# Single-incision mini-slings versus standard synthetic mid-urethral slings for surgical treatment of stress urinary incontinence in women: The SIMS RCT

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The SPFN provided an educational grant funding the principal investigator at the highest-recruiting site to attend the International Continence Society annual scientific conference in Brazil in 2014. He receives travel sponsorship and occasionally speaker's fees from numerous national and international conferences and non-profit organisations when invited as guest speaker and/or expert surgeon. In 2019, and at request from NHS Grampian, he attended two educational meetings for setting up a sacral nerve stimulation service partially funded by Medtronic plc (Dublin, Ireland). He is chief investigator for four NIHR HTA-funded studies. He does not hold (and never held) any shares (or similar) in any of the industrial companies (medical or non-medical). To the best of his knowledge, none of the above has influenced his research or clinical practice.

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# Scientific summary

## The SIMS RCT

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# Scientific summary

## Background

Stress urinary incontinence (SUI) is the most common type of urinary incontinence in premenopausal women. Until recently, synthetic mid-urethral slings (mesh/tape) were the standard surgical treatment for female SUI worldwide, if conservative management failed. Adjustable anchored single-incision mini-slings (SIMSs) are relatively newer; they use less mesh and are designed to reduce perioperative morbidity. However, it is unclear how their success rate and safety compare with those of tension-free standard mid-urethral slings (SMUSs). A number of small studies suggest that SIMS procedures may be non-inferior to SMUSs, while being associated with less postoperative pain; shorter hospital stay; earlier recovery; and, consequently, more cost-effectiveness.

Surgeons and researchers agreed that an adequately powered randomised controlled trial (RCT) with clinical effectiveness as the primary end point was required to inform surgeons, patients and decision-makers what the most clinically effective and cost-effective surgical treatment for primary SUI is that is associated with the least burden on patients' quality of life (QoL) and NHS resources.

## Aims and objectives

The aim of this pragmatic multicentre RCT was to determine the clinical effectiveness and cost-effectiveness of adjustable anchored SIMSs, compared with those of tension-free SMUSs, in the surgical management of female SUI across 3 years of follow-up.

The primary objective was to compare patient-reported success rates, as measured by the Patient Global Impression of Improvement (PGI-I) scale, at 15 months post randomisation (≈ 12 months post surgery), with success defined as outcomes of 'very much improved' or 'much improved'. The main economic objective was to determine the cost-effectiveness of SIMSs, compared with that of SMUSs, measured in terms of incremental cost per quality-adjusted life-year (QALY) from a UK NHS perspective, with QALYs derived from responses to the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), over the follow-up period.

The secondary objectives were to compare:

- safety – we collected all expected adverse events throughout, including pain, mesh exposure, operative complications(lower urinary tract injuries, severe bleeding, bowel injuries), new-onset or worsening urinary urgency, dyspareunia and long-term intermittent self-catheterisation
- objective success rates (24-hour pad test/home cough stress test)
- other patient-reported outcomes, including postoperative pain, recovery time, health-related QoL using the EQ-5D-3L and the International Consultation on Incontinence Questionnaire-Lower Urinary Tract Symptoms-Quality of Life (ICIQ-LUTSqol), impact on other urinary symptoms [using the International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS)], impact on sexual function [using the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire, International Urogynecological Association-Revised (PISQ-IR)], recurrence, further treatments received and costs to the NHS and patients
- patient perspective costs
- incremental cost per QALY gained, derived from responses to the ICIQ-LUTSqol.

## Methods

Research ethics approval and fully informed consent were obtained. We performed a pragmatic, non-inferiority randomised trial across 21 UK hospitals. The pre-planned non-inferiority margin was 10%.

Women were aged ≥ 18 years and had predominant SUI, having failed/declined conservative treatment; they had completed their families and decided to undergo surgery to have a mid-urethral sling inserted. The exclusion criteria were as follows: anterior or apical prolapse that was ≥ stage 2 on the Pelvic Organ Prolapse Quantification system, previous SUI surgery, predominant overactive bladder symptoms, planned concomitant surgery, previous pelvic irradiation, pregnant/planning pregnancy and an inability to understand consent in English.

A total of 600 women were randomised between February 2014 and July 2017.

## Randomisation

Participants were randomised 1 : 1, using a remote web-based system, to the SIMS or the SMUS using minimisation based on centre and previous supervised pelvic floor muscle training (PFMT) in the preceding 2 years.

## Trial interventions

Surgeons were asked to use the surgical techniques with which they were most experienced. Given the pragmatic nature of the trial, deviations could occur for clinical reasons.

Two main types of SIMSs fulfilled the prespecified criteria of robust anchorage and post-insertion adjustability: Ajust™ (C.R. Bard, Inc., New Providence, NJ, USA) and Altis® (Coloplast A/S, Humlebæk, Denmark). SMUSs were either retropubic tension-free vaginal tape or transobturator tension-free vaginal tape (inside–out or outside–in). SIMS procedures were performed under local anaesthetic (LA) unless the participant requested general anaesthetic (GA). Cystoscopy was performed regardless of the trial arm. LA administration and the postoperative voiding assessment had standardised guidance.

## Surgeons' experiences

Participating surgeons were experienced in performing at least one SIMS procedure and one SMUS procedure, as per protocol. Clinical experts from the trial team visited the majority of collaborating hospitals prior to starting local recruitment to observe the collaborating surgeons performing SIMS procedures under LA, confirm surgeons' competence, and discuss standardisation of surgical techniques and protocols.

## Statistical analysis

All primary and secondary outcomes were analysed by the intention-to-treat (ITT) principle, using multiple imputation with chained equations to handle missing outcomes. A prespecified per-protocol analysis assessed the primary outcome for participants who received their allocated randomised surgery. The primary outcome was analysed using logistic regression adjusted for PFMT, and included robust variances for clustering by centre. Secondary outcomes were analysed using linear mixed models, adjusting for baseline versions of the outcome when available, with minimisation variables.

## Health economics

A cost–utility analysis was conducted alongside the RCT. Our health economic evaluation was from a health service provider's (i.e. NHS) perspective; however, we also present data from a wider societal perspective, including participant-incurred costs. Total costs and QALYs were estimated using linear regression models, adjusting for treatment allocation, PFMT band, age and baseline EQ-5D-3L utility score. Analyses were conducted based on multiple imputation of missing data. Extensive scenario and sensitivity analyses were conducted to explore the impact of assumptions on results. Uncertainty was illustrated using scatterplots of the cost-effectiveness plane and cost-effectiveness acceptability curves. A discrete choice experiment (DCE) was developed to value, in terms of willingness to pay (WTP), important patient-centred process attributes and trial outcomes: type of anaesthesia received, time to recover post surgery, PGI-I outcome, complications and the impact of SUI on daily activities. WTP tariffs estimated from the DCE were used to inform a cost–benefit analysis.

## Results

Between 4 February 2014 and 7 September 2017, 1040 potentially eligible participants from 21 centres were screened; 877 were considered eligible and, of those, 600 were randomised. There were four post-randomisation exclusions, two in each group. A total of 596 women were included in the trial, 298 in each group. At 1 and 3 years post randomisation, the participant response rates were 87% and 81%, respectively.

## Baseline characteristics

The mean age of participants was between 50 and 51 years. The mean body mass index was similar in both groups, at very slightly $< 29$ kg/m$^2$. Approximately 85% of participants in both groups had received PFMT in the preceding 2 years. A slightly higher percentage of participants in the SIMS group than in the SMUS group were smokers (17% vs. 14%, respectively) or were on anticholinergic drugs at baseline (20% vs. 12%, respectively).

## Clinical effectiveness

At 15 months post randomisation, adjustable anchored SIMSs were non-inferior to tension-free SMUSs at the 10% margin [SIMS 79% (212/268) vs. SMUS 76% (189/250), risk difference (RD) 4.6, 95% confidence interval (CI) −2.7 to 11.8; *p*-value for non-inferiority $< 0.001$]. The results at 3 years were similar: SIMS 72% (177/246) vs. SMUS 67% (157/235), RD 5.7, 95% CI −1.3 to 12.8; *p*-value for non-inferiority $< 0.001$. Per-protocol analysis results were similar to those of the ITT analysis.

## For safety

The rate of tape/mesh exposure was higher among SIMS participants, with 9 out of 276 (3.3%) reporting tape exposure over the 3-year follow-up, compared with 5 out of 261 (1.9%) in the SMUS group (RD 1.3, 95% CI −1.7 to 4.4; $p = 0.373$). The rate of exposure was higher in the SIMS group than in the SMUS group at 3 months [5/276 (1.8%) vs. 3/261 (1.1%), respectively] and similar in both groups at 15 months [SIMS 2/276 (0.72%) vs. SMUS 2/261 (0.77%)]; it fell in both arms at 24 months [SIMS 1/276 (0.36%) vs. SMUS 0/261 (0%)] and at 36 months [SIMS 1/276 (0.36%) vs. SMUS 0/261 (0%)].

Groin or thigh pain and subsequent use of analgesics were higher in the SIMS group at 15 months [SIMS 41/276 (15%) vs. SMUS 31/261 (12%), RD 3.0, 95% CI −1.1 to 7.1; $p = 0.144$]; however, by

3 years, there was a slightly higher rate of pain among SMUS participants [SIMS 39/276 (14%) vs. SMUS 39/261 (15%), RD −0.8, 95% CI −4.1 to 2.5; $p = 0.613$]. The use of analgesics was stable in both groups. At 15 months, 8.7% (24/276) of the SIMS participants and 5.0% (13/261) of the SMUS participants were using analgesics (RD 3.7, 95% CI 0.0 to 7.4; $p = 0.047$); at 36 months, 7.6% (21/276) of the SIMS participants and 4.6% (12/261) of the SMUS participants were using analgesics (RD 3.0, 95% CI −0.4 to 6.4; $p = 0.081$).

The rates of dyspareunia and coital incontinence were higher in the SIMS group at almost all time points. The rate of dyspareunia was 17% (25/145) in the SIMS group and 5.5% (8/145) in the SMUS group at 15 months (RD 11.8, 95% CI 3.5 to 20.1; $p = 0.008$); at 36 months, it was 12% (17/145) and 4.8% (7/145) in the SIMS and SMUS groups, respectively (RD 7.0, 95% CI 1.9 to 12.1; $p = 0.010$). The trend was similar for coital incontinence: SIMS 11% (16/145) and SMUS 4.8% (7/145) (RD 6.0, 95% CI −0.9 to 12.9; $p = 0.084$), at both 15 and 36 months.

Nine (out of 261) (3.4%) of the SMUS participants and none of the SIMS participants experienced a bladder injury. Blood loss of > 200 ml was similar in both groups [SMUS 5/276 (1.8%) and SIMS 5/261 (1.9%)]. The need for self-catheterisation was slightly greater among SMUS participants at the earlier follow-up points [3 months: SMUS 2.7% (7/261) vs. SIMS 1.1% (3/276)], but by 3 years the rates were similar in both groups [SMUS 1.5% (4/261) vs. SIMS 1.1% (3/276)].

A total of 41 SIMS participants and 36 SMUS participants reported making further relevant visits/consultations to either primary or secondary care. The number of consultations as a result of pain was slightly higher among SIMS than among SMUS participants [24/276 (8.7%) vs. 16/261 (6.1%), respectively]. Twenty-four SIMS participants and 12 SMUS received surgical treatment over the 3 years. These included further surgery for SUI [SIMS 7 (2.5%) vs. SMUS 3 (1.1%)] and complete or partial removal of tape/mesh because of pain [SIMS 4 (1.5%) vs. SMUS 2 (0.77%)] or because of mesh exposure [SIMS 4 (1.4%) vs. SMUS 3 (1.1%)].

## Secondary outcomes

### *Operative outcomes*

More women in the SIMS group than in the SMUS group had their procedure under LA (73% vs. 6.1%, respectively) and had their sling adjusted using a cough stress test (65% vs. 5.7%, respectively). The procedure time for those receiving a SIMS device was slightly shorter than for those receiving a SMUS device (difference −2.2 minutes, 95% CI −5.9 to 1.6 minutes; $p = 0.25$). The postoperative stay was significantly shorter in the SIMS group (difference −2.5 hours, 95% CI −4.7 to −0.3 hours; $p = 0.029$). The analysis of pain scores over the 14 days post operation also shows significantly lower pain scores in the SIMS group (difference −8.3, 95% CI −12.8 to −3.8; $p = 0.001$) and less use of analgesia (difference 0.79, 95% CI 0.64 to 0.98; 0.029). There were no significant differences between groups in participants returning to normal activities within 28 days (difference 1.24, 95% CI 0.86 to 1.80; $p = 0.25$). There was no evidence of a difference for other postoperative outcomes.

### *Objective success*

Objective success was a participant with a 24-hour pad-test weight gain of < 8 g. Participants were asked to complete a pad test only when they returned a completed participant questionnaire at the relevant time point. At all time points, the success rate was higher for the SIMS group, and the effect sizes indicate that SIMSs are non-inferior to SMUSs: at 15 months, the objective success rate was 86% in the SIMS group and 75% in the SMUS group (difference 5.2, 95% CI −5.9 to 16.2; $p = 0.004$); at 24 months, it was 87% in the SIMS group and 86% in the SMUS group (difference 6.3, 95% CI −2.4 to 15.1; $p < 0.001$); and, at 36 months, it was 86% in the SIMS group and 81% in the SMUS group (difference 3.7, 95% CI −5.0 to 12.4; $p = 0.001$). We acknowledge the limitation that only 36% of participants completed the 24-hour pad test.

### *Quality of life and sexual function*

The EQ-5D-3L scores increased from baseline and peaked at 3 months; at 3 years, the EQ-5D-3L scores in both groups were lower than at baseline. Between-group comparisons exclude a significant difference in EQ-5D-3L scores at all time points: at 4 weeks, the difference was 0.026 (95% CI −0.006 to 0.058; $p = 0.11$); at 3 months, it was 0.019 (95% CI −0.022 to 0.059; $p = 0.36$); at 15 months, it was 0.022 (95% CI −0.018 to 0.062; $p = 0.28$); at 2 years, it was 0.035 (95% CI −0.006 to 0.077; $p = 0.097$); and, at 3 years, it was 0.013 (95% CI −0.030 to 0.056; $p = 0.55$). Across all the ICIQ-LUTSqol outcomes, the pattern was similar: small differences favouring SIMSs, but with considerable uncertainty and no clear signal that one treatment was better than the other.

The PISQ-IR sexual function scores show a small improvement from baseline to 15 months in both groups, although this improvement then diminished at 2 and 3 years. The effect size favours the SMUS group, although the difference was small and CIs excluded worthwhile differences at each time point: 15-month difference of 0 (95% CI −0.2 to 0.1; $p = 0.55$), 2-year difference of 0 (95% CI −0.1 to 0.1; $p = 0.90$) and 3-year difference of 0 (95% CI −0.1 to 0.1; $p = 0.92$).

### *Other urinary questionnaire scores*

For all ICIQ-FLUTS domains, differences were small and CIs rule out any worthwhile between-group differences.

Urgency perception was assessed at 15 months and at 2 and 3 years. At all time points, participants in the SIMS group reported less urgency. The effect size on urgency perception was [odds ratio (OR)] 1.3 (95% CI 0.8 to 2.0; $p = 0.26$) at 15 months and (OR) 1.1 (95% CI 0.7 to 1.6; $p = 0.81$) at 36 months. These effect sizes favour the SIMS group, suggesting less urgency, but the CI excludes a significant effect.

### *Health economics*

#### Within-trial analysis

The base-case economic analysis concluded that SIMSs (£1696) were not significantly less costly than SMUSs (£1702) (mean difference −£6, 95% CI −£228 to £208) and were not associated with significantly more QALYs (2.347 vs. 2.342, mean difference 0.005, 95% CI −0.068 to 0.073). There is a 56% probability that SIMSs will be considered cost-effective at the £20,000 threshold value for a QALY.

#### Discrete choice experiment

The results of the DCE base-case model showed that GA was preferred to LA, with those who had GA within the trial indicating a stronger preference for procedures conducted under GA, than those who had LA indicated a preference for LA. Women prefer shorter times to return to normal activities and are willing to pay between £70 and £100 per day of reduction in recovery time following surgery. Women highly valued improvements in PGI-I of between £8173 (improved) and £11,706 (very much improved). However, the value of improvement in outcome was offset by the negative values attached to experience of complications (between £8022 and £10,632 for the avoidance of complications). Women were willing to pay between £1700 and £5700 for treatments that reduced their need to avoid daily activities because of a fear of leaking.

## Conclusions

Single-incision mini-slings are non-inferior to SMUSs in terms of patient-reported and objective success rates over 3 years' follow-up.

The SIMS procedures are more likely to be performed under LA and are associated with less postoperative pain and less use of analgesia up to 14 days post operation. At 3 years, there were no significant differences between groups in the scores of QoL and sexual function questionnaires.

Similarly, there were no significant differences in various domains of the urinary and symptom severity questionnaires.

At 3 years, there was no significant difference in groin/thigh pain between groups; however, participants in the SIMS group were significantly more likely to report dyspareunia and to undergo further surgery for continence and/or for mesh-related adverse events. Both surgical procedures are valued by women, but there was no indication of the most cost-effective treatment option.

## Recommendations for future research

Long-term follow-up to at least 10 years after randomisation is under way to identify the long-term success rates, recurrence rates, adverse events, the need for further continence surgery or surgery to treat adverse events and the long-term cost-effectiveness.

## Trial registration

This trial is registered as ISRCTN93264234.

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