Original article

Analysis of primary and secondary outcome domains reported in randomised trials on surgery for female stress urinary incontinence. A systematic review

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Abstract: *Introduction*. Published randomised controlled trials (RCTs) on surgery for female stress urinary incontinence (SUI) evaluated the efficacy and safety of different surgical options using a variety of outcomes and outcome measures. Our objective was to perform a systematic review of the primary and secondary outcomes, analyse their selection in different RCTs and evaluate research choices and priorities. *Methods*. A literature search was conducted using Embase, Medline and Cochrane databases. The primary and secondary outcomesreported across trials were analysed. We grouped different outcomes into domains (categories). *Results*. One hundred twenty-five RCTs, which enrolled 20757 women, were included in this study. A total of 4 primary and 7 secondary outcome domains were reported. The most prevalent primary outcome domain involved cure rates, being reported by 86.2% of the included RCTs. Complication rates had the highest prevalence among secondary outcome domains, being reported by 71% of RCTs. Sample size calculations were performed in approximately two thirds of studies that used 1 primary outcome and in an even smaller fraction of studies that reported 2 primary outcomes. *Conclusions*. A variation in selection of different primary and secondary outcomes as well as domains was confirmed. Complications may have been underreported as the majority of trials were potentially underpowered to evaluate complication rates.

Keywords: Stress urinary incontinence; Randomised controlled trials; Surgical interventions outcomes; Core outcome sets

INTRODUCTION

Surgical interventions are therapeutic options for women suffering from SUI when other non-surgical measures have failed[1]. These procedures may provide short and long-term benefits, improving the patient's quality of life[2] and reducing the costs on resources used for incontinence management or "routine care"[3]. Given the fact that various interventions are available for the same condition, choosing the appropriate intervention to treat women with SUI can be challenging. Recently, the National Institute for Health and Care Excellence (NICE) guidelines recommended an active involvement of women in the therapeutic choice by providing a patient decision aid tool[1]. Most guidelines base their recommendations on published research, with RCTs being considered to carry a high level of quality of evidence.

Gaining understanding into the choices of outcomes collected and reported in RCTs on interventions for SUI in women will add weight on interpreting the study findings on safety and efficacy of various surgical modalities. However, researchers have reported many different outcomes in RCTs, making data synthesis challenging. Consistency in the selection and definition of primary and secondary outcomes is essential to address this issue. Recently, a greater attention has been paid to the way in which surgical interventions are delivered in RCTs[4] and comparisons between the outcomes presented in study protocols and the actual reported outcomes have been evaluated as part of quality assessment of RCTs. Outcomes' discrepancies are not uncommon in research on surgical interventions and raise concern about what clinical trials conclude, running the risk of poorly-informed treatment options[5]. Recent efforts have focused on establishing a minimum set of outcomes, termed a 'core outcome set'[6] for various conditions[7-10], including pelvic floor disorders[7, 11, 12] in order to address the high variability in outcome reporting.

Combining and comparing different studies' results would be facilitated following a harmonization of study designs. Robust data from high quality meta-analyses could inform clinical practice better and contribute to the provision of better care to women.

Objective

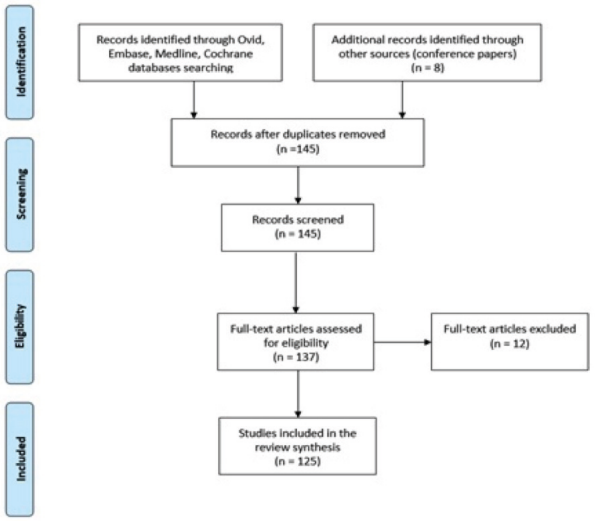
Our objective was to perform a systematic review of the literature, on RCTs on surgical interventions for SUI and evaluate the selection of the primary and secondary outcomes in these studies. Following data collection, we aimed to analyse the selected and reported outcomes in order to understand the research priorities and criteria for the study designs and contribute to the process of developing a core outcome set in the area of female stress urinary incontinence.

METHODS

Protocol and registration

This study is part of a wider project led by CHORUS, an International Collaboration for Harmonising Outcomes, Research, and Standards in Urogynaecology and Women's Health (i-chorus.org)[13], aiming to develop, disseminate and implement a Core Outcome Set for SUI, which has been prospectively registered with the Core Outcome Measures in Effectiveness Trials (COMET) initiative[14] (registration number 981). Ethical approval for this study was not required, as this study was a systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were consulted during the conduct of this review.

Figure 1. Diagram showing study search methodology (according to PRISMA flowchart)



Eligibility criteria

RCTs published in English or in different languages for which English translation was available, evaluating surgical interventions related to female SUI were eligible for inclusion in this study for primary and secondary outcomes analysis. Non-randomized, quasi-randomized, observational studies, systematic reviews and meta-analyses were excluded from this study.

Information sources

A comprehensive literature search was conducted searching Embase, Medline databases and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to May 2019. Relevant studies were searched using the following MeSH terms: 'stress urinary incontinence' and 'surgical interventions' and 'randomised controlled trials'.

Study selection

The process for article selection was completed in consecutive steps that included deduplication of articles, reading of titles, abstracts and texts (when needed) to evaluate for potential eligibility and retrieval of full texts in case of assumed eligibility and reading it in full text. Snowballing of references of full texts was also performed to minimize the possibility for potential article losses. A summary of the article retrieval process is provided in Figure 1.

Data collection process

The data collection was conducted by 2 researchers independently. Verbatim primary and secondary outcomes reported by the studies included were identified and entered into an inventory for further analysis. The outcomes that shared similar definitions were then grouped and entered into the inventory. Also, an inventory of the types of surgical interventions for female SUI evaluated in the RCTs included was created. Some trials compared different techniques of the same procedure, this aspect being reflected in the percentage of the procedures out of the total number of interventions.

Figure 3. Frequency of primary outcome domains reported by RCTs evaluating surgical interventions for SUI

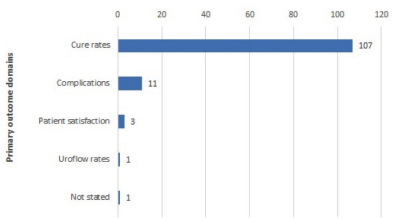
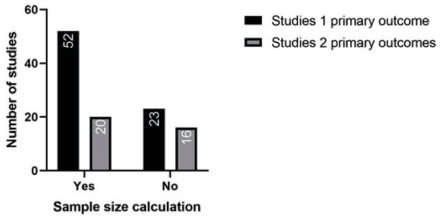


Figure 2. RCTs that reported that sample size calculation was performed vs RCTs that reported that sample size calculation was not performed



The number of surgical interventions and primary and secondary outcomes reported by each trial was assessed and recorded and their frequency was calculated. Descriptive statistics were used to present these data.

RESULTS

Study selection

A total of 125 RCTs (appendix 1), which enrolled 20,757 women, were included in this study according to the methodology presented in Figure 1[15]. Sixty two percent of articles that reported one primary outcome and 48% of articles that reported two primary outcomes performed a sample size calculation (Figure 2). In 14 RCTs it was not stated if sample size calculations were performed or the full texts were not available.

The surgical interventions evaluated in the included RCTs are presented in table 1. TVT was the most studied procedure, the percentage of RCTs that studied that procedure summarizing more than the other interventions all together.

Each trial reported a specific number of outcomes. Most RCTs (66.4%) reported only 1, 32.7% reported 2, while only 1 RCTs did not specify any primary outcome. Secondary outcomes showed a greater heterogeneity, between 0 and 6 primary or secondary outcomes being reported by each trial. Most RCTs (38.4%) reported only 1, followed by 28,7% of RCTs which reported none, 12% reported 3, 8.7% reported 4, 5.6% reported 2, 4% reported 5 and 2.4% reported 6 secondary outcomes, respectively (Table 2).

Outcomes were grouped into outcome domains to classify broad aspects related to the interventions. Four different primary outcome domains and 7 secondary outcome domains were identified across the included trials. The outcome domains, ordered based on their frequency of use across trials, are shown in figures 3 and 4.

Of the 124 included studies, 107 (86.26%) reported primary outcomes that were classified in cure rates domain. More precisely, 39 RCTs (31.4%) reported a composite of subjective and objective cure rates, 37 (29.8%) reported objective

Figure 4. Frequency of secondary outcome domains reported by RCTs evaluating surgical interventions for SUI

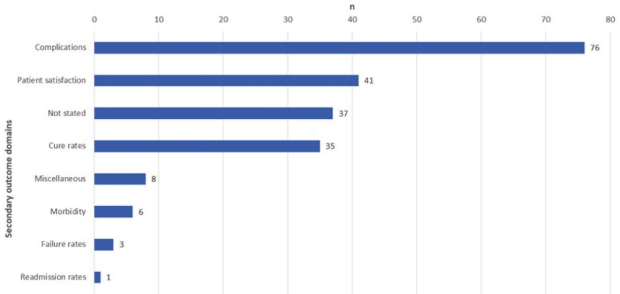


Table 1. Types of surgical interventions evaluated by RCTs

Intervention	Number of times a procedure was evaluated in a RCT	% of total interventions
Retropubic sling	131	50.90%
Transobturator tape	63	24,5%
Bulking	30	11,6%
Single incision minisling	19	7.30%
Colposuspension	14	5,4%

cure rates only, 21 (16.9%) reported subjective cure rates only and 10 (8.06%) reported cure rates of unspecified type. Eleven (8,8%) RCTs reported primary outcomes that were classified in complications domaindomanin. Outcomes reporting domains reflecting patient satisfaction and failure rates, were reported less frequently as primary outcomes, between 2 and 3 times each (Figure 3). One of the included RCTs did not state any primary outcome.

The most frequently reported secondary outcomes were grouped into the complications domain. Seventy one percent of outcomes for which the outcome measures included the necessity of further operative procedures over time, SUI symptoms, number of catheterisations/day fell under this domain. In 42.05% of RCTs, the secondary outcomes were not specified. Based on their frequency, the following categories of secondary outcome domains were patients' satisfaction and cure rates with their corresponding percentages of 46.5%, 39.7%, respectively. The remaining secondary outcomes: miscellaneous, morbidity, failure rates and readmission rates were used between 1 and 8 times each (Figure 4).

DISCUSSION

The choice of primary outcome in a RCTs is of paramount importance as the power calculations for sample sizes are based on this outcome. Equally, the selection and reporting of secondary outcomes is essential as the study may be underpowered to detect true differences between different interventions. It is suprising that a significant number of trials did not report sample size calculation at all. Given the importance of sample size calculation and the other arbitrary power parameters of a study, one assumes that a significant amount of data is not necessarily based on an adequate sample size to draw definitive conclusions and, thus, information may be misleading for current clinical practice.

Our review analysed the selection and reporting of primary and secondary outcomes reported by 125 RCTs. As expected, in the absence of a robust and standardized reporting system, a variety of outcomes were reported by researchers to evaluate surgical procedures for SUI in women[16]. While a composite of objective and subjective cure rates was the most frequently used primary outcome, the complication rates were the most prevalent secondary outcomes across the trials included.

The Consolidated Standards of Reporting Trials (CONSORT) statement suggested that only 1 primary outcome should be used in RCTs[17]. In line with this recommendation, most trials (66.4%) that were included in our analysis reported only 1 primary outcome. However, about one third of the trials reported 2 different primary outcomes.

The heterogeneity related to the number of outcomes appeared even greater in the case of secondary outcomes. Most trials (38.4%) reported a single secondary outcome, while the other two thirds have either not reported any secondary outcome or have reported between 2 and 6 outcomes.

Table 2. Number of selected primary and secondary outcomes per RCTs

Number of selected primary outcomes per RCT	n
0/not stated	(0.8%) 1/125
1	(66.4%) 83/125
2	(32.8%) 41/125
Number of selected secondary outcomes / RCT	
0/not stated	(28.7%) 36/125
1	(38.4%) 48/125
2	(5.6%) 7/125
3	(12%) 15/125
4	(8.7%) 11/125

We recently conducted a systematic review on outcome reporting in RCTs on surgical interventions for female stress incontinence[18]. This is a secondary analysis that focuses on specific choices of primary and secondary outcomes in RCTs. Researchers conducting RCTs very rarely report power calculations of secondary outcomes[19], in most cases the power calculations of each study being solely based on the chosen primary outcomes. Therefore, an outcome's position and prioritization in RCTs should not be overlooked.

An obvious trend that results from the analysis of these data is that most researchers tend to report a single primary and secondary outcome, respectively. However, there is still a lack of reporting-wise uniformity, making any analysis difficult and therefore limiting the ability of research to inform clinical practice.

The Core Outcome Measures in Effectiveness Trials (COMET) Initiative recommended the use of 'core outcome sets' (COS) with the purpose of improving the comparability between trials[20]. COS represent 'agreed standardised sets of outcomes' that constitute 'the minimum that should be measured and reported in all clinical trials of a specific condition'[21]. Apart from COS, clearly defined outcomes and definitions of success or failure are compulsory for interpreting the results of different studies[22]. Given the researcher's tendency to select the outcomes that have the greatest success rates, misleading conclusions may be drawn when multiple outcomes are reported in trials. This selective reporting bias may have as a consequence provision of unreliable evidence to guide clinical practice[23].

In our study, we observed that the primary outcomes tended to focus more on cure rates as opposed to the secondary outcomes, which were particularly focused on complication rates. The quality of these outcomes is directly related to the outcome measures that have been used. It is indeed argued whether an objective cure rate measured by a pad or cough test, for example, represents an appropriate tool because of different standardization measures of these tests encountered across trials[24, 25]. Subjective cure rates are measured based on patient's perception and specific questionnaires were developed to allow quantification. Considering these facts, it appears obvious that it is difficult to achieve a high degree of outcome accuracy.

Our study raises awareness of what is being reported by trials and highlights the heterogeneity in outcome selection in RCTs. A methodology limitation should be taken into account when interpreting the findings of this research. Only data from RCTs were included in this study and therefore a wider assessment of outcomes on surgical interventions for SUI in non-randomised studies was not possible, given that the outcomes reported by other types of research or papers

written in other language than English were not included in the analysis. This study did not aim to investigate what determined the choice of specific outcomes by the researchers who designed the RCTs. Qualitative studies might provide additional insights and help to understand researcher's preference and approach towards outcome reporting. Involvement of patients in study design might help in the process of selection of outcomes that are relevant, engaging a more diverse perspective[26].

CONCLUSIONS

The findings of our study showed that most trials reported only 1 primary and 1 secondary outcome, being in accordance with CONSORT statement. A variation in selection of different primary and secondary outcomes as well as domains was confirmed.

Sample size calculations were performed in approximately two thirds of studies that used 1 primary outcome and in an even smaller fraction of studies that studied 2 primary outcomes and therefore the studies may be underpowered to detect true differences between various interventions.

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REFERENCES

1. National Guideline A. National Institute for Health and Care Excellence: Clinical Guidelines. Urinary incontinence and pelvic organ prolapse in women: management. London: National Institute for Health and Care Excellence (UK) Copyright (c) NICE 2019.; 2019.
2. Tennstedt SL, Litman HJ, Zimmern P, Ghetti C, Kusek JW, Nager CW, et al. Quality of life after surgery for stress incontinence. International urogynecology journal and pelvic floor dysfunction. 2008;19(12):1631-8.
3. Subak LL, Goode PS, Brubaker L, Kusek JW, Schembri M, Lukacz ES, et al. Urinary incontinence management costs are reduced following Burch or sling surgery for stress incontinence. American journal of obstetrics and gynecology. 2014;211(2):171.e1-7.
4. Blencowe NS, Brown JM, Cook JA, Metcalfe C, Morton DG, Nicholl J, et al. Interventions in randomised controlled trials in surgery: issues to consider during trial design. Trials. 2015;16(1):392.
5. Fleming PS, Koletsi D, Dwan K, Pandis N. Outcome discrepancies and selective reporting: impacting the leading journals? PloS one. 2015;10(5):e0127495.
6. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Tunis S, et al. Core Outcome Set-STAndardised Protocol Items: the COS-STAP Statement. 2019;20(1):116.
7. Pergialiotis V, Durnea C, Elfituri A, Duffy J, Doumouchtsis SK. Do we need a core outcome set for childbirth perineal trauma research? A systematic review of outcome reporting in randomised trials evaluating the management of childbirth trauma. BJOG : an international journal of obstetrics and gynaecology. 2018;125(12):1522-31.
8. Nielsen KK, O'Reilly S, Wu N, Dasgupta K, Maindal HT. Development of a core outcome set for diabetes after pregnancy prevention interventions (COS-DAP): a study protocol. Trials. 2018;19(1):708.
9. Dadouch R, Faheim M, Juando-Prats C, Parsons J, D'Souza R. Development of a Core Outcome Set for Studies on Obesity in Pregnant Patients (COSSOPP): a study protocol. 2018;19(1):655.
10. Viau-Lapointe J, D'Souza R, Rose L, Lapinsky SE. Development of a Core Outcome Set for research on critically ill obstetric patients: A study protocol. Obstetric medicine. 2018;11(3):132-6.
11. de Mattos Lourenco TR, Pergialiotis V, Durnea C, Elfituri A, Haddad JM, Betschart C, et al. A systematic review of reported outcomes and outcome measures in randomized controlled trials on apical prolapse surgery. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2019;145(1):4-11.
12. de Mattos Lourenco TR, Pergialiotis V, Duffy JMN, Durnea C. A systematic review on reporting outcomes and outcome measures in trials on synthetic mesh procedures for pelvic organ prolapse: Urgent action is needed to improve quality of research. 2019;38(2):509-24.
13. An International Collaboration for Harmonising Outcomes R, and Standards in Urogynaecology and Women's Health,. Developing a core outcome set for female pelvic floor disorders 2017 [cited 2019 30 June]. Available from: https://i-chorus.org/projects/developing-a-core-outcome-set-for-female-pelvic-floor-disorders-urinary-incontinence-pelvic-organ-prolapse-childbirth-perineal-trauma-and-pelvic-pain-syndromes.
14. Core Outcome Measures in Effectiveness Trials (COMET) Initiative. 2011 [cited 2019 30 June]. Available from: http://www.comet-initiative.org/.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clinical research ed). 2009;339:b2700.
16. Clarke M. Standardising outcomes for clinical trials and systematic reviews. Trials. 2007;8:39.
17. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ (Clinical research ed). 2010;340:c332.
18. Doumouchtsis SK, Pookarnjanamorakot P, Durnea C, Mudiaga Z, Elfituri A, Haddad JM, et al. A systematic review on outcome reporting in randomized controlled trials on surgical interventions for female stress urinary incontinence. A call to develop a core outcome set. BJOG : an international journal of obstetrics and gynaecology. 2019.
19. Jakobsen JC, Ovesen C, Winkel P, Hilden J, Gluud C, Wetterslev J. Power estimations for non-primary outcomes in randomised clinical trials. BMJ open. 2019;9(6):e027092.
20. Williamson P, Clarke M. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative: Its Role in Improving Cochrane Reviews. The Cochrane database of systematic reviews. 2012(5):Ed000041.
21. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. Trials. 2017;18(Suppl 3):280.
22. Lim R, Liong ML, Leong WS, Yuen KH. Which outcome measures should be used in stress urinary incontinence trials? BJU international. 2018;121(5):805-10.
23. Page MJ, McKenzie JE, Kirkham J, Dwan K, Kramer S, Green S, et al. Bias due to selective inclusion and reporting of outcomes and analyses in systematic reviews of randomised trials of healthcare interventions. The Cochrane database of systematic reviews. 2014(10):Mr000035.
24. Simons AM, Yoong WC, Buckland S, Moore KH. Inadequate repeatability of the one-hour pad test: the need for a new incontinence outcome measure. BJOG : an international journal of obstetrics and gynaecology. 2001;108(3):315-9.
25. Carmel ME, Deng DY, Greenwell TJ, Zimmern PE. Definition of Success after Surgery for Female Stress Incontinence or Voiding Dysfunction: An Attempt at Standardization. European urology focus. 2016;2(3):231-7.
26. Rolfe DE, Ramsden VR, Banner D, Graham ID. Using qualitative Health Research methods to improve patient and public involvement and engagement in research. Research involvement and engagement. 2018;4(1):49.

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