Single Incision Mini-Slings for Stress Urinary Incontinence in Women

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Abstract

Background: Until recently, synthetic mid-urethral slings (mesh/tape) were the standard surgical treatment for female stress urinary incontinence worldwide, if conservative management fails. Data are limited to compare the effecteviness and safety of newer single incision mini-slings (minislings) with standard mid-urethral slings (mid-urethral slings).

Methods: We performed a pragmatic, non-inferiority, randomized trial comparing mini-slings or mid-urethral slings among women at 21 UK hospitals over 36-months of follow-up. The primary outcome was patient-reported success (defined as very much/ much improved on the Patient Global Impression of Improvement scale) at 15-months post-randomization (approximately 1 y post-operatively). The non-inferiority margin was 10%.

Results:. There were 298 women randomized to minislings and 298 randomized to mid-urethral slings. The frequency of patient-reported success was 79.1%,(212/268) with minislings versus 75.6%, (189/250) with mid-urethral slings at 15-months (risk difference (RD) (95%CI) 4.6% (-2.7%, 11.8%); $p_{non\text{-}inferiority}$<0.001; and, at 36-months, was 72%(177/246) and 66.8%(157/235), respectively; risk RD 5.7% (-1.3%, 12.8%;). The frequency of groin/thigh pain was 14.9% vs 11.9%, respectively at 15-months, RD 3.0%(-1.1%, 7.1%), , and 14.1%(vs 14.9%, respectively at 36-months RD(95%CI) -0.8%(-4.1%,2.5%). At 36-months, tape/mesh exposure occurred in 3.3% vs 1.9%, respectively (RD 95%CI 1.3%(-1.7%,4.4%)) and further SUI surgery in 2.5% vs 1.1%, respectively (RD 95%CI 1.4%(-1.4%,4.2%)) Quality of life and sexual function outcomes were similar between groups, except that a higher percentage of women in the minisling group had dyspareunia (11.7% vs 4.8%: RD(95% CI) 7.0%(1.9%, 12.1%).

Conclusions: Adjustable single incision mini-slings were non-inferior to standard tension-free mid-urethral slings with respect to patient-reported success rates at 15-months; and success rates remaned similar between groups at the 36- month follow-up. (ISRCTN93264234.)

Introduction

The lifetime risk for primary surgery for stress urinary incontinence (SUI) in women is 3.6% in the UK and 13% in the US.[1, 2] Synthetic mesh mid-urethral slings have until recently been the most common SUI surgical treatment worldwide. In England, 100,516 MUS procedures were performed between 2008 to 2017 compared to 1,195 for all other continence procedures.[3]

The first mid-urethral sling was retropubic tension free vaginal tape (retropubic tape), a minimally invasive day-surgery procedure with excellent short-term outcomes.[4] Retropubic tapes utilises polypropylene mesh strip to create a sub-urethral hammock. Concerns about its blind retropubic trajectory and potential bladder/bowel injury led to developing second generation standard-length mid-urethral slings placed through the transobturator route (outside-in and inside-out obturator tapes).[5, 6]

Studies have shown similar patient-reported success rates between retropubic and obturator tapes.[7] Retropubic tapes had higher rates of bladder injury and postoperative voiding dysfunction, while obturator tapes had higher rates of post-operative groin/thigh pain.[8] More recently, single-Incision Mini-Slings (minislings) were introduced; these used shorter polypropylene mesh and avoided both retropubic trajectory and adductor muscle perforation, hence were proposed to reduce perioperative morbidity.[9]

In a systematic review published in 2014, we found similar patient-reported and objective success rates between minislings (excluding TVT-Secur devices, which were discontinued by the manufacturer for commercial reasons) and mid-urethral slings during median follow-up 18-months;[10] minislings were associated with less postoperative pain and shorter recovery time. However, trials included in this review were small, heterogeneous and had high risk of bias. A Cochrane review recommended an adequately powered RCT with long-term follow-up to evaluate the clinical benefits and risks and cost-effectiveness of minislings.[11]

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We performed a pragmatic multicenter non-inferiority RCT comparing outcomes of adjustable anchored minislings versus tension-free mid-urethral slings, in women with stress urinary incontinence.

Methods

The study was a randomized non-inferiority trial performed at 21 UK hospitals. We report here the clinical outcomes through 36-month follow-up.

We included women ≥18-years who had predominant SUI symptoms , who had failed or or declined conservative treatment and planned to undergo a mid-urethral sling. Exclusion

criteria were:— anterior or apical prolapse ≥stage-2; previous SUI surgery; predominant overactive bladder— symptoms; planned concomitant surgery; previous pelvic irradiation; pregnant/planning pregnancy; inability to understand consent in English.

Eligible women received a study information leaflet and participants gave written informed consent.[12]— Participants were randomized 1:1, using a remote web-based system, to minislings or mid-urethral slings using minimization based on center and previous supervised pelvic floor muscle training within 2-years.

Interventions are described in detail in the protocol.[12] Adjustable anchored minislings met pre-specified criteria, identified from previous research as necessary for their success.[12] Two main types of minislings used were: AJUST® (CR-Bard, Murray Hill, NJ, USA) and ALTIS® (Coloplast Corp, Minneapolis, Minnesota, USA).— Mid-urethral slings were either retro-pubic or obturator (inside-out or outside-in) tapes. The choice of device in both study groups– was according to the surgeons' standard practice. Minislings procedures were performed under local anaesthesia unless a participant requested general anaesthesia. Cystoscopy (rigid or flexible) was performed regardless of study arm. Standardized guidance was provided for participating surgeons regrding local anestthesia— administration and postoperative voiding assessment (Supplementary appendix).

Participating surgeons were experienced in performing at least one type of minislings and mid-urethral slings– as per protocol.[12] Clinical experts in the study team visited 90% of collaborating hospitals prior to starting local recruitment to observe participating surgeons' performing two minislings procedures under local anesthesia, in order to confirm surgeons' competence and to discuss– standardization of surgical techniques and protocols.[12]

Blinding surgeons and participants was not possible given the different anesthesia typically used for the 2 different types of procedures.– All follow-up was patient-reported through postal questionnaires.

Data Collection

We collected patient-reported data at baseline; 4-weeks and 3-months post-operatively; and 15-, 24- and 36-months post randomization (approximately 12-, 21- and 33-months post-surgery), (Table-S1a). The data collected at 4-weeks and 3-months addressed perioperative morbidity and triggered by surgery date.

Outcomes

The primary outcome was patient-reported success (Patient Global Impression of Improvement scale (PGI-I)) at 15-months defined as 'very much improved' or 'much

improved'.[13] All other responses (improved, same, worse, much/very much worse) were considered faliures.

Safety data included all expected adverse events (AEs) during follow-up through 36-months: pain, mesh exposure, operative complications (lower urinary tract injuries, severe bleeding, bowel injuries), new onset or worsening urinary urgency, dyspareunia and intermittent self-catheterization. All serious unexpected AEs were reported by the collaborating hospitals and reviewed by the study sponsor and the independent data monotoring committee.

Secondary outcomes included postoperative pain (to 14-days); recovery (i.e. return to normal activities); objective success; impact of the procedures on participants' symptom severity, quality of life and sexual function using validated tools/questionnaires (Tables S1a and b). Health economic outcomes will be reported separately.

Statistical Analysis

An absolute 10% non-inferiority margin was determined by clinical experts as the maximum acceptable margin should minislings be demonstrated to be superior in other outcomes such as postoperative pain and earlier recovery. Assuming 85% success for both procedures,[14] we required 550 participants for 90% power at 1-sided 2.5% significance; assuming a 15% dropout rate, the planned sample size was 650 total. This was reduced (November 2016), without examining any outcome data, to 600, given difficulties in completing recruitment on time and within budget, thus reducing power from 90% to 88%. Effect sizes are presented as risk differences(RDs) and 95% confidence intervals(CIs). Odds ratios(OR) are also presented. A non-inferiority p-value (p_{NI}) is reported for the primary outcome.

All primary and secondary outcomes were analyzed by intention-to-treat(ITT) using multiple imputation with chained equations to handle missing outcomes. More information on the multiple imputation is in the supplementary appendix. All models adjusted for minimization covariates. The primary outcome was analysed using logistic regression with robust variances for clustering by center. A pre-specified per protocol(PP) sensitivity analysis assessed the primary outcome for participants who received their allocated randomized surgery. Secondary outcomes were analyzed using linear mixed models adjusting for baseline versions of outcome. The 14-day post-operative pain scores were compared using Area Under the Curve(AUC). The number of days of analgesia use was compared (post-hoc) between groups using negative binomial regression. Estimates are presented with 95% confidence intervals,

with no adjustments for multiple testing. All analyses used Stata 15 (details in Supplementary Appendix).[15]

Pre-specified subgroup analyses were performed according to urodynamic diagnosis (urodynamic stress incontinence vs. mixed urinary incontinence)) and age (< median vs ≥ median). We also performed post-hoc subgroup analyses comparing: age <65 vs ≥65; supervised pelvic flor muscle training within preceding 2-years vs. not; and devices withdrawn from clinical practice (minislings: Ajust, and mid-urethral slings: MONARC/ i-STOP/ARIS)) vs. not (minislings: Altis, and mid-urethral slings: TVT/TVT-O, Advantage and Obtyrix) .

Results

600 women were randomized (February 2014-July 2017) from 21 hospitals. Four women were excluded post-randomization, leaving 298 randomized to minislings and 298 to mid-urethral slings: 257(86%) women and 257(86%) received their allocated surgery respectively (Figure-1). At 15- and 36-months post-randomization, participant response rates were 87% and 81%.

Groups were well balanced at baseline (Tables 1,S2), except more women in the minislings group used anti-cholinergic treatment.

Operative data

Crossover between groups occurred in 16(5.8%) women randomized to mini-slings and 4(1.5%) randomized to mid-urethral slings; in-addition, 3 women randomized to minislings underwent other procedures. Crossover was due to patient preference, or unavailability of specific device or experienced surgeon on the day of surgery. Women randomized to mid-urethral slings were more likely to have their procedure performed by a sub-consultant grade surgeon, and less likely to have their procedures under local anesthesia or the sling adjusted using a cough stress test. Most participants received intra-operative local anesthesia infiltration regardless of procedure type. Pain scores over 14-days appeared lower in minislings than mid-urethral slings group. (Table-2)

Patient-reported and Objective Success Rates

At 15-months post-randomization, success rates were 79.1%(212/268) in the minislings group and 75.6%(189/250) in the mid-urethral slings group (RD (95%CI) 4.6%(-2.7%,11.8%); p for non-inferiority (p_{NI}) <0.001). At 36-months follow-up, patient-reported success rates were 72%(177/246) vs 66.8%(157/235) respectively (RD(95%CI) 5.7%(-1.3%,12.8%). The per-protocol estimates at 15-, 24- and 36-months were similar to the ITT analysis (Table-3) .

Figure-S1 shows results of the sensitivity analyses; all were consistent with the primary analysis.

Success rates objectively measured with a 24-hour pad test were 85.7%(102/119) with minislings and 75.5%(83/110) with mid-urethral slings at 15months (RD 5.2 (5.9,16.2)) (Table 3)

In a post-hoc analysis using results of the ICIQ-UI-SF to identify "cure" (defined as no leaking, in response to both "how often do you leak urine?" and "how much urine do you usually leak?") cure rates were 38.6%(93/241) with minislings and 33.2%(72/217) with mid-urethral slings at 15-months (RD 6.4(-1.2,13.9)) (Table-3). Table-S3 shows PGI-I seven-point responses at each time-point.

The results of subgroup analyses were consistent with the overall results.(Figure S1).

Secondary outcomes

There were no material between group differences in scores on several scales assessing lower urinary tract symptoms, domains) or quality of life and sexual function (Table 3). Dyspareunia and coital incontinence were more common with minislings as compared with mid-urethral slings at almost all time points (Tables 4,S4).

Safety:

The frequency of serious AEs was similar between groups (Table-4). Groin or thigh pain were more frequent in the minislings than mid-urethral slings group at 15-months, but similar between groups at 36-months (14.1% vs 14.9%, RD 95%CI -0.8%(-4.1%,2.5%).

Tape/mesh exposure occurred in 3.3% in the minislings group vs 1.9% in the mid-urethral slings group (RD 95%CI 1.3%(-1.7%,4.4%) over 36-months. One minislings participant had persistent tape/mesh exposure following a procedure to bury the exposed mesh and subsequently underwent local excision of the exposed portion.

Twenty-four(8.7%) minislings and 12(4.6%) mid-urethral slings participants received further surgical treatment over 36-months (Table 4), including further SUI surgery (2.5% vs 1.1%, respectively); or]; complete or partial removal of tape/mesh for any reason (2.9% vs 1.9%) ,for pain (1.5% vs 0.8%,respectively) or for mesh exposure (1.4% vs 1.1%, respectively). All four participants (two in each arm) receiving colposuspension/autologous sling and one minislings participant receiving urethral bulking had previously undergone complete or partial tape removal.

Discussion

This mutlicenter trial showed minislings were non-inferior to mid-urethral slings with respect to patient-reported success at 15-months, and through the 36-month follow-up. Findings were similar in per-protocol analysis and among pre-specified subgroups.

Minislings were more likely to be performed under local anesthesia and were associated with less postoperative pain up to two-weeks post-surgery. At 36-months, rates of groin/thigh pain were similar in both groups. However, more women in the minislings group, reported dyspareunia, mesh exposure and/or received further surgery for UI or treatment of AEs. Rates of mesh removal (partial/ complete) for any indication were low and similar between groups..

Our findings of similar success rates with minislings and mid-urethral slings are consistent with previous evidence. 2 Two RCTs -- one comparing minisling-MiniArc to obturator tapes (n=193), and the other comparing minisling-MiniArc to retropubic tapes (n=185) -with 36-months follow-up showed no significant between group differences in patient-reported (PGI-I) or objective success rates.[16, 17] A third RCT comparing minisling-Ajust® vs obturator tapes (n=368) and using assessment tools similar to those we used also showed no significant differences in subjective and objective success rates at 1-year, but minislings resulted in less immediate postoperative pain, shorter operative time, and shorter recovery.[18] Our 2014 systematic review/meta-analysis (26 RCTs/n=3308) similarly showed no significant differences between minislings and mid-urethral slings in patient-reported and objective success rates at 18-month follow-up.[10] More recent review of longer outcome results (≥3-years) showed mid-urethral slings had significantly better objective success rate albiet similar patient-reported success to minislings.[19] The present trial was larger, than prior similar studies and had a consistent methodology. Moreoever, follow-up through postal questionnaires likely helped to minimize the rate of loss to follow up and minimize bias.

Mesh device safety has been the subject of substantial scrutiny over the last decade, owing to patient reports of AEs over extended follow-up, including tape/mesh exposure, groin/thigh pain, and dyspareunia. Lawsuits have been filed against mesh manufacturers in various countries,[20] and some manufacturers have withdrawn their products from clinical practice.[11, 21] The SIMS study was performed during heightened public mesh debate and hence participants and clinicians are unlikely to under report AEs. Clinical guidelines in the USA, Europe and the UK continue to recommend tension-free mid-urethral slings as surgical treatment for female stress urinary incontinence albeit being suspended in the UK since 2018.

The rates of tape/ mesh exposure over 36-month follow-up were 3.3% in the minislings group vs 1.9% in the mid-urethral slings group; these rates did not differ significantly between groups, but the study was not powered for this or other uncommon outcomes. Our results are consistent with our 2014 systematic review ahowing a slightly although not significantly higher rate of mesh exposure in minislings compared with mid-urethral slings (2.3%(15/659) vs 1.4%(8/564), RR 1.43(0.61,-3.35).[10]

Rates of groin or thigh pain appeared higher in the minislings group at 15-months but not at 36-months. In a prior trial (n=60) of minislings(Ajust) or obturator tapes, three women who received minislings reported persistent thigh pain one-year after surgery, versus none in the obturator tapes group.[22] In the TOMUS study (n=597), pain was more commonly reported with obturator vs retropubic tapes (9.4% vs 4%).[23] In the present trial, all four participants receiving tape removal for pain up to 15-months were in the minislings group. However by 36-months, two women in the mid-urethral slings group had undergone partial removal for pain, with no further removals for pain in the minislings group. It is possible that surgeons and/or patients perceived minislings to be easier to remove given they are shorter. However, the authors are aware of one report of difficulties in removing the minislings anchors with vaginal dissection only (personal communication).

In the present report, there were no cases of major visceral injuries, and intra-operative lower utinary tract injuries occurred exclusively in the mid-urethral slings group. However, our 2014 systematic review showed no significant differences in lower urinary tract injuires between minislings and mid-urethral slings in 13 RCTs (RR 0.99(0.38,-2.56)).[10]

More women in the minislings group received further surgery for UI and/or mesh-related AEs, consistent with prior evidence that more women receiving minislings (vs midurethral slings) required further continence surgery (RR 2.0 (95%CI 0.93, 4.31).[10] Dyspareunia was significantly more common with minislings in the present trial. A prior randomized trial (n=205) comparing minislings(Ajust) versus mid-urethral slings showed no significant difference in 3-year rates of dyspareunia between groups., [24] In another randomized trial comparing minislings(Ajust) with obturator tapes, two patients in the minislings group, versus none in the obturator tape group, reported de novo dyspareunia;[25] these cases were thought possibly due to painful anchor in the obturator membrane and one required surgical removal of the anchor. Dyspareunia may also be caused by mesh-related infection, exposure, or abnormal healing leading to scarring.[26]

The main study limitations were the availability of follow-up only to 3-years, lack of blinding (for feasibility reasons) and inadequate power to detect important differences in AEs. Late onset AEs and/ or decline in effectiveness over time have been reported with both minislings

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and mid-urethral slings, and longer-term effectiveness and safety data are needed;[27] 10-year follow-up of study partcipants is planned. More mid-urethral slings were performed by sub-consultant grade surgeons, but we consider this unlikely to have affected results. Unlike the relatively new minislings, placing mid-urethral slings is part of the structured training program of surgeons in the UK; thus senior trainee surgeons and associate specialists who have completed their training are likely to be skilled at performing this procedures.

We had limited data on objective success rates; however, patient-reported outcomes better reflect patients' experience than objective measures, which can overestimate SUI surgery success.[28] Several mesh devices were withdrawn from the market during the heightened mesh debate. However, our study compared two technologies (tension-free mid-urethral slings vs adjustable anchored minislings), not specific devices; moreover, most participants received devices still on the market, and results were similar in this subgroup (Fig S1). Generalizability may be limited by our exclusion of women with anterior or apical prolapse beyond stage-2 and those undergoing concomitant prolapse, and by the relatively young age (mean 50 years) and non obese mean BMI (29 kg/m^2) of particpants. Additonal limitations include the absence of information on the race and ethnicity of participants (Table S) and on pre-operative pain level.

In summary, adjustable anchored minislings were non-inferior to mid-urethral slings with respect to patient-reported success rates at 15-months, and between group differences remained similar at 36-months.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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~~The study data will be shared in accordance with the' National Institute for Health Research position on the sharing of research data'.~~

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Table 1 Baseline Characteristics

	SIMS (N= 298)	**SMUS (N= 298)**
Age (years)	50.4 (11.0); [N=298]	50.7, (10.9); [N=298]
BMI	28.9 (5.5); [N=297]	28.7 (5.6); [N=292]
Parity	2.4 (1.1); [N=296]	2.4 (1.1); [N=294]
Manual job (heavy lifting)	84 (28.2)	84 (28.2)
Smoker	52 (17.4)	43 (14.4)
Pelvic floor muscle training in last 2 years	254 (85.2)	254 (85.2)
24-hour Pad test (pad weight gain – grams)	39 [24,60]; [N=234]	40 [24,67] [N=204]
EQ-5D	0.86 (0.200); [N=286]	0.83 (0.249); [N=284]
ICIQ-UI-SF score*	14.4 (3.3); [N=284]	14.4 (3.6); [N=285]
Dyspareunia ♀	25/145 (17.2)	21/145 (14.5)
Coital Incontinence ♀	60/145 (41.4)	52/145 (35.9)
Anticholinergic drug use	60 (20.1)	35 (11.7)
Diagnosis based on urodynamic testing		
- Stress Incontinence	235 (78.9)	231 (77.5)
- Mixed Incontinence	36 (12.1)	33 (11.1)
Clinical Diagnosis of SUI (No Urodynamics)	14 (4.7)	11 (3.7)
Grade of SurgeonΨ		
- Subspecialist Urogynecologist	65 (23.6)	46 (17.6)
- Consultant Gynecologist	183 (66.3)	160 (61.3)
- Consultant Urologist	23 (8.3)	9 (3.4)
- Associate Specialist/Staff Grade	1 (0.4)	3 (1.1)
- Senior Trainee	4 (1.4)	43 (16.5)
Type of procedure[α]		
- Retropubic Tapes (mid-urethral slings)	7 (2.5)	119 (45.6)
- Obturator Tapes (mid-urethral slings)	9 (3.3)	138 (52.9)
- AJUST (minislings)	62 (22.5)	
- ALTIS (minislings)	195 (70.7)	4 (1.5)

Cells are mean (sd); [valid values] or median [lower quartile, upper quartile]; or n (%)
*ICIQ-UI-SF: International Consultation on Urinary Incontinence Questionnaire – Short Form range 0-21 where a higher score is a poorer outcome.
[α]In the SIMS group, 3 women received other procedures: two participants received mini-arc and one participant received autologous fascia sling.
[Ψ]Grade of Surgeons: Consultant/ Associate Specialist are fully trained independent practitioners equivalent to Attending Surgeons in the USA; Senior Trainee are in the last 2 years in their training scheme and have completed their training in undergoing SMUS. They are equivalent to senior residents/ fellows in the USA. We note that SIMS are not part of the training schemes in the UK.
Supplementary Table S2 provides further details on baseline characteristics

Table 2: Perioperative outcomes*

	SIMS N= 276	SMUS N= 261	SIMS-SUMS (95% CI) **
Procedure Time (in minutes)			
- N - Mean (sd)	N=273, 39.2 (16.8)	N=258, 41.3 (11.6)	-2.162(-5.93,1.61)
Type of anesthesia			
- General anesthesia	70 (25.4)	238 (91.2)	
- Spinal	5 (1.8)	7 (2.7)	
- Local Anesthesia	201 (72.8)	16 (6.1)	
Local Anesthesia received during the procedure	270 (97.8)	235 (90.0)	
Tape was adjusted according to cough stress test	180 (65.2)	15 (5.7)	
Blood Loss			0.72(0.48,1.08)
- <50 ml	134 (48.6)	107 (41.0)	
- 50 – 100 ml	126 (45.7)	129 (49.4)	
- >100 ml	15 (5.4)	23 (8.8)	
Un-planned Operative Events:			
• Need to use more than one kit	7 (2.5)	0 (0.0)	
• Anaesthesia changed	7 (2.5)	1 (0.4)	
• Need to insert trocar more than once	1 (0.4)		
Satisfactory Voiding without any intervention	230 (83.3)	206 (78.9)	4.1%(-6.1%,14.2%)
Post operative hospital Stay (in hours)			
- N - Mean (sd), - ~~Median (IQR)~~	N=276 7.2(8.7)	N=261 9.7(10.7)	-2.547(-4.66,7-0.28)
Return to normal activities within 28 Days N (%)	185(75.2)	160(70.8)	4.2%(-3.4%,11.9%)
Pain score up to 14 days post-operative	N=238 19.8(19.6)	N=213 28.1(22.2)	-8.3(-12.8,-3.8)
Days of Analgesia up to 14 days post-operative	2.7,(3.6);[N=238]	3.5,(3.8);[N=213]	0.79(0.64,0.98)

In the 201 SIMS participants who received local anesthesia 47 had IV sedation, 28 oral sedation and 128 had local anesthesia only. For the 16 SMUS participants 14 had IV sedation, 1 oral sedation and 1 had only local anesthesia.
Blood loss was not recorded in 1 women in the SIMS group and 2 women in the SMUS group,

* Values presented are are either mean (SD) or n(%)

** In this column we present risk differences (RD) for all outcomes except for blood loss, where we present Odds Ratio (OR).

As the 95% confidence intervals were not adjusted for multiplicity they should not be used to infer definitive treatment effects. Detailed information on the models used are in the appendix

Commented [SCM6]: Note in footnote that values are either mean (SD) or n(%)

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Commented [SCM10]: OK as rounded? (You report only out to one digit past decimal for the values you are comparing .. so would do the same in risk diff)

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Table 3 Patient reported and objective outcomes:

	SIMS N (%)	SMUS N (%)	Adjusted risk difference
Patient reported Success (PGI-I)			
15 months (12 months post-surgery) (Primary outcome)	212/268 (79.1)	189/250 (75.6)	4.6(-2.7,11.8); p_{NI}<0.001
36 months (33 months post-surgery)	177/246(72.0)	157/235(66.8)	5.7(-1.3,12.8)
Patient reported cure on ICIQ-UI-SF			
15 months‡	93/241 (38.6)	72/217 (33.2)	6.4(-1.2,13.9)
36-months	68/210(32.4%)	62/202(30.7%)	4.1(-4.0,12.2)
Objective cure on 24 hour pad test			
15 months‡	102/119(85.7%)	83/110(75.5%)	5.2(-5.9,16.2)
36 months	75/87(86.2%)	64/79(81.0%)	3.7(-5.0,12.4)
	SIMS mean(SD)[N]	**SMUS mean(SD)[N]**	**Adjusted mean (SIMS – SMUS) difference and 95% CI**
ICIQ-UI-SF			
15 months‡	4.4(5.0);[N=219]	4.7(5.0);[N=200]	-0.4(-1.2,0.5)
36 months	4.9(4.8);[N=195]	5.3(5.2);[N=187]	-0.5(-1.4,0.4)
ICIQ-FLUTS Filling Score			
15 months‡	3.4(2.4)[N=247]	3.5(2.5)[N=220]	0.1(-0.3,0.5)
36 months	3.6(2.4);[N=214]	3.6(2.4);[N=199]	-0.0(-0.4,0.4)
ICIQ-FLUTS Voiding Score			
15 months‡	2.1(2.3)[N=248]	2.1(2.1)[N=217]	0.0(-0.4,0.3)
36 months	1.9(2.1);[N=215]	2.0(2.1);[N=199]	-0.1(-0.5,0.2)
ICIQ-FLUTS Incontinence Score			
15 months‡	3.9(4.1)[N=241]	4.4(4.3)[N=215]	-0.2(-0.9,0.4)
36 months	4.4(4.2);[N=211]	4.5(4.3);[N=197]	-0.2(-1.0,0.5)
EQ-5D -3L			
15-months‡	0.848(0.243);[N=249]	0.825(0.300);[N=219]	0.022(-0.018,0.062)
36-months	0.836(0.261);[N=217]	0.821(0.294);[N=205]	0.013(-0.030,0.056)
ICIQ-LUTSqol			
15 months‡	26.6(10.2)[N=230]	27.6(10.5)[N=202]	-0.7(-2.5,1.1)
36 months	27.4(10.7);[N=203]	28.3(11.4);[N=181]	-1.1(-3.1,0.8)
Sexual Function PISQ-IR			
15 months‡	3.7(0.5);[N=75]	3.7(0.5);[N=55]	0(-0.2,0.1)
36 months	3.6(0.6);[N=62]	3.5(0.6);[N=54]	0(-0.1,0.1)

‡The 15 and 36 month follow-ups are timed from randomisation and can be considered to be 12 and 33 months after surgery where applicable.
Objective Cure on pad test gain <8mg in 24 hours
Post hoc analysis: Cured on ICIQ-UI-SF=negative response to both “how often do you leak urine?” and “how much urine do you usually leak?”
Confidence intervals presented are at 95% with no adjustment for multiplicity and therefore should not be used to infer definitive treatment effects.
Where an outcome was missing a value has been inserted from multiple imputation using chained equations

- Primary outcome – improvement on the PGI. The PGI-I is dichotomised to one group consisting of those who respond very much improved or much improved and all other responses in the other group. Range 0,1. 1= Sucess, 0=Faliure. Range – integers 1-7. 1= very much improved, 2= much improved, 3= improved, 4= same, 5= worse, 6= much worse, 7= very much worse.
- ICIQ-UI-SF. ICIQ urinary incontinence short form score. Range 0-21. Higher scores indicate poorer outcomes.
- ICIQ-FLUTS filling score. ICIQ female lower urinary tract symptoms filling score questionnaire. Range 0-16. Higher score indicate poorer outcomes
- ICIQ-FLUTS voiding score. ICIQ female lower urinary tract symptoms voiding score questionnaire. Range 0-12. Higher score indicate poorer outcomes
- ICIQ-FLUTS incontinence score. ICIQ female lower urinary tract symptoms incontinence score questionnaire. Range 0-20.. Higher score indicate poorer outcomes
- ICIQ-FLUTS QoL. ICIQ female lower urinary tract symptoms quality of life score questionnaire. Range 19-76. Higher score indicate poorer outcomes
- PISQ-IR score. Pelvic Organ Prolapse/Urinary Incontinence Sexual questionnaire, IUGA-Revised questionnaire. Higher scores indicate better sexual function.

Table 4 Adverse events in the study groups.

	SIMS	SMUS		~~Effect size~~Risk difference (95% CI)
Operative [α]	N = 276 (%)	N= 261 (%)		
Bladder injury	0 (0.0)	9 (3.4)		-3.5(-8.7,1.8);0.18~~3~~
Urethral injury	0 (0.0)	1 (0.4)		-0.4(-1.2,0.4);0.32~~3~~
Blood loss > 200ml	5 (1.8)	5 (1.9)		-0.1(-2.6,2.4);0.94~~3~~
General anesthetic complications	1(0.4)			
Vaginal button hole	6 (2.2)	3 (1.1)		
Anaphylactic reaction to antibiotics *	1(0.4)			
Skin reaction in the area of surgery *		1(0.4)		
Intraoperative tonic clonic seizure *	1(0.4)			
Post-operative - Serious adverse events	N = 298 (%)	N = 298 (%)		
Death [Ψ]		1(0.3)		
Transient Ischemic Attack		1(0.3)		
Overdose of paracetamol **		1(0.3)		
Lung cancer		1(0.3)		
Post-operative - Other adverse events	N = 276 (%)	N= 261 (%)		
Any degree of Groin or Thigh pain				
15 months	41(14.9)	31(11.9)		3.0(-1.1,7.1);0.14~~4~~
36 months	39(14.1)	39(14.9)		-0.8(-4.1,2.5);0.61~~3~~
Using any type of pain killers				
15 months	24(8.7)	13(5.0)		3.7(0.0,7.4);0.047
36 months	21(7.6)	12(4.6)		3.0(-0.4,6.4);0.081
Tape / mesh exposure				
15-months	2(0.7)	2(0.8)		0.0(-1.6,1.5);0.96~~0~~
36-months	1(0.4)			0.4(-0.4,1.1);0.3~~329~~
Dyspareunia[ǂ]	N=145 (%)	N=145 (%)		
15-months	25(17.2)	8(5.5)		11.8(3.5,20.1);0.008
36-months	17(11.7)	7(4.8)		7.0(1.9,12.1);0.010
Additional Surgical Treatments ¥	N= 24/276 (8.7%)	N=12/261 (4.6%)		4.1(-1.1,9.4);0.12~~0~~
For Urinary Incontinence	12(4.3)	6(2.3)		
For Voiding Dysfunction	1(0.4)	2(0.8)		

Commented [SCM12]: OK?
Also, not clear why no risk difference reported for vaginal button hole or for some other variables (would presume numbners too small, but you calculated for op compliations where only 1 vs 0 events)

if you retain p values here (not sure they add much but defer to you) please report in accordance with NEJM style (In general, P values larger than 0.01 should be reported to two decimal places, and those between 0.01 and 0.001 to three decimal places; P values smaller than 0.001 should be reported as P<0.001).

Commented [AM13R12]: May we address this comment after the festive break? I will need the study statistician to present the p values in the requested NEJM style

Commented [SCM14]: would note in footnote that some participants had more than one additional surgery

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	SIMS	SMUS		~~Effect size~~Risk difference (95% CI)
For Pain:	7(2.5)	2(0.8)		
For Mesh Exposure	7(2.5)	3(1.1)		

Confidence intervals presented are at 95% with no adjustment for multiplicity and therefore should not be used to infer definitive treatment effects.
*Intraoperative serious adverse events ᵀPost randomisation (SIMS 298 and SMUS 298) ᵒPost treatment (SIMS n=276 and SMUS 261) ❟ Questions were sent to half of the Cohort (=290) while the rest of the cohort received formal PISQ-IR). Ψ death at home attributed tio drug overdose 3 yrs post intervention – details and death certificate not available). Vaginal Button Hole = Surgical injury to lateral vaginal sulcus
Supplementary Table S4 include details of additional surgical treatments and other adverse events
** Timing relative to surgical procedure: 10 days
¥ A number of participants had more than one additional surgery

Commented [SCM12]: OK?
Also, not clear why no risk difference reported for vaginal button hole or for some other variables (would presume numbners too small, but you calculated for op compliations where only 1 vs 0 events)

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