PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Abdel-fattah, Mohamed; Maclennan, Graeme; Kilonzo, M; Assassa, R Phil; McCormack, Kirsty; Davidson, Tracey; McDonald, Alison; NDow, James; Wardle, Judith; Norrie, John

VERSION 1 - REVIEW

REVIEWER	Suneetha Rachaneni Derriford Hospital, UK
REVIEW RETURNED	04-Jan-2017

GENERAL COMMENTS	I congratulate the authors for a very well designed research protocol to evaluate two different surgical techniques for stress urinary incontinence. I have identified a few shortcomings: A more structured introduction on the necessity of a further RCT comparing SIMS to SMUS will help understand the study question. There seem to be other RCTs between TVT-O and adjustable mini-slings with 1-5 year follow-up. A punching paragraph on the shortcomings of the previous studies and the add-on value this RCT will provide will be helpful. The reader would like to know how the authors identified equipoise in the clinical community with regards to the study question. Did they carry out a survey to know the clinician's views? If a survey was carried out, a paragraph on the clinicians views will be needed. There are too many unexplained abbreviations in the study flow chart which are not elaborated anywhere close by. A list of abbreviations close to the flow chart will help increase the readers understanding. SMUS group seem to include both TVTs and TOTs in one arm of the RCT. The authors seem to have overlooked the differences in the outcomes and the complications of retropubic and transobturator tapes by clubbing them into one group. Comparison of either TVT only or TOT alone versus SIMS might provide more accurate data for the clinicians to help alter their practice. Readers will benefit from an explanation of the reliability and accuracy of certain outcome parameters in the study like 'Home continence stress test'.

REVIEWER	Sue Ross University of Alberta Canada
REVIEW RETURNED	05-Jan-2017

GENERAL COMMENTS	Thanks for inviting me to review this meticulous protocol describing a very well designed large surgical RCT. The highly-respected authors are to be congratulated on the quality and completeness of the protocol. I have just one concern about the research. It seems that each surgeon will specialize in just one of the procedures (SMUS (RP-TVT or TO-TVT) or SIMS), therefore the randomization effectively allocates the patient to a composite of (device/procedure + surgeon). This is certainly a pragmatic way to deal with random allocation in a large trial being conducted in many centres, and the protocol discusses the analytical methods proposed to address this issue. Nonetheless, I still regard this as a limitation, and feel this comment will recur later when the trial is published. I do not understand why the protocol is being published at this late stage, when recruitment is complete (first recruit 2 April 2014, final recruit 30 November 2016). There is little point in a reviewer commenting on the actual content of the protocol when the study is almost finished. In fact, I assume that at least half of the recruits have already reached the primary endpoint of 12 months (follow-up will continue to 3 years after surgery so all recruits are still being followed-up). I assume that the main point of publishing the paper now is to simplify publishing the papers that will follow the completion of different endpoints (eg 12 months, 3 years). This is a worthwhile goal. It might be helpful for the authors to clarify some actual target dates and achieved completion dates. It was necessary to cross-check the paper with the ISRCTN record to find out what had happened. The authors are to be commended on the success of their endeavours to date. Recruitment of 650 patients well ahead of their original target is very impressive. I wish them equal success in follow-up of the patients to 3 years and look forward to learning about the results.

REVIEWER	Stefano Salvatore Dept of Obstetrics and Gynaeocology, San Raffaele and Vita e Salute University, Milan, Italy
REVIEW RETURNED	08-Jan-2017

GENERAL COMMENTS	This is an interesting and well designed study ptotocol aiming to compare standard mid-urethral slings with adjustable single incision slings for female urinary stress incontinence. I have, however, 3 comments before accepting it for publication: 1. the decision of not being specific in selecting the adjustable minisling (Adjust or Altis) may be not appropriate since no randomized comparisons data are available in literature. Even more impotrant is the free choice for standard slings where not just the type, but also the approach (retropubic or transobturator) may determine difficult interpretation of results. To reduce this weakness

	I would strongly sugest to identify a specific sling for each single arm. 2. According to the inclusion criteria, women with an age of 18 or older can be included. I would personally consider older women (> 40 yrs or after finishing childbearing) particularly when a graft material is inserted (as in the case of a sling), for the scarcity of data (as well mentioned by the author themselves) regarding the possible effects of a future pregnancy and vaginal delivery on a woman who had a sling.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Suneetha Rachaneni
Institution and Country: Derriford Hospital, UK
Please state any competing interests: None declared

Please leave your comments for the authors below

I congratulate the authors for a very well designed research protocol to evaluate two different surgical techniques for stress urinary incontinence – Thanks. I have identified a few shortcomings:

A more structured introduction on the necessity of a further RCT comparing SIMS to SMUS will help understand the study question. There seem to be other RCTs between TVT-O and adjustable mini-slings with 1-5 year follow-up. A punching paragraph on the shortcomings of the previous studies and the add-on value this RCT will provide will be helpful.

Authors Response: Thanks – the shortcomings of pervious clinical trials are detailed in section 1.2 Rationale of the trial.

From this detailed section, we quote: "….. 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".

In-addition, at the end of that section we make a strong argument for the current lack of robust assessment of the cost-effectiveness of single incision mini-slings which is one of the strengths of the SIMS study. As with any other new health technology, robust health economic assessment is essential before they can be embedded in standard clinical practice.

The reader would like to know how the authors identified equipoise in the clinical community with regards to the study question. Did they carry out a survey to know the clinician's views? If a survey was carried out, a paragraph on the clinicians views will be needed. Thanks. Surgical equipoise is difficult to be reliably assessed. Nevertheless, it is well-recognised in the clinical community that the research question in the SIMS trial represents an area of sufficient clinical un-certainty and a clear gap in the evidence based literature/ practice in the field. This was clearly identified by the Cochrane review on single incision mini-slings1 which made the following recommendation: "Additional high-quality trials are required to definitively answer the question whether single-incision slings are equivalent to standard mid-urethral slings for the treatment of stress urinary incontinence in women. Specifically these trials need to be adequately powered with appropriate outcome measures, so that conclusions may be drawn regarding individual single-incision slings as a meta-analysis of a combination of these slings introduces significant het-erogeneity. Future trials of single-incision slings should compare them against standard retropubic and transobturator slings with meticulous descriptions of the fixation system and defined primary and secondary outcomes. Long-term follow-up

of at least five years is required for assessment of long-term benefits and, particularly, risks". The SIMS study is well-designed to answer these important questions and bridge the current evidence gaps.
Nevertheless in the trial preparation stage, we informally surveyed the opinion of surgeons from the British Society of Urogynaecologists regarding the potential participation in the SIMS RCT and whether they felt that such RCT is timely required. Sixty three surgeons responded (30%) and all agreed that it is an area of sufficient uncertainty and a well-designed RCT is timely: 34/63 (54%) indicated a definite willingness to participate and further 14/63 (22%) indicated they may participate pending review of the protocol/ being convinced; while 15/63 (24%) did not wish to participate.

- There are too many unexplained abbreviations in the study flow chart which are not elaborated anywhere close by. A list of abbreviations close to the flow chart will help increase the readers understanding.

Authors Response: Thanks – A list of abbreviations is now added at the start of the protocol.

- SMUS group seem to include both TVTs and TOTs in one arm of the RCT. The authors seem to have overlooked the differences in the outcomes and the complications of retropubic and transobturator tapes by clubbing them into one group. Comparison of either TVT only or TOT alone versus SIMS might provide more accurate data for the clinicians to help alter their practice. Thanks.
We definitely did not overlook this important point. As per the protocol, in this RCT we compare 2 concepts of mid-urethral slings (MUS) for surgical treatment of stress urinary incontinence (SUI) in women. These technology concepts were generally described in the European Guidelines on Management of UI in 20092:

A. Tension free mid-urethral slings: these include all standard MUS (SMUS; such as retropubic and transobturator tension free vaginal tapes (RP-TVT & TO-TVT))
B. Anchored mid-urethral slings: these include Adjustable Anchored single incision mini-slings (SIMS) such as AjustTM and Altis®.

The Cochrane review of minimally invasive MUS3 at the time of protocol preparation and indeed the updated version in 20154; concluded that there was no evidence of significant differences in patient-reported success rates between RP-TVT & TO-TVT. The recent SCENIHR report5 represents the most up-to-date review of evidence and made a similar conclusion. Patient-reported success is the primary outcome for the SIMS study and therefore the control arm for the proposed RCT was designed as a pragmatic combination of these 2 types of SMUS.

Nevertheless, the investigators recognise the differences between both the RP-TVT and TO-TVT and planned a pre-specified subgroup analysis of SIMS vs Adjustable Anchored SIMS vs. each type of SMUS (i.e. RP-TVT and TO-TVT separately for all the primary and secondary outcomes including objective success rate and adverse events.

We also note that the protocol clarifies that the SIMS trial encompasses all adjustable anchored SIMS that meet pre-determined independently verified criteria of robust anchoring and post-insertion adjustability. The 5 inclusion criteria are clearly stated in the protocol (section 2.2).

- Readers will benefit from an explanation of the reliability and accuracy of certain outcome parameters in the study like 'Home continence stress test (HCST)'. Validated questionnaires and tools are used to assess all the patient-reported and objective outcomes.

Authors Response: The HCST is an invention of the primary author that is currently being validated.

Within the SIMS trial, the Objective success rate is assessed by 24 hour pad test at 12 months and yearly up to 3 years. We aim to explore the potential of the HCST to capture this data compared to the standard 24 hour pad test at baseline and follow-up.

Reviewer: 2
Reviewer Name: Sue Ross
Institution and Country: University of Alberta, Canada
Please state any competing interests: None declared

Please leave your comments for the authors below

Thanks for inviting me to review this meticulous protocol describing a very well designed large surgical RCT. The highly-respected authors are to be congratulated on the quality and completeness of the protocol.

Authors Response: Many thanks Indeed

I have just one concern about the research. It seems that each surgeon will specialize in just one of the procedures (SMUS (RP-TVT or TO-TVT) or SIMS), therefore the randomization effectively allocates the patient to a composite of (device/procedure + surgeon). This is certainly a pragmatic way to deal with random allocation in a large trial being conducted in many centres, and the protocol discusses the analytical methods proposed to address this issue. Nonetheless, I still regard this as a limitation, and feel this comment will recur later when the trial is published.

Authors Response: Thanks. As per the protocol; it was necessary that the trial ensures adequate surgical expertise for both technologies assessed. The authors agree that it may well be that one surgeon only in each centre is competent in performing single-incision slings - the relatively new technology. This will be addressed in the analysis plan.

- I do not understand why the protocol is being published at this late stage, when recruitment is complete (first recruit 2 April 2014, final recruit 30 November 2016). There is little point in a reviewer commenting on the actual content of the protocol when the study is almost finished. In fact, I assume that at least half of the recruits have already reached the primary endpoint of 12 months (follow-up will continue to 3 years after surgery so all recruits are still being followed-up). I assume that the main point of publishing the paper now is to simplify publishing the papers that will follow the completion of different endpoints (eg 12 months, 3 years). This is a worthwhile goal.

Authors Response: Thanks. We note that the recruitment period has been extended to end of July 2017 – this has now been clarified in addressing the next point.

- It might be helpful for the authors to clarify some actual target dates and achieved completion dates. It was necessary to cross-check the paper with the ISRCTN record to find out what had happened.

Authors Response: Thanks – now added at the ISRCTN section.

- The authors are to be commended on the success of their endeavours to date. Recruitment of 650 patients well ahead of their original target is very impressive. I wish them equal success in follow-up of the patients to 3 years and look forward to learning about the results.
Sue Ross

Reviewer: 3
Reviewer Name: Stefano Salvatore
Institution and Country: Dept of Obstetrics and Gynaeocology, San Raffaele and Vita e Salute University, Milan, Italy
Please state any competing interests: None

Please leave your comments for the authors below

This is an interesting and well designed study protocol aiming to compare standard mid-urethral slings with adjustable single incision slings for female urinary stress incontinence.

I have, however, 3 comments before accepting it for publication:

1. the decision of not being specific in selecting the adjustable minisling (Adjust or Altis) may be not appropriate since no randomized comparisons data are available in literature. Even more impotrant is the free choice for standard slings where not just the type, but also the approach (retropubic or transobturator) may determine difficult interpretation of results. To reduce this weakness I would strongly sugest to identify a specific sling for each single arm.

Authors Response: Thanks - please see our response to reviewer 1 on this point.

2. According to the inclusion criteria, women with an age of 18 or older can be included. I would personally consider older women (> 40 yrs or after finishing childbearing) particularly when a graft material is inserted (as in the case of a sling), for the scarcity of data (as well mentioned by the author themselves) regarding the possible effects of a future pregnancy and vaginal delivery on a woman who had a sling.

Authors Response: Thanks. In the protocol it was agreed to include women >18 years old however it is standard clinical practice in the UK that women are offered surgical treatment for SUI when their families are completed. The Patient Information Sheet clearly explained this fact in-addition to the effect of pregnancy on the operation. The protocol states in section 3.2.2 that the participants should “Have completed their families and are not pregnant”.

References:
1. https://doi.org/10.1002/14651858.CD008709.pub2
2. Lucas MG, Bosch RJL, Burkhard FC, et al. EAU guidelines on surgical treatment of urinary incontinence. Eur Urol 2012;62:1118–29
3. Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database of Systematic Reviews 2009;Issue 4 Art. No.: CD006375. DOI: 10.1002/14651858.CD006375.pub2.
4. Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev 2015; 7: CD006375.
5. http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_049.pdf

VERSION 2 – REVIEW

REVIEWER	Suneetha Rachaneni Derriford Hospital,Plymouth
REVIEW RETURNED	07-Feb-2017

GENERAL COMMENTS	Introduction has been significantly improved to provide background

	to understand the study question

REVIEWER	Sue Ross University of Alberta, Canada
REVIEW RETURNED	03-Feb-2017

GENERAL COMMENTS	Thanks, the authors have addressed my concerns.