allocation ratio using the randomisation application at the trial office at CHaRT. This randomisation application will be available 24 hours a day, 7 days a week as both an Interactive Voice Response (IVR) telephone system and as an internet based application. The randomisation will use a minimisation algorithm based on centre and previous supervised Pelvic Floor Muscle Training within the last two years [PFMT: Yes/No]. Women will be further randomised to receive short versus detailed sexual function questionnaire.

2.4.4. Follow-up procedures

Eligible patients that have given signed informed consent to participate in the study will be randomised to either SIMS or SMUS. They will be asked, at baseline, to complete the pre-operative questionnaire pack which includes few questions on participants' demographic details and pre-operative health/ medications. It also includes validated questionnaires for symptom severity of UI and its impact on quality of life (QoL) and sexual function: the EQ-5D; ICIQ-SF; Urgency perception scale (UPS); ICIQ-LUTSqol; ICIQ-FLUTS; ICIQ-FLUTSsex (or PISQ-IR); and to perform 24-hours pad test and home continence stress test (see Appendix 3 Objective Assessment of Urinary Incontinence Within the SIMS Trial - Protocol).

At day 1 to day 14 they will be asked to complete the pain score and use of analgesics questions by self-completed post-operative diary. At 4 weeks post-operative participants

will be asked to complete a short questionnaire (on the last section of the diary) to capture pain, use of analgesia, complications, return to work/ normal activities, PGI-I and EQ-5D. At 3 months post-operative, participants will be asked to complete a number of questionnaires: to measure the PGI-I; EQ-5D; ICIQ-SF; UPS; questions related to health services resource; and to report any complications or further treatment received for UI. In addition, at 12, 24 and 36 months post-randomisation, participants will be asked to complete a questionnaire to measure the PGI-I, recurrence, further treatment received and questions related to health services resource use, in-addition to all baseline assessment pack. Taking into account the inevitable waiting time between randomisation and receiving the surgical treatment (average surgical waiting list is 8-12weeks) and in-addition the clinical importance of assessing the outcomes at 12 month postoperative, we aim to send the 1 year follow-up pack at 15 month post-randomisation. This strategy will ensure that the vast majority of participants are at least 12 month post-operative at time of capturing the primary outcome. In-addition, at 20 months participants will be asked to fill out an additional economic data questionnaire, which will include the patient time and travel costs questionnaire. Sending this questionnaire at 20 months will minimise patient burden when completing the annual questionnaire. The discrete choice experiment (DCE) will be completed at the end of the 3 year follow-up period.

Questionnaires and up to two reminders will be sent to participants by post. Non-responders to the 12m post-randomisation questionnaire will be contacted by phone for a short interview to capture the primary outcome (PGI-I; a single item question to mark the outcome of the operation as described in section 5.1). If the participant indicates at this phone call her wish to withdraw from the study a "Change of Status Form" will be completed as below. Participants will be sent a voucher (of modest value) as a token of appreciation for completion and return of the 3 month and follow-up questionnaires.

2.4.5. Change of Status/Withdrawal procedures

Participants will remain on the trial unless they choose to withdraw consent or if they are unable to continue for a clinical reason. If a participant withdraws consent, participant questionnaires will not be collected. A member of the research team will contact the participant by phone and complete the "change of status form" which includes the participant's instructions on what parts, or whole, of the study they may wish to withdraw from. Unless a participant specifically declines the research team will continue to collect relevant data from their health care records such as ONS and NHS central registries. All other changes in status with the exception of formal withdrawal of consent will mean the participant is still followed up for all study outcomes wherever possible.

2.4.6. *Subsequent arrangements (if applicable)*

Informing key people

Following formal trial entry:

The Study Office will:

i) Inform the participant's General Practitioner (by letter enclosing information about SIMS and Study Office contact details).

The local Research Nurse will:

i) File the Hospital Copy of the Consent form in the hospital notes along with information about SIMS; give one copy to the patient; file one copy to the local site file and send one copy to the Study Office in Aberdeen.
ii) Use the SIMS internet database to enter data regarding the participant, including data required to complete randomisation
iii) Data entry onto the study database as soon as practical.
iv) Forward a copy of study documentation when and as requested by the Study Office in Aberdeen to facilitate quality control.

Notification of/by GPs

GPs are asked to contact the Study Office if one of the participants moves, becomes too ill to continue or dies, or any other notifiable event or possible serious adverse event occurs. Alternatively, staff at the Study Office may contact the GP.

2.5. SAFETY

The SIMS trial involves procedures for the surgical management of SUI in women which are well established in clinical practice. Adverse effects may occur during or after any type of surgery.

2.5.1. Definitions

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant. Each initial AE will be considered for severity, causality or expectedness and may be reclassified as a serious event.

Adverse events are not:

- Continuous and persistent disease or symptom, present before the trial, which fails to improve; such as urgency, urgency incontinence, voiding dysfunction, pain or dyspareunia
- Treatment failure: persistence or recurrence of urinary incontinence.

Worsening pain or where the site of pain changes is an adverse event.

A **serious adverse event** (SAE) is any AE, that:

- results in death;
- is life threatening (i.e. the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe);
- results in persistent or significant disability or incapacity;
- requires an un-planned re-admission to the hospital (defined as "participant admitted as an in-patient with ≥ 1 night hospital stay"). This excludes hospital ward attenders for minor issues such as lower UTI, voiding difficulties or other issues considered by the PI to be minor. This information will be routinely collected on the postoperative form and/ or the Supplementary hospital visit form as appropriate.
- requires prolongation of existing hospitalisation (defined as >36 hours postoperative hospital stay). This excludes prolongation of hospital stay for minor issues such as voiding difficulties; such information will be routinely collected on the Operation and clinical data form. Prolongation of hospital stay due to social/ geographical reasons will not be considered.
- Is otherwise considered medically significant by the investigator

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition, or complication arising from either, will not be considered as an (S)AE.

Specific expected adverse events:

In this surgical trial the following events are potentially expected:

Intra-operative complications: Bleeding, bladder/urethral injury, bowel injury, nerve injury (obturator/ dorsal nerve of clitoris), injury to blood vessels, hypersensitivity to the local/

general anaesthetics and/ or any of the medications or materials used; pain; shaking/ dizziness, change of procedure or device and / or type of anaesthesia.

Immediate Postoperative complications: Pain in the hip/ thigh/ or the vagina, Infection (chest, urinary tract), bleeding, fever, haematuria, syncope, dizziness, voiding difficulties/ urinary retention and thromboembolism.

Later Postoperative complications: Pain in the hip/ thigh/ or the vagina, mesh extrusion, mesh erosion to the vagina or lower urinary tract, haematoma, abscess formation and nerve injury. In-addition, new onset or worsening of any of the following: dyspareunia, vaginal discharge, voiding difficulties/ urinary retention, long-term self-catheterisation, urgency/ urgency incontinence.

2.5.2 Procedures for detecting, recording, evaluating & reporting AEs, SAEs

2.5.2.1 Detecting AEs and SAEs

All AEs and SAEs must be recorded from the time a participant consents to join the study until follow-up is complete.

Follow-up questionnaires will enquire about any AE/SAE occurrence; in-addition, participants will also be asked if they have been admitted to hospital and/or seen a healthcare professional.

2.5.3 Recording AEs and SAEs

Depending on severity, when an AE/SAE occurs, it is the responsibility of the Investigator (or delegated medical personnel) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator (or the delegated medical personnel) should then record all relevant information in the CRF and if required on the SAE form.

Information on SAE to be collected includes type and date of event, Investigator assessment of severity and causality and any investigation/ treatment required.

Planned hospital visits for conditions other than those associated with urinary incontinence and/ or its treatment will not be collected or reported. Further UI treatment will be recorded as a secondary outcome measure, but will not be reported as serious adverse events.

2.5.4 Evaluating AEs and SAEs

All adverse events will be assessed in respect of seriousness, relationship to study intervention, whether expected or unexpected, and therefore, whether constituting a Serious Adverse Event (SAE) by the local PI, CI or their deputies.

Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined in Section 4.1.

Assessment of Causality

The Investigator must make an assessment of whether the AE/SAE is likely to be related to any of the research procedures according to the following definitions:

- **Related**: resulted from any of the procedures required by the protocol, whether or not this procedure is the specific intervention under investigation and whether or not it would have been administered outside the study as normal care.

- **Unrelated**: where an event is not considered to be related to any of the research procedures.

Assessment of Severity

The Investigator should make an assessment of severity for each AE/SAE and complete a SAE form should any of the SAE criteria in 4.1 be met.

Assessment of Expectedness

When assessing expectedness refer to the expected events (Section 4.1)

An example for the assessment of an AE; Intra-operative bleeding will be collected as an AE on the operative form, however if >500mls a SAE form will be completed.

2.5.5 Reporting AEs and SAEs

Reporting responsibilities of the CI

When an SAE form is uploaded onto the trial website, the Trial Manager and CI will be automatically notified. The CI or Trial Manager will notify the sponsor within 24 hours of receiving completed forms for "un-expected" and 7 days of receiving completed forms for an "expected" SAE. The sponsor will then provide the final assessment of the SAE.

The CI (or Trial Manager) will report any "related *and* unexpected SAEs" to the main REC and the DMC within 15 days of the CI becoming aware of it. All other SAEs will be summarised and reported to the Ethics Committee, the Funder, the DMC and the Trial Steering Committee in their regular progress reports.

If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

2.6. OUTCOME MEASURES

This RCT will assess and compare adjustable anchored SIMS vs. tension-free SMUS in respect of: patient-reported success rates; objective success rates; impact on urinary symptoms, complications, recovery, health-related QoL and sexual function; costs to health services up to 3 years follow-up. We will use the same assessment tools and QoL instruments were used in our pilot RCT which observed a 97% response rate.

2.6.1. Primary outcome measure

The primary outcome measure will be patient-reported success rate measured by the validated PGI-I at 12-months. Patient-reported success rates reflect patients' experience compared to the objective measures, which can overestimate the success of SUI surgery.[27] The primary outcome is assessed by the PGI-I: a 1-item questionnaire designed to assess the patient's impression of changes in her urinary symptoms. The PGI-I asks the patient to best describe her urinary symptoms, compared with how they were before the study intervention, on a 7-point scale scored as: (1) "very much better," (2) "much better," (3) "a little better," (4) "no change," (5) "a little worse," (6) "much worse," or (7) "very much worse." 'Success' will be defined as responses of 'very much better' or 'much better'; this will determine whether the women are satisfied with their operation and hence consider their symptoms are resolved and not seek further treatments. The primary economic outcome will be incremental cost per QALY gained at 12-months. The above measures will also be assessed at 2 and 3 years.

2.6.2. Secondary outcome measures

2.6.2.1 Complications including: lower urinary tract injuries; haemorrhage (blood loss ≥ 200mls); post-operative voiding dysfunction; pain, mesh extrusion/erosion, dyspareunia, long-term self-catheterisation, new-onset or

worsening urgency/ urgency incontinence.; assessed as appropriate at 3 and 12 months then yearly up-to 3 years

2.6.2.2 Post-operative pain using a pain Numerical Rating Scale (NRS): assessed day 1-14.

2.6.2.3 Objective success rates: assessed by 24 hour pad test at 12 months and yearly up to 3 years.

2.6.2.4 Other lower urinary tract symptoms using the International Consultation on Incontinence Questionnaire - Female Lower Urinary Tract Symptoms long form (ICIQ-FLUTS) and/or short form (ICIQ-SF) at 3and 12-months and yearly up to 3 years.

2.6.2.5 Health-related QoL profile (area under the curve) derived from EQ-5D, pain scores and ICIQ-LUTSqol measurements at 1,3 and 12-months and yearly up to 3 years

2.6.2.6 Impact on sexual function derived from ICIQ-FLUTsex/ or PISQ-IR measurements at; 12-months and yearly up to 3 years.

2.6.2.7 Recurrence of SUI, re-operation rates for SUI, further treatment received such as physiotherapy, medical treatment (Selective Nor-adrenaline Re-uptake Inhibitors and/ or Anti-muscarinic treatment).

2.6.2.8 Secondary economic outcomes include;

- NHS and patient primary and secondary care resource use and costs at 12-months and yearly up to 3 years.
- Incremental cost-effectiveness derived from responses to the ICIQ-LUTS over the follow-up period at 12-months and yearly up to 3 years.
- Incremental net benefit (NB) calculated from the responses to the discrete choice experiment (DCE) at end of the 3yr follow-up.

2.7. DATA COLLECTION AND PROCESSING

2.7.1. Measuring outcomes

Participant follow-up questionnaires will be triggered by date of surgery up-to 3months then by date of randomisation thereafter.

2.7.2. Schedule of data collection

The components of follow-up are shown in the table 1 below:

Table 1 Source and timing of measures

	Baseline	Surgery details	Day 1-14	4-weeks	3-months	12-months*	20-months	Year 2	Year 3
Clinical/surgery details	○	○							
Pain NRS/ Daily Text messaging			●	●					
Recovery				●	●				
PGI-I				●	●	●		●	●
EQ-5D	○			●	●	●		●	●
ICIQ-LUTSqol	○				●	●		●	●
ICIQ-FLUTS	○					●		●	●
ICIQ-SF & UPS	○				●	●		●	●
ICIQFLUT-Sex/ or PISQ-IR	○					●		●	●
24-hours pad test	○					●		●	●
Home continence stress test	○					●		●	●
Health care resource utilisation/complications/recurrence/furth					●	●		●	●

er treatment									
Time & travel questionnaire							●		
DCE,									●

○ Clinic/Hospital ● Out-with clinic (e.g. post, email, phone, etc)

* Taking into account the inevitable waiting time between randomisation and receiving the surgical treatment (average surgical waiting list is 8-12weeks) and in-addition the clinical importance of assessing the outcomes at 12 month postoperative, we aim to send the 1 year follow-up pack at 15 month post-randomisation. This strategy will ensure that the vast majority of participants are at least 12 month post-operative at time of capturing the primary outcome.

2.7.3. Data processing

Research Nurses will enter locally-collected data in the centres. Staff in the Study Office will work closely with local Research Nurses to ensure that the data are as complete and accurate as possible. Follow up questionnaires to participants will be sent from and returned to the Study Office in Aberdeen. Extensive range and consistency checks will further enhance the quality of the data.

2.8. SAMPLE SIZE, PROPOSED RECRUITMENT RATE AND MILESTONES

2.8.1. Sample size

A non-inferiority design is appropriate for this trial because the proportion having success at 12 months in women managed with SMUS is high. Adjustable anchored SIMS is not hypothesised to increase this proportion; however may have other potential benefits as outlined previously. It is therefore important to show that SIMS is clinically non-inferior to SMUS and to measure these other dimensions (such as cost-effectiveness, mediated through shorter stay and earlier recovery, QoL mediated through less pain, and any safety signals via the complication rate) in an adequately powered, pragmatic RCT with long enough follow up. It is essential therefore that the study is powered to demonstrate non-inferiority within an appropriate margin, and hence this clinical outcome is the correct choice as primary outcome. A 10% inferiority margin has been deemed by expert clinicians as the maximum inferiority margin in clinical effectiveness that would be accepted should SIMS prove to be superior in other outcomes such as shorter hospital stay, less postoperative pain, earlier recovery and more cost-effective. In such case, adjustable anchored SIMS would then reliably be able to be considered as a first line surgical treatment of women with primary SUI.

Published literature suggests that the P1, the percentage success rate at 12-months in the SMUS arm will be about 85%; identical results were confirmed by our pilot RCT. Estimating P2, the percentage of success in the adjustable anchored SIMS arm, is more difficult due to lack of published evidence; a crude meta-analysis of the 12 month outcome data from our multicentre pilot RCT and few other small studies indicates a similar P2 of 85%.

Power estimates were explored by simulating trials of fixed sample size (using equal allocation) with binary responses generated by P1 = 85% and P2 = 85%. Power was then estimated as the proportion of simulated trials where the lower bound of the 2-sided confidence interval satisfied P1-P2 > -10%. Simulations, run in Stata 11.2, show that a trial of 275 per arm or 550 in total is required for the lower bound of the estimated 95% confidence interval to rule inferiority at the specified level with 90% power. Adjustment for potential 15% drop-out inflates the trial to 650 in total. For comparison, a trial of this size would have above 80% power to test superiority on secondary outcomes of difference in means of size one quarter of a standard deviation (or 90% power to detect an effect size of 0.28 standard deviations).

In our multicentre pilot RCT;[17] 131/137 women (95.6%) completed the 12 month follow-up and showed no significant differences in the patient-reported success rate (OR 0.895; 95%CI 0.344, 2.330; p=1.000) between adjustable anchored SIMS (Ajust®) vs. SMUS (TVT-O™) groups. These results, together with similar results from other studies detailed above[16–21] provide assurances for the reliability of our sample size calculations. A statistical reviewer previously queried whether we had considered the implications if in fact the success of the 2 procedures were not identical but slightly different. If we consider success rates of 84% and 85%, the study retains 90% power to detect a slightly larger margin of non-inferiority of around 11%, and so to all intents and purposes a sample size of 650 remains adequate.

2.8.2. Recruitment rates and milestones

Our recruitment rate estimates are based on data from the pilot multicentre RCT comparing adjustable anchored SIMS (Ajust®) with SMUS (TVT-O™). We believe that these centres are representative of the UK; 137 women were recruited across 6 centres at a rate of 3.4 per centre per month. Overall, 137/181 (76%) patients were willing to be randomised; however we have used a more conservative estimate of 50% in our recruitment projection. Therefore, it has been estimated that in order to approach 1300 eligible patients to randomise the required 650 patients, 25 centres would need a throughput of at least 90 eligible patients per centre per year to recruit 3 patients per month. The recruitment projection is based on 18 months of recruitment (months 7-24 inclusive) and allows for set-up, holidays and waiting list times. We expect a staggered recruitment of centres with all centres active by the end of Month 18. The first 45 patients will be recruited by Month 12, 256 patients by Month 18 and the remaining 367 patients by Month 24 making a total of 668 patients.

The Gantt Chart and Recruitment Projection are in Appendix 4.

3. ANALYSES PLAN

3.1. Statistical Analysis

Treatment groups will be described at baseline and follow-up using numbers (with percentages), means (with standard deviations) and medians (with inter-quartile ranges) where relevant. Primary and secondary outcomes will be compared using generalised linear models, with adjustment for design covariates. As standard we also adjust all our surgical RCTs for centre/surgeon effects; adjustment for centre/surgeon will be by random effect in the trial analysis.

For the primary outcome, we plan to dichotomise the PGI-I responses with ‘success’ defined as ‘very much better’ or ‘much better’ and the rest of responses as failures; this will determine whether the women are satisfied with their operation and hence consider their symptoms are resolved and do not seek further treatments. In-addition, this definition of “success” is widely used within the research field of surgical treatment of SUI, and was used in our pilot RCT, and therefore will allow comparing our results to other trials in the literature. We will also perform a secondary analysis using ordinal regression on the 7-point PGI-I scale, so potentially using more of the information in the outcome. However, we do not propose adopting this ordinal regression as the primary analysis since the underlying proportional odds model makes strong assumptions about the consistency of treatment effect across the levels of response, and particularly in the context of a non-inferiority design there may be departures from those assumptions that would interfere with establishing whether the simple hypothesis around the (non-inferiority) of the binary ‘success’ under the two operations had been shown.

The statistical analysis of the primary outcome will be by the usual intention-to-treat (ITT) and also a suitably defined per protocol (PP) analysis (to reflect the unique nature of non-

inferiority designs and the issue that ITT for such designs may not be the most conservative analysis and inflate the true type I error rate, given that in a non-inferiority design the null hypothesis is that the interventions are not non-inferior or equivalent). If the two approaches return material differences in interpretation this will be investigated carefully. Results will be displayed as estimates and 95% confidence intervals derived from appropriate generalised linear models. Confidence intervals around observed differences will then be compared to the pre-specified non-inferiority margin.

Secondary outcomes will be analysed similarly. Outcomes such as post-operative pain will be assessed under a superiority hypothesis as we believe that this will be lower in the intervention arm. As stated in the sample size section, there is above 80% power to detect a difference of a quarter of a standard deviation under a superiority hypothesis. Subgroup analyses (appropriately analysed by testing treatment by subgroup interaction) will explore possible treatment effect modification. All analyses will follow a carefully documented Statistical Analysis Plan. Pre specified subgroups are:

- Mixed incontinence versus pure stress incontinence
- Urodynamic versus Clinically diagnosisis of Stress Urinary Incontinence.
- 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

Effect of Pregnancy: MUS procedures are generally offered to women after having completed their families and therefore subsequent pregnancy is usually a rare event that is unlikely to be balanced between both trial arms. If a woman falls pregnant after receiving treatment within the RCT, her data will be censored at the time of confirmed pregnancy for the primary analysis. This small number of women will still be followed up for all outcome data as usual, and if the numbers warrant, a sensitivity analysis including them will be undertaken on the primary outcome.

The Trial Steering Committee and an independent Data Monitoring and Ethics Committee (DMC) will be asked to review and comment on the Statistical Analysis Plan prior to analysis. There are no plans for any formal interim analyses to be seen by the DMC. A single main analysis will be performed on the 12 month primary outcome and repeated on the 2 and 3 year outcomes. The DMC will meet before recruitment begins, or as soon as practical, to agree the terms of reference and other procedures.

3.2. ECONOMIC EVALUATION

Our primary health economic evaluation will be from a health service provider's (NHS) perspective; however we will also present data from a wider societal perspective. These data will include costs to patients of time and travel, costs to carers and family members and costs to society as a whole, estimated from lost productivity as a result of time off work / away from normal activities.

3.2.1. Collection of resource use and cost data

Health care resource use will be collected using patient administered questionnaires asking patients to retrospectively recall their contacts with health care professionals relating to their incontinence. This questionnaire will be administered at 3 & 12 months then yearly for 3 years. It is generally accepted that patient recall is accurate up to 12 months and it is highly unlikely that a patient would not remember significant events relating to their disease over this time period. Data collected will include secondary care contacts (hospital inpatient admissions, outpatient appointments) and primary care contacts (e.g. GP contacts, nurse

contacts, physiotherapist consultations) and prescription drug medications. These health care utilisation data will be combined with unit cost information for the use of specific resources using standard sources.[29-31] Data on costs for each group (SIMS and SMUS) will be summed to provide an average cost per patient trial participant. Sensitivity analysis will be used to explore various distributions of cost data as well as various methods for the imputation of missing and censored data. We will provide a comprehensive range of deterministic sensitivity analyses to test any assumptions we make in our analysis on the overall results. For example, we will test best and worst case scenarios for the intervention cost (whether all procedures in the SIMS arm are conducted under GA or LA). The impact of any missing data and methods of data imputation on our results will also be tested. We will test the impact of these and a range of other sensitivity analyses, to be determined as the trial progresses on all our results (e.g. cost utility analysis and cost benefit analysis).

3.2.2. Participant costs

Out of pocket patient expenses (including the purchase of containment products), private health care costs, travel costs and costs associated with lost days at work will also be collected using the patient administered questionnaire and incorporated into the patient perspective analysis. Costs of family members and/or carers will also be collected as part of the trial and reported.

3.2.3 Quality of life

Health state valuations will be based upon the responses to the ICIQ-LUTSqol (baseline, 3, 12 months and annually over the follow up period) and EQ-5D administered at baseline, 1, 3 & 12 month and annually over the follow up period. These data will be transformed into utility values using standard algorithms. QALYs will be calculated, using the area under the curve methods, with any differences between groups being reported. Both measures will be compared and contrasted and tested for comparability in measuring outcomes for these women.

3.2.4. Cost effectiveness

The analysis will use the estimates of mean costs and QALYs as described for each trial participant to estimate the incremental cost-effectiveness ratio at 12-month follow-up period and where appropriate the analysis will mirror that of the statistical analyses. Cost-effectiveness (cost per QALY gained) will also be reported over the 3 year follow up period. The results of the analysis will be presented as incremental costs, effects and incremental cost per QALY. Bootstrapping of cost and QALY differences as well as a range of one way and multi-way deterministic sensitivity analyses will be conducted to address uncertainty in the estimates. Cost per QALY data will also be presented in the form of cost-effectiveness acceptability curves (CEAC).

3.2.5. Discrete choice experiment (DCE)

Previous research[32] has suggested that EQ-5D questionnaire may not fully capture the benefits from successfully treating incontinence. They may not fully represent patient preferences for treatments and their associated outcomes. Therefore, we will conduct a discrete choice experiment (DCE) to elicit preference for the process, patient experience and health outcomes. A DCE presents respondents with a series of hypothetical choices that describe the choice alternatives by their underlying attributes and ask respondents which alternative they prefer. The values of the attributes vary across choice scenarios, and by observing the choices people make it is possible to infer their preferences over the attributes of the goods under study. The extent to which an individual values an intervention depends upon the levels of these attributes.[33] DCEs are commonly used to identify people's preferences in a variety of non-market situations/services/commodities.[34-36]

The attributes and levels for the DCE will be informed by systematic literature searching and advice sought from clinical experts. Attributes might include preferences for general / local anaesthetic, preferences for pain levels, cure and improvement rates, impact on

activities of daily living, etc. These attributes and levels will be combined to identify profiles that will be used to develop scenarios to present the study participants. The questionnaire will be piloted amongst a convenience sample to refine all practical aspects of the survey and to ensure that trade-offs can be made between the identified attributes. Once the pilot is complete and the questionnaire has been refined it will be administered to the trial participants at the end of the 3yrs follow-up.

Experimental design techniques will be used to 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. The resultant costs and utilities will be used to estimate preference based quality weights for this condition.

4. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

4.1. Study Office in Aberdeen

The Study Office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. The Trial Manager in CHaRT at Aberdeen will take responsibility for the day to day transaction of study activities. The Data co-ordinator will provide clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data using the study web data entry portal). The CHaRT Quality Assurance Manager will oversee the demonstration that CHaRT's standard operating procedures for trials are being followed, including observance of the appropriate principles of GCP.

At the centres, the recruitment coordinators/ research nurses will be responsible for all local processes involved in identifying, consenting, and randomising the participants, along with facilitating the delivery of the intervention, under the supervision of the lead surgeon.

The SIMS Study Office Team will meet formally at least monthly during the course of the study to ensure smooth running and trouble-shooting. Finally, we intend to produce a regular SIMS Newsletter for participants and collaborators to inform everyone of progress and maintain enthusiasm.

4.2. Local organisation in sites

The Local PI and research nurse will be responsible for all aspects of local organisation including identifying, consenting, and randomising the participants, along with facilitating the delivery of the intervention and notification of any problem or unexpected developments for the duration of the trial. They will be responsible for ensuring that study data is collected for baseline assessments, collecting and recording participant study data on study specific Case Report Forms and will log all the details onto the remote web-based data capture system as soon as practical after completion. The local PI will return all study documents to the study office in Aberdeen when requested.

4.3. Project Management Group (PMG)

The study will be supervised by a Project Management Group (PMG). The chair of this group will be the Chief Investigator (Mohamed Abdel-Fattah) and will consist of representatives from the Study Office and grant holders. The PMG will meet every 3 months, including face-to-face in month 1 and month 6 in the first year. It is expected that,

once the project is underway, the majority of these meetings will be held by teleconference; however, the PMG will also meet face-to-face at least annually. In addition, the PMG will also meet at the annual Trial Steering Committee meeting.

4.4. Trial Steering Committee (TSC)

The study is overseen by a Trial Steering Committee (TSC). The membership of this committee is comprised of the four independent members along with the Co-Chief Investigators (John Norrie & Mohamed Abdel-Fattah) or a nominated delegate. The trial sponsors, other SIMS grant-holders and key members of the central office (e.g. the trial manager) can participate in TSC meetings but are not members. The funders will be notified in advance of meetings and a representative invited to attend. Other relevant experts may be invited to attend as appropriate. Details of the membership of the TSC can be found at the start of this protocol. CHaRT has adopted the TSC Charter adapted from the DAMOCLES Charter for DMCs and suggests to the independent TSC members that they adopt the Terms of Reference contained within. The TSC will meet approximately yearly.

4.5. Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be convened. The DMC will be made up of members listed at the start of this protocol, one of whom is an experienced statistician. After the trial has been initiated the DMC will initially meet to agree its terms of reference and other procedures. CHaRT has adopted the DAMOCLES Charter for DMCs and suggests to the independent DMC members that they adopt the Terms of Reference contained within.

The committee will meet regularly to monitor the unblinded trial data and serious adverse events and make recommendations as to any modifications that are required to be made to the protocol or the termination of all or part of the trial.

4.6. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

4.6.1. Research Governance

The trial will be run under the auspices of CHaRT based at HSRU, University of Aberdeen. This will ensure compliance with Research Governance, and provide centralised trial administration, database support and economic and statistical analyses. CHaRT is a registered Clinical Trials Unit with particular expertise in running multicentre RCTs of complex and surgical interventions.

The PMG will ensure, through the TSC that adequate systems are in place for monitoring the quality of the study (compliance with GCP) and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the study.

4.6.2. Data protection

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Participant's details will be stored on a secure database under the guidelines of the 1998 Data Protection Act and regular checks and monitoring are in place to ensure compliance. Data are stored securely in accordance with the Act and archived to a secure data storage facility. The senior IT manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Participants will be allocated an individual specific trial number and their details will be anonymised on the secure database. We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired.

4.6.3. Sponsorship

The University of Aberdeen and NHS Grampian are the co-sponsors for the trial.

4.7. QUALITY ASSURANCE

The trial will be monitored to ensure that the study is being conducted as per protocol, adhering to Research Governance, and the appropriate regulations. The approach to, and extent of, monitoring (specifying both central and on-site monitoring) will be specified in a trial monitoring plan which is usually initially determined by a risk assessment, undertaken prior to start of trial.

4.8. DATA HANDLING, RECORD KEEPING AND ARCHIVING

Clinical data will be entered into the database by the local investigator and/or research nurse working in each hospital site, together with data from questionnaires completed at clinic. Questionnaires returned by post to the trial office will be entered there. Staff in the trial office will work closely with local research nurses to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

The co-sponsors are responsible for ensuring that trial data is archived appropriately. Essential data shall be retained for a period of at least 10 years following close of study.

4.9. SATELLITE STUDIES

It is recognised, that the value of the study may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advance with the PMG. REC approval will be sought for any new proposal, if appropriate.

5. ETHICS AND REGULATORY APPROVALS

5.1. Ethics Approval: The North of Scotland Research Ethics Committee has reviewed and approved this study. The study will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines. We believe this study does not pose any specific risks to individual participants beyond standard surgical procedures, nor does it raise any extraordinary ethical issues. Annual progress reports and a final report at the conclusion of the trial will be submitted to the North of Scotland REC within the timelines defined in the regulations.

5.2. Finance and Insurance: The trial is funded by a grant awarded by the NIHR Health Technology Assessment programme. The necessary trial insurance is provided by the University of Aberdeen.

6. Authorship Publication

All RCTs conducted by CHaRT have a commitment to publish the findings of the research. At a minimum this trial will have a results paper published in a peer- reviewed medical/scientific journal. If all grant-holders and researcher staff fulfil authorship rules, group authorship will be used under the collective title of 'the SIMS Trial Group'. The CI, and possibly other members of the trial group will take responsibility for drafting the paper and this will be recognised by line" the CI (as primary author), followed by the other authors *and* the SIMS Trial Group'.

For reports which arise from the trial but where some members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to CI and the named individual(s) *for* the SIMS Trial Group.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the Project Management Group.

We intend to maintain interest in the study by publication of SIMS newsletters at intervals for staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final SIMS Newsletter to all involved in the trial. Further details on the publication policy can be found in Appendix 5.

6. Discussion

The SIMS study is a key outcome study that should answer the important research question of whether adjustable SIMS should be utilized in clinical practice as a first line surgical treatment option for women with primary SUI.

This study is a pragmatic patient-oriented trial aiming to capture a true representation of the actual patient population. The inclusion/exclusion criteria were chosen to allow the capturing of the relevant patient group.

This trial seeks to follow standard local patterns and pathways of care with the only additional intervention being randomisation between the two treatment strategies under test and collection of baseline and outcome information.

The results will inform clinicians and policy makers on the cost-effectiveness of this relatively new technology compared to the SMUS. The long-term follow-up in the SIMS study is crucial to address the long-term successes rate and adverse events of MUS in general and SIMS in specific.

6.1. Dissemination:

The dissemination plans include (1) HTA monograph; (2) presentation at international scientific meetings; (3) publications in high-impact open access peer-reviewed journals; (4) presentations at health economic and health services research meetings. The results of the trial will be included in the updates of NICE (National Institute of Clinical Excellence) and EAU (European Association of Urology) guidelines; these two specific guidelines directly influence practice of all the UK and worldwide specialists respectively. In-addition, a plain English language summary of the main findings and results will be presented for relevant patient organisations and communities, including the bladder and bowel foundation. This will ensure user relevance in dissemination of the results.

6.2. Trial Status

The SIMS study is currently recruiting in 20 UK research centres. The first patient was randomised on 4th February 2014 with follow-up completed at end of February 2020.

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Authors' Contributions: MAF concieved the idea and wrote the protocol; JN contributed to the study design and the statistical analysis; GML contributed to the study design, the sample size calculation and wrote the statistical analysis plan; MK designed and wrote the economic analysis plan; PA contributed to the clinical aspects of the protocol; JND contributed to the study design and clinical aspects of the protocol; JW contributed the layman summary as the patient representative; KM contributed to the study design, flow/ gantt charts; TD and AMD contributed to the trial oversight and the protocol amendments.

Competing Interests: MAF has been previously speaker and or trainer for Bard, Astellas, Pfizer, AMS and Coloplast. He received travel grants to attend medical conferences from various companies and previously performed a research-led project funded by a research Grant from Coloplast which was received and administered by University of Aberdeen. MAF was the Chairman of Scottish Pelvic Floor Network which received support from different pharmaceutical and devices Companies. MAF and Phil Assassa have provided industry-sponsorship proctorship training sessions to a number of surgeons training in SIMS prior to the study. None of the co-applicants have any financial interest, shares or sit on the advisory board for any relevant device companies.

Appendix 1

Local Anaesthesia (LA) Guidance for SIMS RCT

Pre-operative Analgesia:

All participants, in both arms, should receive within 30-60 minutes of the operation:

- Paracetamol Oral/PR 1gm and NSAID (Diclofenac Sodium -100mg or Ibuprufen 400mg – Oral/ PR) and,
- Oral opiate analgesia (Oral morphine 10-20 mg or MST Continus 10-30mg) if not contra-indicated; (the lower doses are to be used in women ≥ 65 years) and,
- EMLA cream applied vaginally to the sub-urethral area by the patient/ nurse (a 5% emulsion preparation, containing 2.5% each of lidocaine/prilocaine)
- Optional:
  - Instillagel 5ml intra-urethral by the nurse (anaesthetic, lubricant).
  - For anxious patients: oral anxiolytic (Temazepam 10-20 mg) can be given if not contra-indicated (if so please consider omitting the opiate analgesia).
  - Consider oral /IM anti-emetics in women receiving opiate analgesia

Local Anaesthesia:

- Fast-acting LA: Infiltrate 4-5 mls of Lignocaine 1% with adrenaline 1:200,000 (max dose 3.5mg/kg bodyweight) into the peri-urethral area at site of future application of instruments (using orange needle 25G). This is fast acting LA, in-addition to the EMLA cream, will allow you to apply instruments to the peri-urethral area.

- Long-acting LA: Infiltrate ± 40mls of Levo-Bupivacaine 2.5mg/ml (Chirocaine - max dose 1.5 mg/kg bodyweight) OR, Bupivacaine 0.25% with adrenaline 1:200,000 (Carbostesin - max dose 2 mg/kg bodyweight) into:

  a) the vaginal angles (using green needle 21G) until the bilateral vaginal sulci are obliterated (5 mls on each side)

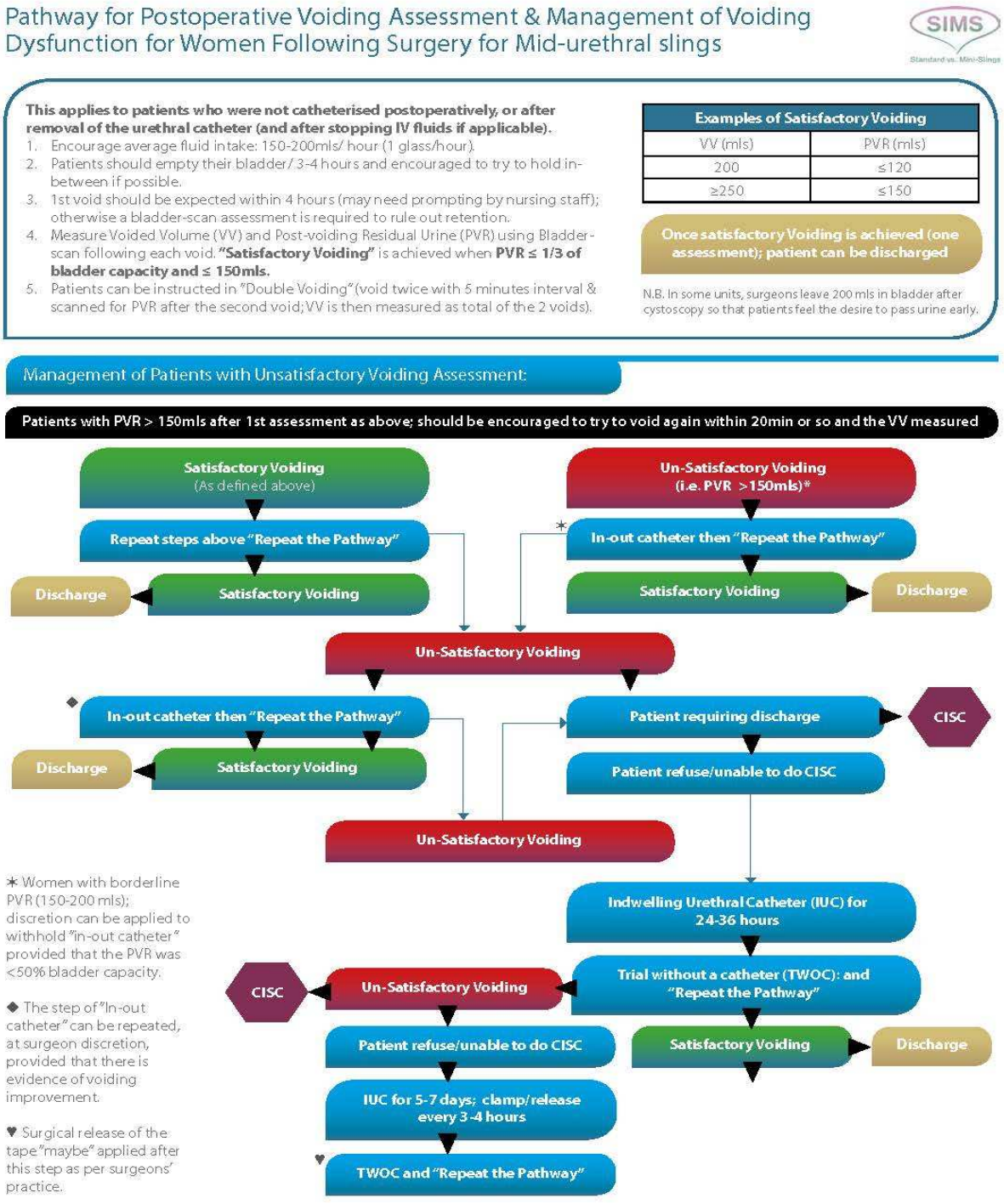
  b) the obturator membrane and muscles (using curved black spinal needle 22G to hook behind the inferior pubic ramus; 10 mls on each side).

- Once the para-urethral tunnels are dissected up-to the obturator membranes, further infiltration (using Pudendal block or Spinal needle), into the exact site of insertion of the SIMS anchor is recommended using fast acting LA (5mls) and followed by long-acting LA (5mls) on each side.

- ❖ Patients should accompanied by a dedicated nurse during the operation for support.
- ❖ All doses should to be tailored to patients' medical condition and weight.
- ❖ We recommend you adhere to this guidance however deviation in the way of infiltration or the type of LA is accepted provided you keep within the general types and appropriate doses described.

SIMS - RCT LA Guidance V2 - Feb 2014

Appendix 2: Postoperative Voiding Assessment Protocol:



Appendix 3: Objective Assessment of Urinary Incontinence within the SIMS Trial - Protocol

- Participants will receive: ≥4 pre-weighed pads in two transparent self-sealing plastic bags (for the 24 hour pad test), 2 tissue continence sheets (for the home continence stress tests - HCST), instructions on how to perform the tests and a test evaluation questionnaire.

- Each participant will be asked to:-
    - Perform a standardised HCST.
    - Perform the 24-hours pad test (as described by the international continence society) using the provided pre-weighed pads.
    - Repeat the HCST at the end of the 24 hour pad test.
    - Report all their observations on the provided test questionnaire.

- At the end of the tests, women will be asked to complete an open question regarding their experience of the tests. Women's satisfaction/convenience with each test will also be assessed using 10-point Likert scales.

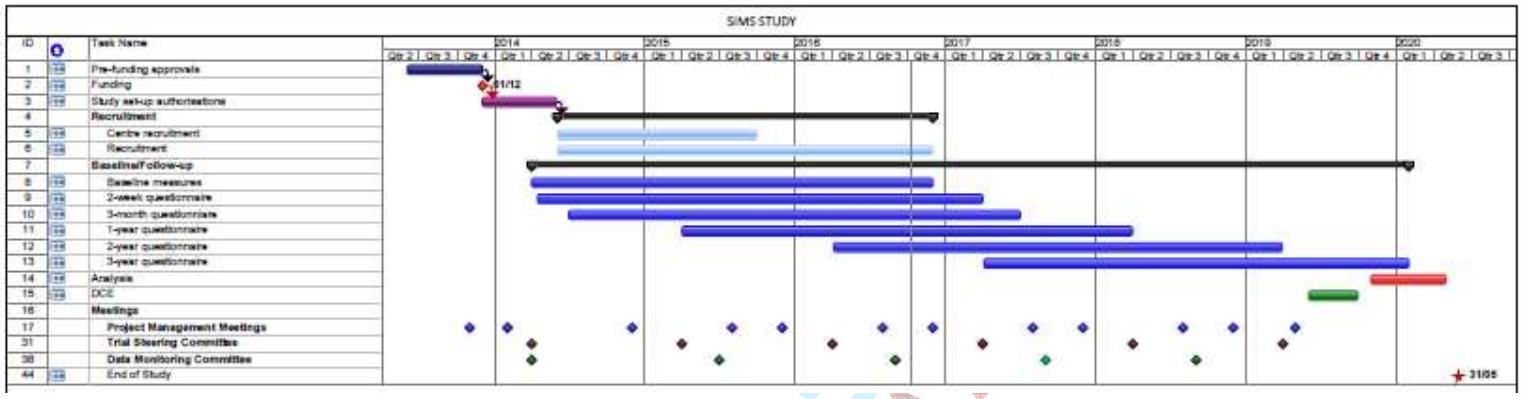
- **Pre-operatively**, participants will be asked to perform this test 24 hours prior to their operation and return any used pads and the test questionnaire to the local RN/team on the day of their surgery. The returned pads will be weighed using a gram sensitive scale and the pad gain, if any, will be calculated and recorded.

- **At 1, 2 and 3 years postoperative**, participants will return the completed test questionnaire and any used pads in the self-addressed pre-paid envelope provided within 24 hours of completion.

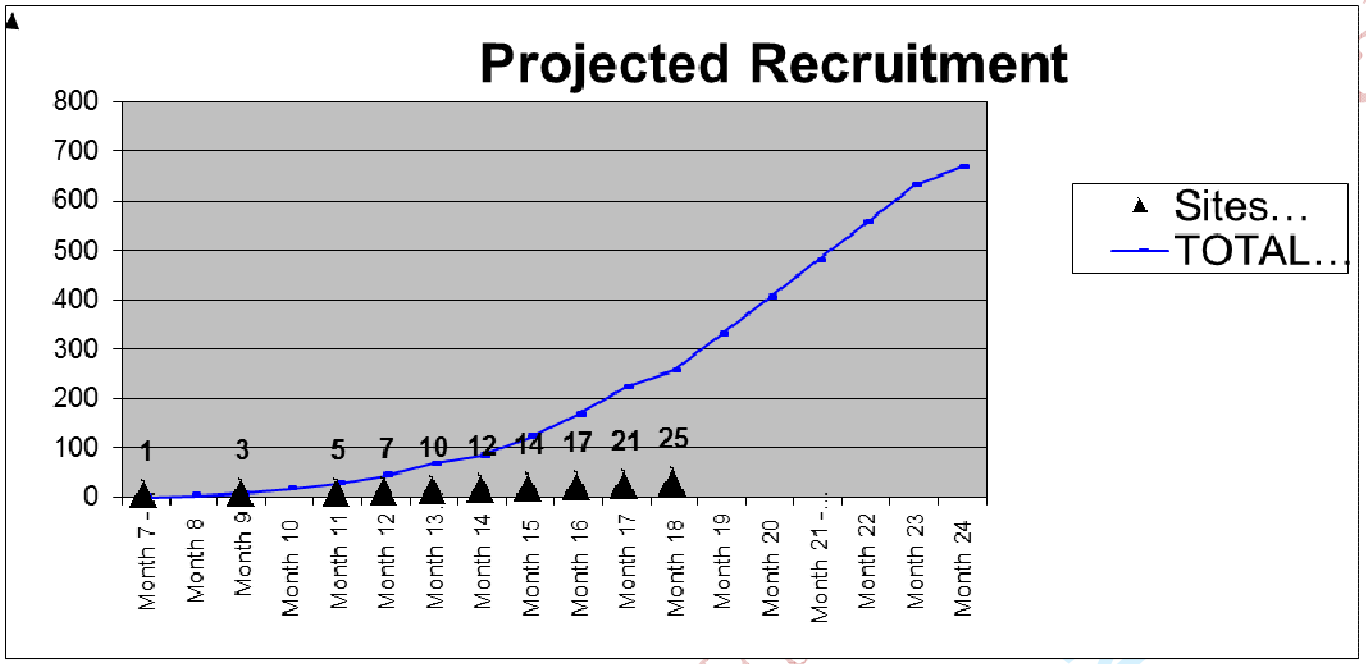
- The returned pads will be weighed by the researcher using a gram sensitive scale and the pad gain, if any, will be calculated and recorded.

Appendix 4A:

The Gantt chart:



Appendix 4B: Recruitment projection:



BMJ Open

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

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

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Abstract:

Introduction:

Single incision mini-slings(SIMS) represent the 3rd generation of mid urethral slings(MUS). They have been developed with the aim of offering a true ambulatory procedure for treatment of female stress urinary incontinence(SUI) with reduced morbidity and earlier recovery while maintaining similar efficacy to Standard mid-urethral slings(SMUS). The aim of this study is to determine the clinical and cost- effectiveness of adjustable anchored SIMS compared to tension-free SMUS in the surgical management of female SUI, with 3-years follow-up.

Methods and analysis:
A pragmatic multicentre non–inferiority randomised controlled trial

The primary outcome measure is the patient-reported success rate measured by the Patient Global Impression of Improvement(PGI-I) at 12-months. The primary economic outcome will be incremental cost per QALY gained at 12-months.

Secondary outcome measures include: Adverse events; Objective success rates; Impact on other lower urinary tract symptoms; Health-related quality of life (QoL) profile and sexual function; and re-operation rates for SUI.. **Secondary economic outcomes include:** NHS and patient primary and secondary care resource use and costs; Incremental cost-effectiveness; and Incremental net benefit.

The statistical analysis of the primary outcome will be by intention-to-treat (ITT) and also a per protocol (PP) analysis. Results will be displayed as estimates and 95% confidence intervals. Confidence intervals around observed differences will then be compared to the pre-specified non-inferiority margin. Secondary outcomes will be analysed similarly.

Ethics and dissemination:
The North of Scotland Research Ethics Committee has approved this study(13/NS/0143).

The dissemination plans include HTA monograph; presentation at international scientific meetings; and publications in high-impact open access journals; the results will be included in the updates of NICE and EAU (European Association of Urology) guidelines; these two specific guidelines directly influence practice in the UK and worldwide specialists respectively. In-addition, plain English language summary of the main findings/results will be presented for relevant patient organisations.

Registration details: ISRCTN93264234
The SIMS study is currently recruiting in 20 UK research centres. The first patient was randomised on 4th February 2014 with follow-up completed at end of February 2020.

Strengths and limitations of this study:

Strengths:

- The study design is a multicentre randomised controlled trial; the gold standard study design to assess surgical interventions.
- The pragmatic nature of the study (with few inclusion or exclusion criteria) ensures the generalisability of the results (i.e. the findings will be applicable to most women and most surgeons in the NHS).
- The study protocol ensures surgeons' experience in both study arms prior to participation. This avoids the potential bias associated with limited surgical experience with relatively new surgical techniques.
- Primary outcome is the patient-reported success rate obtained by a validated instrument. Patient-reported outcomes are recognised as the most relevant clinical trial outcomes in this field.
- Outcomes are obtained by postal questionnaires; this eliminates the assessor bias.
- An integrated health economic analysis is a major strength
- The analysis plan for this non-inferiority design randomised trial includes both Intention to treat and per-protocol analysis
- Similar protocol was used in other similar trials worldwide allowing comparison of the results and relevant meta-analysis.

Limitations:

- The lack of an objective assessment post-intervention can be seen by some as a limitation.

GLOSSARY OF ABBREVIATIONS	
AE	Adverse Event
AUC	Area under the curve
BSUG	British Society of Urogynaecology
CEAC	Cost-effectiveness Acceptability Curve
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CI	Confidence Interval p11
CONSORT	Consolidated Standards of Reporting Trials
CTU	Clinical Trial Unit
DCE	Discrete Choice Experiment
DMC	Data Monitoring Committee
EQ-5D	EuroQol Group's 5 dimension health status questionnaire
FU	Follow up
GA	General Anaesthetic
GCP	Good Clinical Practice
GP	General Practitioner
HCST	Home continence stress test
HRQoL	Health Related Quality of Life
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
ICIQ-FLUTS	International Consultation on Incontinence Modular Questionnaire – Female Lower Urinary Tract Symptoms
ICIQ-FLUTS-SEX	International Consultation on Incontinence Modular Questionnaire – Female Lower Urinary Tract Symptoms – Gender specific sexual matters module
ICIQ-LUTS QOL	International Consultation on Incontinence Modular Questionnaire – Female Lower Urinary Tract Symptoms – Condition specific quality of life module
ICIQ-SF	International Consultation on Incontinence Modular Questionnaire – short form
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to treat
IVR	Interactive Voice Response (randomisation)
LA	Local anaesthetic
LUT	Lower urinary tract
MS	Multiple Sclerosis
MUS	Mid-urethral slings
N	Newtons
NB	Net benefit
NHS	National Health Service
NHSG	National Health Service Grampian
NICE	National Institute for Clinical Excellence
NIHR	National Institute Health Research
NRS	Numerical rating scale
OAB	Overactive bladder
OR	Odds Ratio
PFMT	Pelvic Floor Muscle Training
PI	Principal Investigator
PIL	Patient Information Leaflet
PISQ-IR	Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire

PMG	Project Management Group
POP-Q	Pelvic organ prolapse quantification system
PP	Per protocol
PVR	Post-voiding residual urine volume
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
RN	Research nurse
RP-TVT	Retropubic tension-free vaginal tape
RR	Risk Ratio
SAE	Serious Adverse Event
SD	Standard Deviation
SIMS	Single-incision mini-slings
SMUS	Standard mid-urethral slings
SOP	Standard Operating Procedures
SUI	Stress urinary incontinence
SUSAR	Suspected Unexpected Serious Adverse Reaction
TO-TVT	Transobturator tension-free vaginal tape
TSC	Trial Steering Committee
TVT	Tension free vaginal tape
TVT-O	Tension free vaginal tape – Obturator
UI	Urinary incontinence
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
UoA	University of Aberdeen
UPS	Urgency perception scale
VD	Voiding Dysfunction
WMD	Weighted means difference
WTP	Willingness to pay

INTRODUCTION

1.1. Background

Urinary incontinence (UI) is a common and distressing condition for women particularly over the age of 40 years.[1] In the UK, it is estimated that 6 million (40%) of this age group have clinically significant UI symptoms, 1 million (6.2%) are bothered by symptoms and 0.33 million (2.2%) find them socially disabling.[2] UI has a negative impact on a woman's social, physical and psychological wellbeing; leading to embarrassment, low self-esteem and social isolation. UI is associated with negative effects on the productivity of working women, with some avoiding employment because of fear of embarrassing situations.[3] UI has significant cost implications to the individual and the health service. 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] Costs borne by women in terms of out of pocket expenses were £230 million[5] or £290 per woman per year.[6] All values reported are inflated to 2009 values. It is therefore clear that 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.

SUI is the most common type of UI in premenopausal women, accounting for almost 50% of cases.[7] It is defined as involuntary leakage of urine on effort, or exertion, or on sneezing or coughing. Initial management of SUI includes conservative therapy such as pelvic floor muscle training (PFMT), biofeedback, electrical stimulation or drugs. When conservative therapy fails, in about one third of cases, surgery is the next option.[7] 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/ procedure[8] i.e. a total of £22.5 million/year. The Cochrane review of minimally invasive MUS[9] concluded that there was no evidence of significant differences in patient-reported outcomes between RP-TVT & TO-TVT and therefore the control arm for the proposed RCT is a pragmatic combination of these 2 types of SMUS. Analysis of BSUG database showed that the vast majority of SMUS in UK are done under GA or deep intra-venous patient sedation.[10]

SIMS represent the 3rd generation of mid urethral slings (MUS); they have been developed with the aim to offer a true ambulatory procedure for treatment of SUI with reduced morbidity, earlier recovery while maintaining similar efficacy to SMUS. NICE undertook an Interventional Procedure overview of SIMS[1] for the management of SUI in women in July 2007 (NICE guidance/ IP398): there was no RCT evidence and only small case series data were available. The report concluded that the current evidence on the safety and efficacy of SIMS was inadequate in quality and quantity, and recommended that SIMS should only be performed in the context of research. Similarly, the Cochrane review of minimally invasive MUS found no randomised evidence evaluating SIMS.[9]

1.2. Rationale for the study

The European guidelines[11] on the management of urinary incontinence describe two concepts of MUS for the surgical treatment of SUI in women: (1) Tension-free MUS that include all MUS that depend on their post-insertion fixation mechanism on friction to nearby tissues within their relatively long trajectory of insertion such as SMUS (both RP-TVT and TO-TVT); one type of non-anchored SIMS (Contasure-Needleless) also fits into this group. (2) Anchored MUS that include all other SIMS and other anchored slings such as Remeex TRT; the latter is mainly used in women with recurrent SUI.[12,13] SIMS fundamentally differs from SMUS because they have a shorter trajectory of insertion and therefore need a robust anchoring mechanism to the obturator complex with a strong post-insertion pull-out force. All currently available SIMS share the same tape material (type 1 polypropylene) and the insertion technique through a single vaginal incision; however, they differ in the type/robustness of the anchorage mechanism used.[14,15] A number of recently developed

SIMS, such as Ajust, Altis, and TFS, have an added advantage that allow post-anchorage adjustment of the sling tension and have been shown in independent animal studies, assessing their immediate and delayed extraction forces, to be associated with the strongest and most robust anchoring mechanism to the obturator complex.[14,15]

A multicentre prospective cohort study of adjustable anchored SIMS- Ajust® in 100 women has shown its acceptability (75%) and feasibility (97%) to be done under local anaesthesia (LA).[16] We recently concluded our multicentre prospective pilot RCT[17] where 137 women were randomised to adjustable anchored SIMS-Ajust® (n=69), performed under LA, vs. SMUS (TVT- O™; n=68). At a minimum of 12 months follow-up (FU); there were no significant differences in the patient-reported success rate (OR 0.895; 95% CI 0.344, 2.330; p= 1.000), objectives success rate (OR 0.929; 95%CI 0.382, 2.258; p=1.00) and re-operation rates (OR 0.591; 95% CI 0.136, 2.576; p=0.721) between both groups. Comparable number of women reported significant improvement in their QOL (quality of life) (p=0.190) and sexual function (p=0.699) in both groups. Similar results were recently reached by a Deutsch group in similar small RCT, Similarly, a number of observational studies assessing adjustable anchored SIMS, from various countries (UK, France, Italy, USA and Israel), with varying cohort sizes, and length of FU (6-12 month) have shown similar patient-reported and objective success rates of 85% - 91%.[18-21]

A recent updated systematic review and meta-analysis[22] comparing the effectiveness and complications of SIMS versus SMUS for the surgical management of female SUI; included a total of 26 RCTs (n = 3308 women). The results showed that, after excluding RCTs evaluating TVT-Secur which was clinically irrelevant having been excluded from clinical practice, that there was no evidence of significant differences between SIMS and SMUS in patient-reported cure rates (risk ratio [RR]: 0.94; 95% confidence interval [CI], 0.88–1.00) and objective cure rates (RR: 0.98; 95% CI, 0.94–1.01) at a mean follow-up of 18.6 months. These results pertained on comparing SIMS versus TO-TVT and RP-TVT separately. SIMS had significantly lower postoperative pain scores (weighted means difference [WMD]: -2.94; 95% CI, -4.16 to -1.73) and earlier return to normal activities and to work (WMD: -5.08; 95% CI, -9.59 to -0.56 and WMD: -7.20; 95% CI, -12.43 to -1.98, respectively). SIMS had a non-significant trend towards higher rates of repeat continence surgery (RR: 2.00; 95% CI, 0.93–4.31). The authors performed an exploratory subgroup analysis of four RCTs evaluating adjustable anchored SIMS (Ajust and TFS) versus TO-TVT and found no evidence of significant differences in patient- reported or objective cure rates. However, it is important to note that they found no RCTs evaluating Altis.[22] The authors concluded that on excluding TVT-Secur, there was no evidence of significant differences in patient-reported and objective cure between currently used SIMS and SMUS at midterm follow-up while associated with more favourable recovery time. The authors urged caution in interpretation of results due to the heterogeneity of the small trials included, lack of blinding of the assessors which can be source of bias, level of incomplete data leading to attrition bias, and the relatively short term of follow-up.

Evidence of longer term outcomes for adjustable anchored SIMS are now emerging. In July 2012, Sivaslioglu et al,[23] reported the 5-year follow up for their RCT (n=80) comparing adjustable anchored SIMS-TFS® vs. SMUS. The results showed objective and patient-reported success rates of 83% & 89% in the SIMS-TFS® group compared to 75% & 78% in the SMUS group; the difference was not statistically significant (p=0.16). Most recently, Naumann et al[24] reported their prospective observational study of 51 women who underwent SIMS-Ajust® with 20-29 month follow- up; the patient-reported success rate was 86%.

The cost-effectiveness of any new technology is a pre-requisite for its adoption in clinical practice and therefore we have conducted the first health economic analysis of adjustable anchored SIMS - Ajust® versus SMUS-TVT-O™ [25] which was performed alongside our pilot RCT (n=137).[17] The health economic outcome measures were incremental costs to

the health services, patient QALYs and incremental cost per QALY. Results have shown an incremental total cost savings to the health service of £142/procedure with adjustable anchored SIMS, not counting the further potential economic gain of earlier return to work in these women. There were no significant differences in QALYs generated compared to SMUS; 95%CI -0.008 to 0.002. Assuming these results were generalisable to all currently performed MUS procedures in England and Wales (approximately 11,000 in 2010),[10] our analyses suggest the potential for substantial cost savings to the NHS in the UK of about £1.5 million per year. However, these results have to be confirmed in the definitive RCT.

The above evidence has led to a consensus amongst urologists and urogynaecologists that an adequately powered RCT with clinical effectiveness as the primary end point is now timely and required to inform surgeons, patients and decision makers with the most clinically-effective, cost- effective surgical treatment for primary SUI, that is associated with the least burden on patients QoL and NHS resources.

1.3 STUDY OBJECTIVES

The aim of this 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 hypothesis being tested is that patient-reported success rate following surgical treatment with adjustable anchored SIMS procedures is non-inferior to tension–free SMUS while the former is associated with less post-operative pain, shorter hospital stay, earlier recovery and consequently earlier return to usual activities/ work and is more cost-effective than SMUS.

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 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-LUTS qol) over the follow up period.

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 (ICIQ-FLUT- Sex/ PISQ-IR), complication rates, disease recurrence and costs to the NHS and patients.

2. Methods:

2.1. Study Design

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. The trial structure is presented below (Figure 1).

2.2. Intervention to be evaluated

The interventions being compared are: 1) tension-free standard mid-urethral slings (SMUS) including RP-TVT & TO-TVT and 2) 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: mono-filament & 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 outcomes.

SMUS will be performed under general anaesthetic (GA) or deep intravenous sedation while adjustable anchored SIMS will be done under local anaesthetic (LA) as an opt-out policy (i.e. LA will be the standard type of anaesthesia for adjustable anchored SIMS unless specifically declined by a participant requesting GA). Furthermore, participant's requests for conversion to GA will be respected at any stage of the procedure. A standard LA protocol, which we have previously published and successfully used in two previous studies[16,17] will be used as a guidance (Appendix 1).

All participants, in both arms, will receive pre-operative analgesia (30-60 minutes prior to the operation): Paracetamol and Non-steroidal anti-inflammatory drug NSAID (Diclofenac Sodium or Ibuprofen); a vaginal application of EMLA cream (a 5% emulsion preparation, containing 2.5% each of lidocaine/prilocaine) and optional 10ml of intra-urethral Instillagel (anaesthetic, antiseptic lubricant). All participants would receive preoperative/ intra-operative prophylactic broad spectrum antibiotics. A cystoscopy (rigid or flexible) will be performed in all women following insertion of the sling, regardless of the study arm. It is worth noting that rigid cystoscopy was well tolerated by all women under LA in the pilot RCT. No vaginal packs or catheters would be routinely inserted. Postoperatively all participants will undergo voiding assessment including assessment for post-voiding residual urine volume (PVR) using a bedside bladder-scanner (Appendix 2, guidance protocol & flowchart for postoperative voiding assessment).

2.1.1 Adjustable anchored single-incision mini-slings (SIMS)

A standard combination of fast and delayed action LA (dose dependant on participant's body weight) will be infiltrated vaginally into either side of the urethra, the vaginal angles (sulci) and behind the inferior pubic ramus into the obturator complex (e.g. using a curved black spinal needle and/or pudendal block needle). Women will be accompanied by a nurse for support. All participating surgeons will use an adjustable anchored SIMS that meet the pre-specified criteria described below. A standardised insertion technique will be used by all surgeons following the original description of the particular SIMS used. Most adjustable anchored SIMS, however, have a fairly similar procedure of insertion. We describe below the standard insertion steps for the adjustable anchored SIMS (Ajust®-CR Bard and Altis®-Coloplast): women will be positioned in Lithotomy position with hips flexed at 90-100 degree. LA

infiltration as above; a sub-urethral vertical vaginal incision (~1.5 cm) will be made; bilateral para-urethral tunnels created reaching to the posterior margin of the inferior pubic ramus but without piercing the obturator membrane. Further infiltration of LA into the obturator membrane; SIMS, with the 'fixed anchor' end mounted on the applicator, would be introduced through the pre-dissected para-urethral tunnel until reaching behind the inferior pubic ramus. The applicator would then pivot slowly behind the ramus and through the obturator complex allowing the fixed anchor to maintain its position in the obturator membrane and muscles at points equivalent to 10 & 2 O'clock in relation to the urethral orifice. The insertion steps would be repeated on to the other side allowing the 'adjustable anchor' to be fixed in the contra-lateral obturator complex. The SIMS is now robustly anchored and the tension would then be adjusted as required to achieve continence whilst avoiding voiding difficulty. Performing the cough stress test can prove very helpful in this adjustment process and is recommended .The adjustable anchor would then be locked in case of the Ajust (not required with Altis), a cystoscopy will be performed to exclude perforation and the vaginal incision closed.

2.1.2 Standard tension-free mid-urethral slings (SMUS):

The choice of SMUS whether retropubic or transobturator will depend on surgeons' experience. We expect a 50% representation of each type of SMUS in the control arm.

2.1.3 Retropubic Tension Free Vaginal Tape (RP-TVT):

RP-TVT will be Type-1 polypropylene Mesh (mono-filament and macro-porous - pore size ≥75 um). The Tension Free Vaginal Tape (TVT®) procedure was developed by Ulmsten and Petros.[26] The procedure will be done under GA or intravenous sedation as per the standard practice of each surgeon. The bladder will be emptied with a Foley catheter. Close to the superior rim of the pubic bone, two 1-cm long transverse incisions 3cm either side of the midline will be made after injection of LA into the abdominal skin just above the symphysis pubis, down along the back of the pubic bone to the retropubic space and vaginally into the peri- urethral area. An incision ~1.5 cm long will be made in the midline of the suburethral vaginal wall; followed by dissection of the peri-uretheral tunnels to allow introduction of the TVT® needle. A stent will be inserted into the Foley catheter to deviate the urethra-vesical junction away from the path of the needle. The TVT® needle perforates the urogenital diaphragm and will be brought up to the abdominal incision 'shaving' the back of the pubic bone. The procedure will then be repeated on the other side, and a cystoscopy will be performed to exclude perforation. The cough stress test may then be performed, according to surgeon's standard technique, and the sling adjusted in a tension-free fashion and the incisions are closed.

2.1.4 Transobturator Tension Free Vaginal Tape (TO-TVT):

TO-TVT will be Type-1 polypropylene Mesh (mono-filament and macro-porous - pore size ≥75 um). All procedures will be performed under GA as originally described by Delrome[27] and de-Leval[28] for the outside-in and inside-out routes respectively. Women are positioned in Lithotomy position with hips flexed at 100-110 degrees and LA may be infiltrated into the vaginal angles; the latter is not a standard practice however is recommended in a similar regime to the one used in the adjustable SIMS insertion (above). ~1.5 cm sub-urethral longitudinal vaginal incision will be made and bilateral para-urethral tunnels created reaching to the posterior margin of the inferior pubic ramus. Bilateral groin incisions are made 1-2cm lateral to the labio-femoral fold and 2 cm above level of urethra. The transobturator trocar is inserted from groin incisions at 90 degree to pierce the obturator muscles and membranes and then guided by the surgeon's finger to the vaginal incision. TO-TVT is then mounted on the trocar and the trocar is withdrawn in reverse order. The previous 2 steps are repeated on the contra-lateral side achieving TO-TVT sub-urethral placement and the TO-TVT is then adjusted tension-free. For the inside-out technique of insertion, TO-TVT would be introduced in the reverse route from the vaginal incision towards the groin using the winged guide to protect

the lower urinary tract (LUT). A cystoscopy will be performed to exclude LUT injury. Vaginal and skin incisions will then be closed.

2.3. 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.

Setting: Secondary and tertiary care acute hospital settings across the UK. NHS Grampian will be the clinical co-ordinating centre and house the Chief Investigator (CI).

Each unit will have at least one participating surgeon who is competent in performing SIMS under LA prior to enrolling in the RCT. Ideally, the surgeon will have performed 20 adjustable anchored SIMS procedures (with 10 performed under LA); within prospective audit and results submitted to a national surgical database. The CI, or a delegated expert in SIMS, will provide training in SIMS under LA for enrolling surgeons as necessary and will ensure adequate expertise of surgeons in both arms. Surgeons will be experienced in at least one type of SMUS (RP-TVT or TO-TVT) and will have performed an adequate workload in the preceding 2 years.

2.3.1. Selection of participants

As standard practice, clinicians will assess patients likely to require surgery for SUI. A log will be taken of all potentially eligible patients assessed in order to document the reasons for non-inclusion in the study (e.g. reason they were ineligible, or declined to participate) to inform the CONSORT diagram.

Brief details of potentially eligible patients will be recorded in the screening logs at each site (these will be an aid to monitoring potential participant inclusion).

2.3.2. Planned inclusion and exclusion criteria

Inclusion criteria:

Women aged 18 years or over with SUI, who have been referred to one of the collaborating units from across the UK, and for whom surgery has been indicated. Women will have completed their families, failed or declined conservative treatment (supervised pelvic floor muscle training - PFMT). All women will have urodynamic stress incontinence, or urodynamic mixed urinary incontinence with predominant SUI bothering symptoms. The small group of women with pure symptoms & signs of SUI ***and*** no symptoms of overactive bladder (OAB) or voiding dysfunction (VD) can be included without urodynamic investigations as per the updated NICE guidelines.

Pre-operative urodynamic investigations include: free uroflowmetry, post-voiding residual urine volume assessment and subtracted filling cystometry. Other tests such as Urethral pressure profile and Leak point pressure pressures are not mandatory however are welcome as they will inform a number of the pre-planned secondary outcomes.

Exclusion criteria:

Women will be excluded if they have one or more of the following:

- Anterior or Apical Prolapse ≥ POP-Q Stage 2 (POP-Q = pelvic organ prolapse quantification score)
- Previous incontinence surgery (for SUI)
- Mixed incontinence with pre-dominant OAB symptoms (defined as OAB failed to be controlled on conservative treatment such as Bladder retraining, PFMT and/or anti-muscarinic treatment)
- Neurological conditions e.g. MS, spinal cord injuries.
- Concomitant surgery at time of SUI surgery.

- Previous Pelvic irradiation
- Pregnancy or planning for a family.
- Inability to understand the information leaflet and consent form in English

2.4. Recruitment and Study Procedures

2.4.1. Identifying participants

Local procedures at the participating hospitals are different and the timing and mode of approach to patients and the consent process will vary to accommodate both the variability at the sites and the needs of the patients. Where possible, the Patient Information Sheet will be sent to patients together with their clinic appointments ensuring that they have ample time (>24 hours) for consideration before being approached by the research team at the clinic.

Patients likely to require surgery for SUI and who meet the eligibility criteria will be identified at the pre-assessment clinics, urodynamic clinics and outpatient urology/ gynaecology clinics by the consultant, research nurse (RN) or a designated team member. The consultant/ research nurse (RN) will introduce the study to the patient and provide her with the Patient Information Sheet as appropriate; answer any queries and if appropriate the participant may sign the consent form; receive the baseline assessment pack for completion at home and bring back on the day of surgery or send back to the site using pre-paid post.

Patients whose first approach is at the clinic will be given as much time as they require to consider participation; patients may make a decision to participate at this time or may agree to be contacted at home by the local RN. If a patient agrees to be contacted at home she will receive a telephone call from the local RN to discuss any queries. If a patient agrees to the study at that stage, then arrangements will be made for baseline assessment and consenting; this could be done as a separate appointment or at a pre-admission clinic. As above, participants can complete the baseline assessment pack at home and bring back on the day of surgery or send back to the site using pre-paid post. These arrangements can be individualised for each centre.

2.4.2. Informed consent

The patient information leaflet explains that the trial is investigating the use of either adjustable single-incision mini-slings (SIMS) or standard tension-free mid-urethral slings (SMUS) for the surgical management of stress urinary incontinence (SUI) in women. Signed informed consent forms will be obtained from the participants in all centres. Participants who cannot give informed consent (e.g. due to incapacity) will be not be eligible for participation. The participant's permission will be sought to inform their general practitioner that they are taking part in this trial.

2.4.3. Randomisation and allocation

Eligible and consenting participants will be randomised to one of the two study groups in a 1:1 allocation ratio using the randomisation application at the trial office at CHaRT. This randomisation application will be available 24 hours a day, 7 days a week as both an Interactive Voice Response (IVR) telephone system and as an internet based application. The randomisation will use a minimisation algorithm based on centre and previous supervised Pelvic Floor Muscle Training within the last two years [PFMT: Yes/No]. Women will be further randomised to receive short versus detailed sexual function questionnaire.

2.4.4. Follow-up procedures

Eligible patients that have given signed informed consent to participate in the study will be randomised to either SIMS or SMUS. They will be asked, at baseline, to complete the pre-operative questionnaire pack which includes few questions on participants' demographic details and pre-operative health/ medications. It also includes validated questionnaires for symptom severity of UI and its impact on quality of life (QoL) and sexual function: the EQ-

5D; ICIQ-SF; Urgency perception scale (UPS); ICIQ-LUTSqol; ICIQ-FLUTS; ICIQ-FLUTSsex (or PISQ-IR); and to perform 24-hours pad test and home continence stress test (see Appendix 3 Objective Assessment of Urinary Incontinence Within the SIMS Trial - Protocol).

At day 1 to day 14 they will be asked to complete the pain score and use of analgesics questions by self-completed post-operative diary. At 4 weeks post-operative participants will be asked to complete a short questionnaire (on the last section of the diary) to capture pain, use of analgesia, complications, return to work/ normal activities, PGI-I and EQ-5D. At 3 months post-operative, participants will be asked to complete a number of questionnaires: to measure the PGI-I; EQ-5D; ICIQ-SF; UPS; questions related to health services resource; and to report any complications or further treatment received for UI. In addition, at 12, 24 and 36 months post-randomisation, participants will be asked to complete a questionnaire to measure the PGI-I, recurrence, further treatment received and questions related to health services resource use, in-addition to all baseline assessment pack. Taking into account the inevitable waiting time between randomisation and receiving the surgical treatment (average surgical waiting list is 8-12weeks) and in-addition the clinical importance of assessing the outcomes at 12 month postoperative, we aim to send the 1 year follow-up pack at 15 month post-randomisation. This strategy will ensure that the vast majority of participants are at least 12 month post-operative at time of capturing the primary outcome. In-addition, at 20 months participants will be asked to fill out an additional economic data questionnaire, which will include the patient time and travel costs questionnaire. Sending this questionnaire at 20 months will minimise patient burden when completing the annual questionnaire. The discrete choice experiment (DCE) will be completed at the end of the 3 year follow-up period.

Questionnaires and up to two reminders will be sent to participants by post. Non-responders to the 12m post-randomisation questionnaire will be contacted by phone for a short interview to capture the primary outcome (PGI-I; a single item question to mark the outcome of the operation as described in section 5.1). If the participant indicates at this phone call her wish to withdraw from the study a “Change of Status Form” will be completed as below. Participants will be sent a voucher (of modest value) as a token of appreciation for completion and return of the 3 month and follow-up questionnaires.

2.4.5. Change of Status/Withdrawal procedures

Participants will remain on the trial unless they choose to withdraw consent or if they are unable to continue for a clinical reason. If a participant withdraws consent, participant questionnaires will not be collected. A member of the research team will contact the participant by phone and complete the “change of status form” which includes the participant’s instructions on what parts, or whole, of the study they may wish to withdraw from. Unless a participant specifically declines the research team will continue to collect relevant data from their health care records such as ONS and NHS central registries. All other changes in status with the exception of formal withdrawal of consent will mean the participant is still followed up for all study outcomes wherever possible.

2.4.6. *Subsequent arrangements (if applicable)*

Informing key people

Following formal trial entry:

The Study Office will:

i) Inform the participant’s General Practitioner (by letter enclosing information about SIMS and Study Office contact details).

The local Research Nurse will:

i) File the Hospital Copy of the Consent form in the hospital notes along with information about SIMS; give one copy to the patient; file one copy to the local site file and send one copy to the Study Office in Aberdeen.

ii) Use the SIMS internet database to enter data regarding the participant, including data required to complete randomisation
iii) Data entry onto the study database as soon as practical.
iv) Forward a copy of study documentation when and as requested by the Study Office in Aberdeen to facilitate quality control.

Notification of/by GPs

GPs are asked to contact the Study Office if one of the participants moves, becomes too ill to continue or dies, or any other notifiable event or possible serious adverse event occurs. Alternatively, staff at the Study Office may contact the GP.

2.5. SAFETY

The SIMS trial involves procedures for the surgical management of SUI in women which are well established in clinical practice. Adverse effects may occur during or after any type of surgery.

2.5.1. Definitions

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant. Each initial AE will be considered for severity, causality or expectedness and may be reclassified as a serious event.

Adverse events are not:

- Continuous and persistent disease or symptom, present before the trial, which fails to improve; such as urgency, urgency incontinence, voiding dysfunction, pain or dyspareunia
- Treatment failure: persistence or recurrence of urinary incontinence.

Worsening pain or where the site of pain changes is an adverse event.

A **serious adverse event** (SAE) is any AE, that:

- results in death;
- is life threatening (i.e. the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe);
- results in persistent or significant disability or incapacity;
- requires an un-planned re-admission to the hospital (defined as “participant admitted as an in-patient with ≥ 1 night hospital stay”). This excludes hospital ward attenders for minor issues such as lower UTI, voiding difficulties or other issues considered by the PI to be minor. This information will be routinely collected on the postoperative form and/ or the Supplementary hospital visit form as appropriate.
- requires prolongation of existing hospitalisation (defined as >36 hours postoperative hospital stay). This excludes prolongation of hospital stay for minor issues such as voiding difficulties; such information will be routinely collected on the Operation and clinical data form. Prolongation of hospital stay due to social/ geographical reasons will not be considered.
- Is otherwise considered medically significant by the investigator

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition, or complication arising from either, will not be considered as an (S)AE.

Specific expected adverse events:

In this surgical trial the following events are potentially expected:

Intra-operative complications: Bleeding, bladder/urethral injury, bowel injury, nerve injury (obturator/ dorsal nerve of clitoris), injury to blood vessels, hypersensitivity to the local/ general anaesthetics and/ or any of the medications or materials used; pain; shaking/ dizziness, change of procedure or device and / or type of anaesthesia.

Immediate Postoperative complications: Pain in the hip/ thigh/ or the vagina, Infection (chest, urinary tract), bleeding, fever, haematuria, syncope, dizziness, voiding difficulties/ urinary retention and thromboembolism.

Later Postoperative complications: Pain in the hip/ thigh/ or the vagina, mesh extrusion, mesh erosion to the vagina or lower urinary tract, haematoma, abscess formation and nerve injury. In-addition, new onset or worsening of any of the following: dyspareunia, vaginal discharge, voiding difficulties/ urinary retention, long-term self-catheterisation, urgency/ urgency incontinence.

2.5.2 Procedures for detecting, recording, evaluating & reporting AEs, SAEs

2.5.2.1 Detecting AEs and SAEs

All AEs and SAEs must be recorded from the time a participant consents to join the study until follow-up is complete.

Follow-up questionnaires will enquire about any AE/SAE occurrence; in-addition, participants will also be asked if they have been admitted to hospital and/or seen a healthcare professional.

2.5.3 Recording AEs and SAEs

Depending on severity, when an AE/SAE occurs, it is the responsibility of the Investigator (or delegated medical personnel) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator (or the delegated medical personnel) should then record all relevant information in the CRF and if required on the SAE form.

Information on SAE to be collected includes type and date of event, Investigator assessment of severity and causality and any investigation/ treatment required.

Planned hospital visits for conditions other than those associated with urinary incontinence and/ or its treatment will not be collected or reported. Further UI treatment will be recorded as a secondary outcome measure, but will not be reported as serious adverse events.

2.5.4 Evaluating AEs and SAEs

All adverse events will be assessed in respect of seriousness, relationship to study intervention, whether expected or unexpected, and therefore, whether constituting a Serious Adverse Event (SAE) by the local PI, CI or their deputies.

Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined in Section 4.1.

Assessment of Causality

The Investigator must make an assessment of whether the AE/SAE is likely to be related to any of the research procedures according to the following definitions:

- **Related**: resulted from any of the procedures required by the protocol, whether or not this procedure is the specific intervention under investigation and whether or not it would have been administered outside the study as normal care.

- **Unrelated**: where an event is not considered to be related to any of the research procedures.

Assessment of Severity

The Investigator should make an assessment of severity for each AE/SAE and complete a SAE form should any of the SAE criteria in 4.1 be met.

Assessment of Expectedness

When assessing expectedness refer to the expected events (Section 4.1)

An example for the assessment of an AE; Intra-operative bleeding will be collected as an AE on the operative form, however if >500mls a SAE form will be completed.

2.5.5 Reporting AEs and SAEs

Reporting responsibilities of the CI

When an SAE form is uploaded onto the trial website, the Trial Manager and CI will be automatically notified. The CI or Trial Manager will notify the sponsor within 24 hours of receiving completed forms for "un-expected" and 7 days of receiving completed forms for an "expected" SAE. The sponsor will then provide the final assessment of the SAE.

The CI (or Trial Manager) will report any "related *and* unexpected SAEs" to the main REC and the DMC within 15 days of the CI becoming aware of it. All other SAEs will be summarised and reported to the Ethics Committee, the Funder, the DMC and the Trial Steering Committee in their regular progress reports.

If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

2.6. OUTCOME MEASURES

This RCT will assess and compare adjustable anchored SIMS vs. tension-free SMUS in respect of: patient-reported success rates; objective success rates; impact on urinary symptoms, complications, recovery, health-related QoL and sexual function; costs to health services up to 3 years follow-up. We will use the same assessment tools and QoL instruments were used in our pilot RCT which observed a 97% response rate.

2.6.1. Primary outcome measure

The primary outcome measure will be patient-reported success rate measured by the validated PGI-I at 12-months. Patient-reported success rates reflect patients' experience compared to the objective measures, which can overestimate the success of SUI surgery.[27] The primary outcome is assessed by the PGI-I: a 1-item questionnaire designed to assess the patient's impression of changes in her urinary symptoms. The PGI-I asks the patient to best describe her urinary symptoms, compared with how they were before the study intervention, on a 7-point scale scored as: (1) "very much better," (2) "much better," (3) "a little better," (4) "no change," (5) "a little worse," (6) "much worse," or (7) "very much worse." 'Success' will be defined as responses of 'very much better' or 'much better'; this will determine whether the women are satisfied with their operation and hence consider their symptoms are resolved and not seek further treatments. The primary economic outcome will be incremental cost per QALY gained at 12-months. The above measures will also be assessed at 2 and 3 years.

2.6.2. Secondary outcome measures

2.6.2.1 Complications including: lower urinary tract injuries; haemorrhage (blood loss ≥ 200mls); post-operative voiding dysfunction; pain, mesh extrusion/erosion, dyspareunia, long-term self-catheterisation, new-onset or worsening urgency/ urgency incontinence.; assessed as appropriate at 3 and 12 months then yearly up-to 3 years

2.6.2.2 Post-operative pain using a pain Numerical Rating Scale (NRS): assessed day 1-14.

2.6.2.3 Objective success rates: assessed by 24 hour pad test at 12 months and yearly up to 3 years.

2.6.2.4 Other lower urinary tract symptoms using the International Consultation on Incontinence Questionnaire - Female Lower Urinary Tract Symptoms long form (ICIQ-FLUTS) and/or short form (ICIQ-SF) at 3and 12-months and yearly up to 3 years.

2.6.2.5 Health-related QoL profile (area under the curve) derived from EQ-5D, pain scores and ICIQ-LUTSqol measurements at 1,3 and 12-months and yearly up to 3 years

2.6.2.6 Impact on sexual function derived from ICIQ-FLUTsex/ or PISQ-IR measurements at; 12-months and yearly up to 3 years.

2.6.2.7 Recurrence of SUI, re-operation rates for SUI, further treatment received such as physiotherapy, medical treatment (Selective Nor-adrenaline Re-uptake Inhibitors and/ or Anti-muscarinic treatment).

2.6.2.8 Secondary economic outcomes include;

- NHS and patient primary and secondary care resource use and costs at 12-months and yearly up to 3 years.
- Incremental cost-effectiveness derived from responses to the ICIQ-LUTS over the follow-up period at 12-months and yearly up to 3 years.
- Incremental net benefit (NB) calculated from the responses to the discrete choice experiment (DCE) at end of the 3yr follow-up.

2.7. DATA COLLECTION AND PROCESSING

2.7.1. Measuring outcomes

Participant follow-up questionnaires will be triggered by date of surgery up-to 3months then by date of randomisation thereafter.

2.7.2. Schedule of data collection

The components of follow-up are shown in the table 1 below:

Table 1 Source and timing of measures

	Baseline	Surgery details	Day 1-14	4-weeks	3-months	12-months*	20-months	Year 2	Year 3
Clinical/surgery details	○	○							
Pain NRS/ Daily Text messaging			●	●					
Recovery				●	●				
PGI-I				●	●	●		●	●
EQ-5D	○			●	●	●		●	●
ICIQ-LUTSqol	○				●	●		●	●
ICIQ-FLUTS	○					●		●	●
ICIQ-SF & UPS	○				●	●		●	●
ICIQFLUT-Sex/ or PISQ-IR	○					●		●	●
24-hours pad test	○					●		●	●
Home continence	○					●		●	●

stress test									
Health care resource utilisation/complications/recurrence/further treatment					●	●		●	●
Time & travel questionnaire							●		
DCE,									●

○ Clinic/Hospital ● Out-with clinic (e.g. post, email, phone, etc)

* Taking into account the inevitable waiting time between randomisation and receiving the surgical treatment (average surgical waiting list is 8-12weeks) and in-addition the clinical importance of assessing the outcomes at 12 month postoperative, we aim to send the 1 year follow-up pack at 15 month post-randomisation. This strategy will ensure that the vast majority of participants are at least 12 month post-operative at time of capturing the primary outcome.

2.7.3. Data processing

Research Nurses will enter locally-collected data in the centres. Staff in the Study Office will work closely with local Research Nurses to ensure that the data are as complete and accurate as possible. Follow up questionnaires to participants will be sent from and returned to the Study Office in Aberdeen. Extensive range and consistency checks will further enhance the quality of the data.

2.8. SAMPLE SIZE, PROPOSED RECRUITMENT RATE AND MILESTONES

2.8.1. Sample size

A non-inferiority design is appropriate for this trial because the proportion having success at 12 months in women managed with SMUS is high. Adjustable anchored SIMS is not hypothesised to increase this proportion; however may have other potential benefits as outlined previously. It is therefore important to show that SIMS is clinically non-inferior to SMUS and to measure these other dimensions (such as cost-effectiveness, mediated through shorter stay and earlier recovery, QoL mediated through less pain, and any safety signals via the complication rate) in an adequately powered, pragmatic RCT with long enough follow up. It is essential therefore that the study is powered to demonstrate non-inferiority within an appropriate margin, and hence this clinical outcome is the correct choice as primary outcome. A 10% inferiority margin has been deemed by expert clinicians as the maximum inferiority margin in clinical effectiveness that would be accepted should SIMS prove to be superior in other outcomes such as shorter hospital stay, less postoperative pain, earlier recovery and more cost-effective. In such case, adjustable anchored SIMS would then reliably be able to be considered as a first line surgical treatment of women with primary SUI.

Published literature suggests that the P1, the percentage success rate at 12-months in the SMUS arm will be about 85%; identical results were confirmed by our pilot RCT. Estimating P2, the percentage of success in the adjustable anchored SIMS arm, is more difficult due to lack of published evidence; a crude meta-analysis of the 12 month outcome data from our multicentre pilot RCT and few other small studies indicates a similar P2 of 85%.

Power estimates were explored by simulating trials of fixed sample size (using equal allocation) with binary responses generated by P1 = 85% and P2 = 85%. Power was then estimated as the proportion of simulated trials where the lower bound of the 2-sided confidence interval satisfied P1-P2 > -10%. Simulations, run in Stata 11.2, show that a trial of 275 per arm or 550 in total is required for the lower bound of the estimated 95% confidence interval to rule inferiority at the specified level with 90% power. Adjustment for potential 15% drop-out inflates the trial to 650 in total. For comparison, a trial of this size would have above 80% power to test superiority on secondary outcomes of difference in

means of size one quarter of a standard deviation (or 90% power to detect an effect size of 0.28 standard deviations).

In our multicentre pilot RCT;[17] 131/137 women (95.6%) completed the 12 month follow-up and showed no significant differences in the patient-reported success rate (OR 0.895; 95%CI 0.344, 2.330; p=1.000) between adjustable anchored SIMS (Ajust®) vs. SMUS (TVT-O™) groups. These results, together with similar results from other studies detailed above[16–21] provide assurances for the reliability of our sample size calculations. A statistical reviewer previously queried whether we had considered the implications if in fact the success of the 2 procedures were not identical but slightly different. If we consider success rates of 84% and 85%, the study retains 90% power to detect a slightly larger margin of non-inferiority of around 11%, and so to all intents and purposes a sample size of 650 remains adequate.

2.8.2. Recruitment rates and milestones

Our recruitment rate estimates are based on data from the pilot multicentre RCT comparing adjustable anchored SIMS (Ajust®) with SMUS (TVT-O™). We believe that these centres are representative of the UK; 137 women were recruited across 6 centres at a rate of 3.4 per centre per month. Overall, 137/181 (76%) patients were willing to be randomised; however we have used a more conservative estimate of 50% in our recruitment projection. Therefore, it has been estimated that in order to approach 1300 eligible patients to randomise the required 650 patients, 25 centres would need a throughput of at least 90 eligible patients per centre per year to recruit 3 patients per month. The recruitment projection is based on 18 months of recruitment (months 7-24 inclusive) and allows for set-up, holidays and waiting list times. We expect a staggered recruitment of centres with all centres active by the end of Month 18. The first 45 patients will be recruited by Month 12, 256 patients by Month 18 and the remaining 367 patients by Month 24 making a total of 668 patients.

Due to lower than predicted recruitment a further extension has been granted to enable recruitment to reach at least 600 participants This increases the recruitment period so that last participant will be recruited in month 44.

Please see the Gantt Chart (Figure 2) and Recruitment Projection (Appendix 4).

3. ANALYSES PLAN

3.1. Statistical Analysis

Treatment groups will be described at baseline and follow-up using numbers (with percentages), means (with standard deviations) and medians (with inter-quartile ranges) where relevant. Primary and secondary outcomes will be compared using generalised linear models, with adjustment for design covariates. As standard we also adjust all our surgical RCTs for centre/surgeon effects; adjustment for centre/surgeon will be by random effect in the trial analysis.

For the primary outcome, we plan to dichotomise the PGI-I responses with ‘success’ defined as ‘very much better’ or ‘much better’ and the rest of responses as failures; this will determine whether the women are satisfied with their operation and hence consider their symptoms are resolved and do not seek further treatments. In-addition, this definition of “success” is widely used within the research field of surgical treatment of SUI, and was used in our pilot RCT, and therefore will allow comparing our results to other trials in the literature. We will also perform a secondary analysis using ordinal regression on the 7-point PGI-I scale, so potentially using more of the information in the outcome. However, we do not propose adopting this ordinal regression as the primary analysis since the underlying proportional odds model makes strong assumptions about the consistency of

treatment effect across the levels of response, and particularly in the context of a non-inferiority design there may be departures from those assumptions that would interfere with establishing whether the simple hypothesis around the (non-inferiority) of the binary 'success' under the two operations had been shown.

The statistical analysis of the primary outcome will be by the usual intention-to-treat (ITT) and also a suitably defined per protocol (PP) analysis (to reflect the unique nature of non-inferiority designs and the issue that ITT for such designs may not be the most conservative analysis and inflate the true type I error rate, given that in a non-inferiority design the null hypothesis is that the interventions are not non-inferior or equivalent). If the two approaches return material differences in interpretation this will be investigated carefully. Results will be displayed as estimates and 95% confidence intervals derived from appropriate generalised linear models. Confidence intervals around observed differences will then be compared to the pre-specified non-inferiority margin.

Secondary outcomes will be analysed similarly. Outcomes such as post-operative pain will be assessed under a superiority hypothesis as we believe that this will be lower in the intervention arm. As stated in the sample size section, there is above 80% power to detect a difference of a quarter of a standard deviation under a superiority hypothesis. Subgroup analyses (appropriately analysed by testing treatment by subgroup interaction) will explore possible treatment effect modification. All analyses will follow a carefully documented Statistical Analysis Plan. Pre specified subgroups are:

- Mixed incontinence versus pure stress incontinence
- Urodynamic versus Clinically diagnosisis of Stress Urinary Incontinence.
- 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

Effect of Pregnancy: MUS procedures are generally offered to women after having completed their families and therefore subsequent pregnancy is usually a rare event that is unlikely to be balanced between both trial arms. If a woman falls pregnant after receiving treatment within the RCT, her data will be censored at the time of confirmed pregnancy for the primary analysis. This small number of women will still be followed up for all outcome data as usual, and if the numbers warrant, a sensitivity analysis including them will be undertaken on the primary outcome.

The Trial Steering Committee and an independent Data Monitoring and Ethics Committee (DMC) will be asked to review and comment on the Statistical Analysis Plan prior to analysis. There are no plans for any formal interim analyses to be seen by the DMC. A single main analysis will be performed on the 12 month primary outcome and repeated on the 2 and 3 year outcomes. The DMC will meet before recruitment begins, or as soon as practical, to agree the terms of reference and other procedures.

3.2. ECONOMIC EVALUATION

Our primary health economic evaluation will be from a health service provider's (NHS) perspective; however we will also present data from a wider societal perspective. These data will include costs to patients of time and travel, costs to carers and family members and costs to society as a whole, estimated from lost productivity as a result of time off work / away from normal activities.

3.2.1. **Collection of resource use and cost data**

Health care resource use will be collected using patient administered questionnaires asking patients to retrospectively recall their contacts with health care professionals relating to their incontinence. This questionnaire will be administered at 3 & 12 months then yearly for 3 years. It is generally accepted that patient recall is accurate up to 12 months and it is highly unlikely that a patient would not remember significant events relating to their disease over this time period. Data collected will include secondary care contacts (hospital inpatient admissions, outpatient appointments) and primary care contacts (e.g. GP contacts, nurse contacts, physiotherapist consultations) and prescription drug medications. These health care utilisation data will be combined with unit cost information for the use of specific resources using standard sources.[29-31] Data on costs for each group (SIMS and SMUS) will be summed to provide an average cost per patient trial participant. Sensitivity analysis will be used to explore various distributions of cost data as well as various methods for the imputation of missing and censored data. We will provide a comprehensive range of deterministic sensitivity analyses to test any assumptions we make in our analysis on the overall results. For example, we will test best and worst case scenarios for the intervention cost (whether all procedures in the SIMS arm are conducted under GA or LA). The impact of any missing data and methods of data imputation on our results will also be tested. We will test the impact of these and a range of other sensitivity analyses, to be determined as the trial progresses on all our results (e.g. cost utility analysis and cost benefit analysis).

3.2.2. Participant costs

Out of pocket patient expenses (including the purchase of containment products), private health care costs, travel costs and costs associated with lost days at work will also be collected using the patient administered questionnaire and incorporated into the patient perspective analysis. Costs of family members and/or carers will also be collected as part of the trial and reported.

3.2.3 Quality of life

Health state valuations will be based upon the responses to the ICIQ-LUTSqol (baseline, 3, 12 months and annually over the follow up period) and EQ-5D administered at baseline, 1, 3 & 12 month and annually over the follow up period. These data will be transformed into utility values using standard algorithms. QALYs will be calculated, using the area under the curve methods, with any differences between groups being reported. Both measures will be compared and contrasted and tested for comparability in measuring outcomes for these women.

3.2.4. Cost effectiveness

The analysis will use the estimates of mean costs and QALYs as described for each trial participant to estimate the incremental cost-effectiveness ratio at 12-month follow-up period and where appropriate the analysis will mirror that of the statistical analyses. Cost-effectiveness (cost per QALY gained) will also be reported over the 3 year follow up period. The results of the analysis will be presented as incremental costs, effects and incremental cost per QALY. Bootstrapping of cost and QALY differences as well as a range of one way and multi-way deterministic sensitivity analyses will be conducted to address uncertainty in the estimates. Cost per QALY data will also be presented in the form of cost-effectiveness acceptability curves (CEAC).

3.2.5. Discrete choice experiment (DCE)

Previous research[32] has suggested that EQ-5D questionnaire may not fully capture the benefits from successfully treating incontinence. They may not fully represent patient preferences for treatments and their associated outcomes. Therefore, we will conduct a discrete choice experiment (DCE) to elicit preference for the process, patient experience and health outcomes. A DCE presents respondents with a series of hypothetical choices that describe the choice alternatives by their underlying attributes and ask respondents which alternative they prefer. The values of the attributes vary across choice scenarios, and by observing the choices people make it is possible to infer their preferences over the

attributes of the goods under study. The extent to which an individual values an intervention depends upon the levels of these attributes.[33] DCEs are commonly used to identify people's preferences in a variety of non-market situations/services/commodities.[34-36]

The attributes and levels for the DCE will be informed by systematic literature searching and advice sought from clinical experts. Attributes might include preferences for general / local anaesthetic, preferences for pain levels, cure and improvement rates, impact on activities of daily living, etc. These attributes and levels will be combined to identify profiles that will be used to develop scenarios to present the study participants. The questionnaire will be piloted amongst a convenience sample to refine all practical aspects of the survey and to ensure that trade-offs can be made between the identified attributes. Once the pilot is complete and the questionnaire has been refined it will be administered to the trial participants at the end of the 3yrs follow-up.

Experimental design techniques will be used to 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. The resultant costs and utilities will be used to estimate preference based quality weights for this condition.

4. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

4.1. Study Office in Aberdeen

The Study Office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. The Trial Manager in CHaRT at Aberdeen will take responsibility for the day to day transaction of study activities. The Data co-ordinator will provide clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data using the study web data entry portal). The CHaRT Quality Assurance Manager will oversee the demonstration that CHaRT's standard operating procedures for trials are being followed, including observance of the appropriate principles of GCP.

At the centres, the recruitment coordinators/ research nurses will be responsible for all local processes involved in identifying, consenting, and randomising the participants, along with facilitating the delivery of the intervention, under the supervision of the lead surgeon.

The SIMS Study Office Team will meet formally at least monthly during the course of the study to ensure smooth running and trouble-shooting. Finally, we intend to produce a regular SIMS Newsletter for participants and collaborators to inform everyone of progress and maintain enthusiasm.

4.2. Local organisation in sites

The Local PI and research nurse will be responsible for all aspects of local organisation including identifying, consenting, and randomising the participants, along with facilitating the delivery of the intervention and notification of any problem or unexpected developments for the duration of the trial. They will be responsible for ensuring that study data is collected for baseline assessments, collecting and recording participant study data on study specific Case Report Forms and will log all the details onto the remote web-based data capture

system as soon as practical after completion. The local PI will return all study documents to the study office in Aberdeen when requested.

4.3. Project Management Group (PMG)

The study will be supervised by a Project Management Group (PMG). The chair of this group will be the Chief Investigator (Mohamed Abdel-Fattah) and will consist of representatives from the Study Office and grant holders. The PMG will meet every 3 months, including face-to-face in month 1 and month 6 in the first year. It is expected that, once the project is underway, the majority of these meetings will be held by teleconference; however, the PMG will also meet face-to-face at least annually. In addition, the PMG will also meet at the annual Trial Steering Committee meeting.

4.4. Trial Steering Committee (TSC)

The study is overseen by a Trial Steering Committee (TSC). The membership of this committee is comprised of the four independent members along with the Chief Investigator or a nominated delegate. The trial sponsors, other SIMS grant-holders and key members of the central office (e.g. the trial manager) can participate in TSC meetings but are not members. The funders will be notified in advance of meetings and a representative invited to attend. Other relevant experts may be invited to attend as appropriate. Details of the membership of the TSC can be found at the start of this protocol. CHaRT has adopted the TSC Charter adapted from the DAMOCLES Charter for DMCs and suggests to the independent TSC members that they adopt the Terms of Reference contained within. The TSC will meet approximately yearly.

4.5. Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be convened. The DMC will be made up of members listed at the start of this protocol, one of whom is an experienced statistician. After the trial has been initiated the DMC will initially meet to agree its terms of reference and other procedures. CHaRT has adopted the DAMOCLES Charter for DMCs and suggests to the independent DMC members that they adopt the Terms of Reference contained within.

The committee will meet regularly to monitor the unblinded trial data and serious adverse events and make recommendations as to any modifications that are required to be made to the protocol or the termination of all or part of the trial.

4.6. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

4.6.1. Research Governance

The trial will be run under the auspices of CHaRT based at HSRU, University of Aberdeen. This will ensure compliance with Research Governance, and provide centralised trial administration, database support and economic and statistical analyses. CHaRT is a registered Clinical Trials Unit with particular expertise in running multicentre RCTs of complex and surgical interventions.

The PMG will ensure, through the TSC that adequate systems are in place for monitoring the quality of the study (compliance with GCP) and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the study.

4.6.2. Data protection

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Participant's details will be stored on a secure database under the guidelines of the 1998 Data Protection Act and regular checks and monitoring are in place to ensure compliance. Data are stored securely in accordance with the Act and archived to a secure data storage facility. The senior IT manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Participants will be allocated an individual specific trial number and their details will be

anonymised on the secure database. We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired.

4.6.3. Sponsorship

The University of Aberdeen and NHS Grampian are the co-sponsors for the trial.

4.7. QUALITY ASSURANCE

The trial will be monitored to ensure that the study is being conducted as per protocol, adhering to Research Governance, and the appropriate regulations. The approach to, and extent of, monitoring (specifying both central and on-site monitoring) will be specified in a trial monitoring plan which is usually initially determined by a risk assessment, undertaken prior to start of trial.

4.8. DATA HANDLING, RECORD KEEPING AND ARCHIVING

Clinical data will be entered into the database by the local investigator and/or research nurse working in each hospital site, together with data from questionnaires completed at clinic. Questionnaires returned by post to the trial office will be entered there. Staff in the trial office will work closely with local research nurses to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

The co-sponsors are responsible for ensuring that trial data is archived appropriately. Essential data shall be retained for a period of at least 10 years following close of study.

4.9. SATELLITE STUDIES

It is recognised, that the value of the study may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advance with the PMG. REC approval will be sought for any new proposal, if appropriate.

5. ETHICS AND REGULATORY APPROVALS

5.1. Ethics Approval: The North of Scotland Research Ethics Committee has reviewed and approved this study. The study will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines. We believe this study does not pose any specific risks to individual participants beyond standard surgical procedures, nor does it raise any extraordinary ethical issues. Annual progress reports and a final report at the conclusion of the trial will be submitted to the North of Scotland REC within the timelines defined in the regulations.

5.2. Finance and Insurance: The trial is funded by a grant awarded by the NIHR Health Technology Assessment programme. The necessary trial insurance is provided by the University of Aberdeen.

6. Authorship and Publication Policy:

All RCTs conducted by CHaRT have a commitment to publish the findings of the research. At a minimum this trial will have a results paper published in a peer- reviewed medical/scientific journal. If all grant-holders and researcher staff fulfil authorship rules, group authorship will be used under the collective title of 'the SIMS Trial Group'. The CI, and possibly other members of the trial group will take responsibility for drafting the paper and this will be recognised by line" the CI (as primary author), followed by the other authors *and* the SIMS Trial Group'.

For reports which arise from the trial but where some members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to CI and the named individual(s) *for* the SIMS Trial Group.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the Project Management Group.

We intend to maintain interest in the study by publication of SIMS newsletters at intervals for staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final SIMS Newsletter to all involved in the trial. Further details on the publication policy can be found in Appendix 5.

6. Discussion

The SIMS study is a key outcome study that should answer the important research question of whether adjustable SIMS should be utilized in clinical practice as a first line surgical treatment option for women with primary SUI.

This study is a pragmatic patient-oriented trial aiming to capture a true representation of the actual patient population. The inclusion/exclusion criteria were chosen to allow the capturing of the relevant patient group.

This trial seeks to follow standard pathways of care with the only additional intervention being randomisation between the two treatment strategies under test and collection of baseline and outcome information.

The results will inform clinicians and policy makers on the cost-effectiveness of this relatively new technology compared to the SMUS. The long-term follow-up in the SIMS study is crucial to address the long-term successes rate and adverse events of MUS in general and SIMS in specific.

6.1. Dissemination:

The dissemination plans include (1) HTA monograph; (2) presentation at international scientific meetings; (3) publications in high-impact open access peer-reviewed journals; (4) presentations at health economic and health services research meetings. The results of the trial will be included in the updates of NICE (National Institute of Clinical Excellence) and EAU (European Association of Urology) guidelines; these two specific guidelines directly influence practice of all the UK and worldwide specialists respectively. In-addition, a plain English language summary of the main findings and results will be presented for relevant patient organisations and communities, including the bladder and bowel foundation. This will ensure user relevance in dissemination of the results.

6.2. Trial Status

The SIMS study is currently recruiting in 20 UK research centres. The first patient was randomised on 4th February 2014 with follow-up completed at end of February 2020.

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Competing Interests: MAF has been previously speaker and or trainer for Bard, Astellas, Pfizer, AMS and Coloplast. He received travel grants to attend medical conferences from various companies and previously performed a research-led project funded by a research Grant from Coloplast which was received and administered by University of Aberdeen. MAF was the Chairman of Scottish Pelvic Floor Network which received support from different pharmaceutical and devices Companies. MAF and Phil Assassa have provided industry-sponsorship proctorship training sessions to a number of surgeons training in SIMS prior to the study. None of the co-applicants have any financial interest, shares or sit on the advisory board for any relevant device companies.

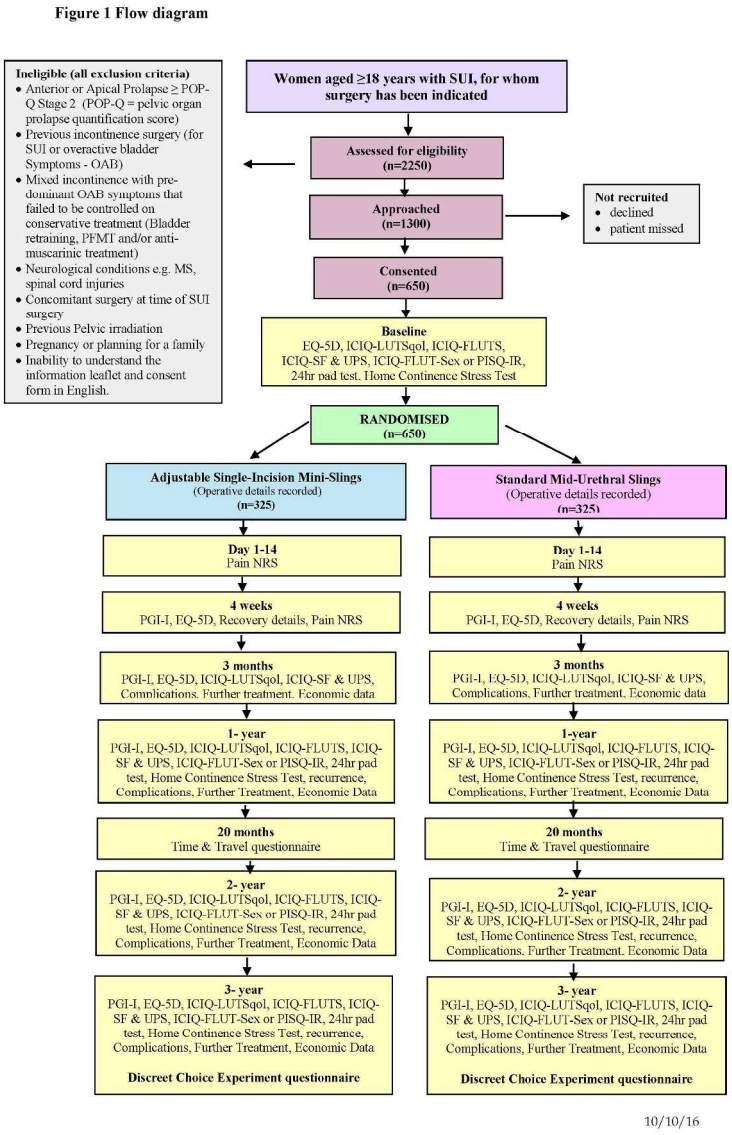


Figure 1: SIMS Study Flow Chart

210x297mm (300 x 300 DPI)

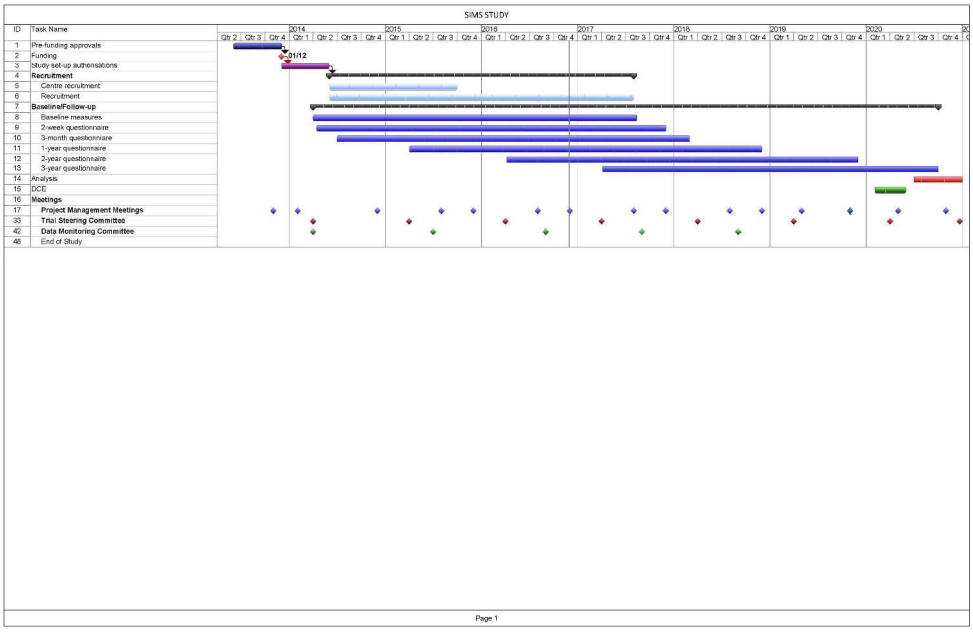


Figure 2: SIMS Study Gantt Chart

297x210mm (300 x 300 DPI)

Appendix 1

Local Anaesthesia (LA) Guidance for SIMS RCT

Pre-operative Analgesia:

All participants, in both arms, should receive within 30-60 minutes of the operation:

- Paracetamol Oral/PR 1gm and NSAID (Diclofenac Sodium -100mg or Ibuprufen 400mg – Oral/ PR) and,
- Oral opiate analgesia (Oral morphine 10-20 mg or MST Continus 10-30mg) if not contra-indicated; (the lower doses are to be used in women ≥ 65 years) and,
- EMLA cream applied vaginally to the sub-urethral area by the patient/ nurse (a 5% emulsion preparation, containing 2.5% each of lidocaine/prilocaine)
- Optional:
  - Instillagel 5ml intra-urethral by the nurse (anaesthetic, lubricant).
  - For anxious patients: oral anxiolytic (Temazepam 10-20 mg) can be given if not contra-indicated (if so please consider omitting the opiate analgesia).
  - Consider oral /IM anti-emetics in women receiving opiate analgesia

Local Anaesthesia:

- Fast-acting LA: Infiltrate 4-5 mls of Lignocaine 1% with adrenaline 1:200,000 (max dose 3.5mg/kg bodyweight) into the peri-urethral area at site of future application of instruments (using orange needle 25G). This is fast acting LA, in-addition to the EMLA cream, will allow you to apply instruments to the peri-urethral area.

- Long-acting LA: Infiltrate ± 40mls of Levo-Bupivacaine 2.5mg/ml (Chirocaine - max dose 1.5 mg/kg bodyweight) OR, Bupivacaine 0.25% with adrenaline 1:200,000 (Carbostesin - max dose 2 mg/kg bodyweight) into:

  a) the vaginal angles (using green needle 21G) until the bilateral vaginal sulci are obliterated (5 mls on each side)

  b) the obturator membrane and muscles (using curved black spinal needle 22G to hook behind the inferior pubic ramus; 10 mls on each side).

- Once the para-urethral tunnels are dissected up-to the obturator membranes, further infiltration (using Pudendal block or Spinal needle), into the exact site of insertion of the SIMS anchor is recommended using fast acting LA (5mls) and followed by long-acting LA (5mls) on each side.

❖ Patients should accompanied by a dedicated nurse during the operation for support.

❖ All doses should to be tailored to patients' medical condition and weight.

❖ We recommend you adhere to this guidance however deviation in the way of infiltration or the type of LA is accepted provided you keep within the general types and appropriate doses described.

SIMS - RCT LA Guidance V2 - Feb 2014

Pathway for Postoperative Voiding Assessment & Management of Voiding Dysfunction for Women Following Surgery for Mid-urethral slings

This applies to patients who were not catheterised postoperatively, or after removal of the urethral catheter (and after stopping IV fluids if applicable).

1. Encourage average fluid intake: 150-200mls/ hour (1 glass/hour).
2. Patients should empty their bladder/ 3-4 hours and encouraged to try to hold in-between if possible.
3. 1st void should be expected within 4 hours (may need prompting by nursing staff); otherwise a bladder-scan assessment is required to rule out retention.
4. Measure Voided Volume (VV) and Post-voiding Residual Urine (PVR) using Bladder-scan following each void. **"Satisfactory Voiding"** is achieved when **PVR ≤ 1/3 of bladder capacity and ≤ 150mls.**
5. Patients can be instructed in "Double Voiding" (void twice with 5 minutes interval & scanned for PVR after the second void; VV is then measured as total of the 2 voids).

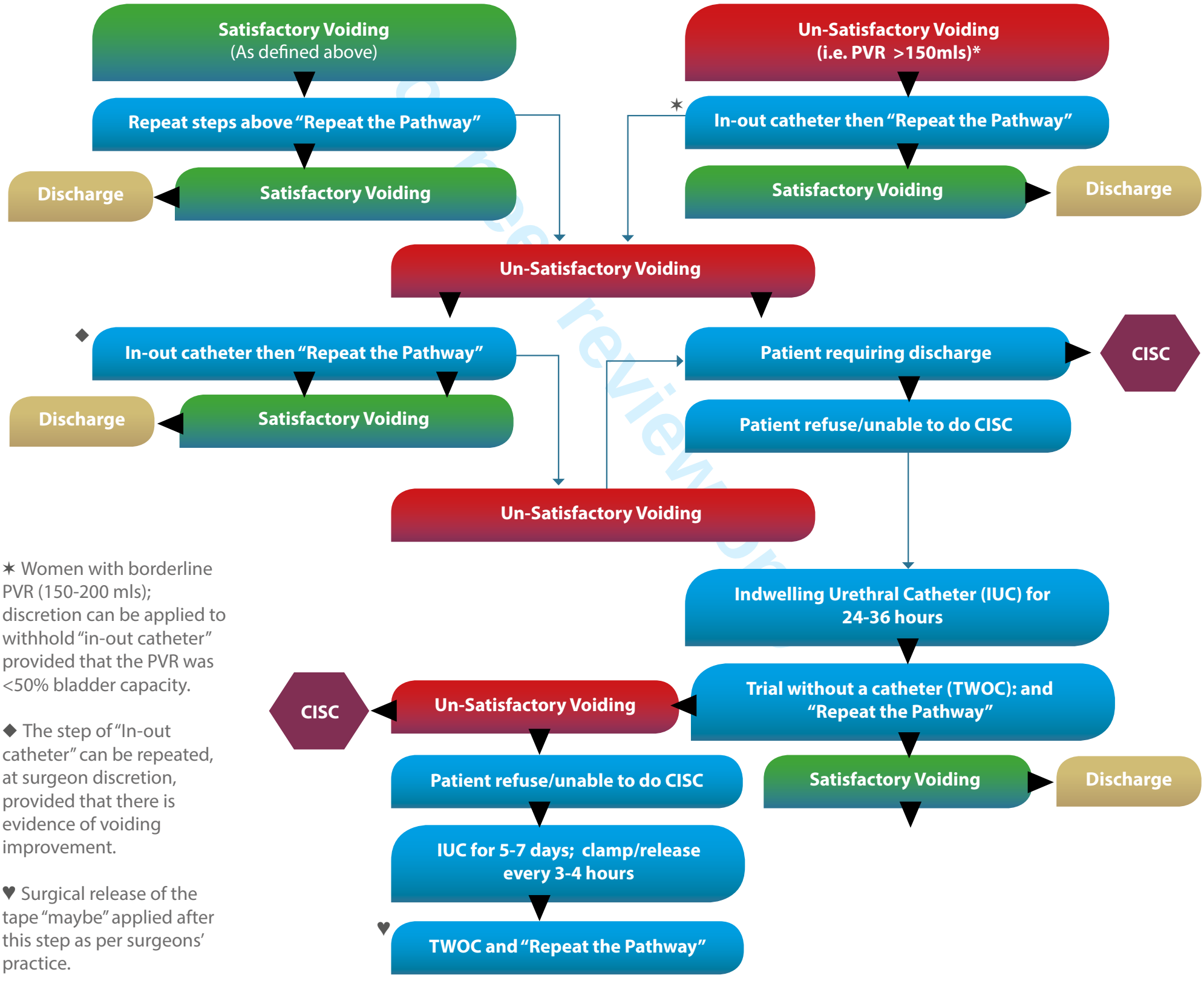
Examples of Satisfactory Voiding	
VV (mls)	PVR (mls)
200	≤120
≥250	≤150

Once satisfactory Voiding is achieved (one assessment); patient can be discharged

N.B. In some units, surgeons leave 200 mls in bladder after cystoscopy so that patients feel the desire to pass urine early.

Management of Patients with Unsatisfactory Voiding Assessment:

Patients with PVR > 150mls after 1st assessment as above; should be encouraged to try to void again within 20min or so and the VV measured



✶ Women with borderline PVR (150-200 mls); discretion can be applied to withhold "in-out catheter" provided that the PVR was <50% bladder capacity.

◆ The step of "In-out catheter" can be repeated, at surgeon discretion, provided that there is evidence of voiding improvement.

♥ Surgical release of the tape "maybe" applied after this step as per surgeons' practice.

Managagement of CISC

Frequency of CISC/ day can be indicated by the level of the PVR (or per surgeon practice as no robust clinical evidence to base a recommendation) – see example below:

PVR (> mls)	CISC/ day
50 - 300	2
300 - 400	3
>400	4

Patients would be instructed to keep records of VV & PVR (for 2 days/ week) and follow-up is arranged (can be phone/ email/ in-person) in 1-2 weeks to check the volumes and the need to continue on CISC. If continuing, please check if any difficulties performing; whether the frequency needs to be altered and date of next review.

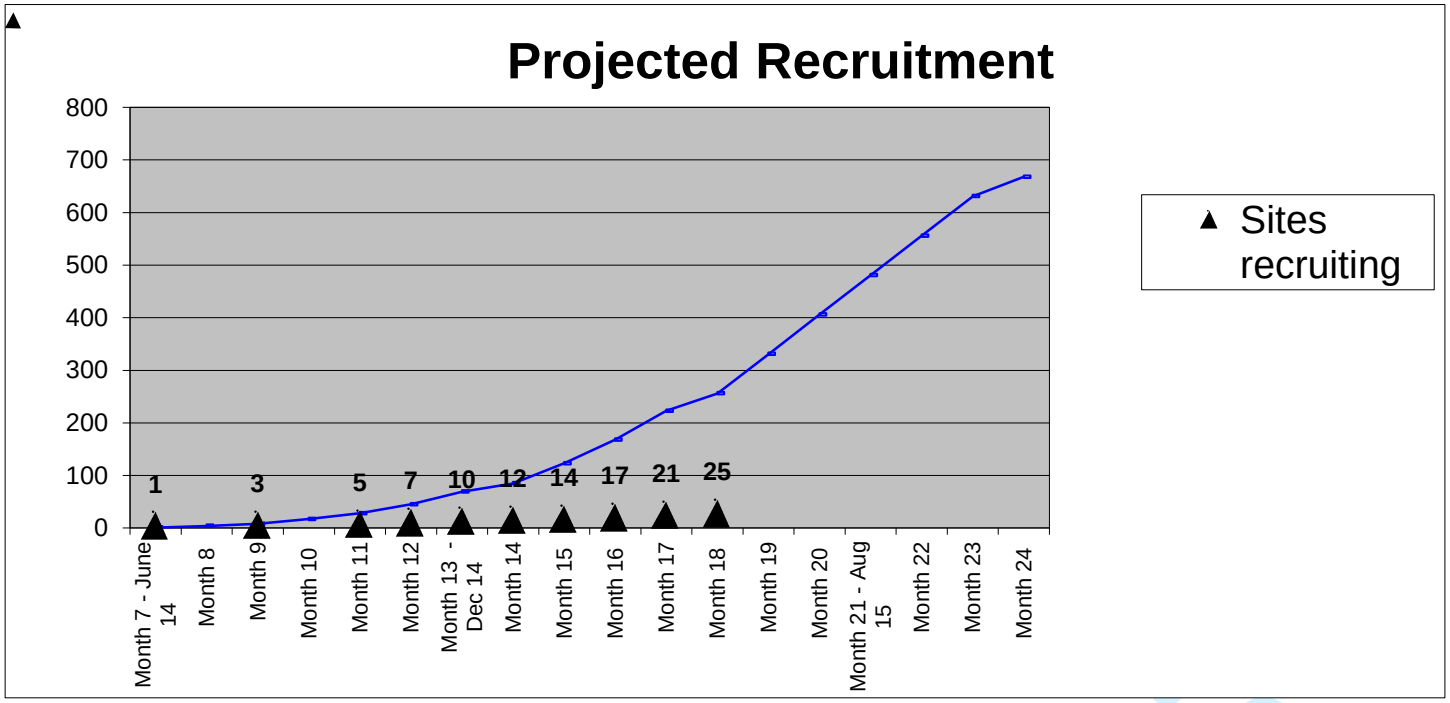
No need for "routine prescribing" of prophylactic antibiotics however local estrogen treatment can be considered in postmenopausal women.

Appendix 3: Objective Assessment of Urinary Incontinence within the SIMS Trial - Protocol

- Participants will receive: ≥4 pre-weighed pads in two transparent self-sealing plastic bags (for the 24 hour pad test), 2 tissue continence sheets (for the home continence stress tests - HCST), instructions on how to perform the tests and a test evaluation questionnaire.

- Each participant will be asked to:-
    - Perform a standardised HCST.
    - Perform the 24-hours pad test (as described by the international continence society) using the provided pre-weighed pads.
    - Repeat the HCST at the end of the 24 hour pad test.
    - Report all their observations on the provided test questionnaire.
- At the end of the tests, women will be asked to complete an open question regarding their experience of the tests. Women's satisfaction/convenience with each test will also be assessed using 10-point Likert scales.
- **Pre-operatively**, participants will be asked to perform this test 24 hours prior to their operation and return any used pads and the test questionnaire to the local RN/team on the day of their surgery. The returned pads will be weighed using a gram sensitive scale and the pad gain, if any, will be calculated and recorded.
- **At 1, 2 and 3 years postoperative**, participants will return the completed test questionnaire and any used pads in the self-addressed pre-paid envelope provided within 24 hours of completion.
- The returned pads will be weighed by the researcher using a gram sensitive scale and the pad gain, if any, will be calculated and recorded.

Appendix 4: Recruitment projection:



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	____ 2-3_____
Protocol version	3	Date and version identifier	_____n/a_____
Funding	4	Sources and types of financial, material, and other support	_____1_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1_____
	5b	Name and contact information for the trial sponsor	_____24_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____16 & 24___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___ 22 & 23____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9 - 10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16 - 17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 p29, Table 1, p17

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__18 - 19____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___19_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____12_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____n/a_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_12-13 & 16-17__ Trial Master File
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____19_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___17 & 24____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___19 - 20_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____20_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____20_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____23_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___ n/a _____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____14 - 16___
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____23 - 24___
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____24_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____n/a_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	23
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	n/a
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	25
	31b	Authorship eligibility guidelines and any intended use of professional writers	24
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.