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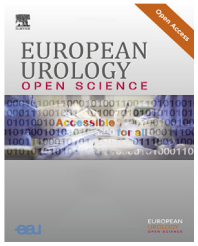

European Association of Urology

Trial Protocol

SATURN: A European, Prospective, Multicentre Registry for Male Stress Urinary Incontinence Surgery

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1. Introduction and hypotheses

Male stress urinary incontinence (SUI) occurs mostly after surgery and radiotherapy for prostate cancer, but has also been reported after benign prostate surgery and in neurogenic patients. SUI has a potentially devastating impact on quality of life and more specifically on social functioning. The prevalence of male SUI varies enormously among publications. This is mainly due to differences in the applied definition of SUI, participating centres, techniques of the applied surgery, and the period of follow-up after surgery when SUI was evaluated [1].

The treatment of male SUI has evolved from nonsurgical external containment devices, such as pads, diapers, condom catheter, or penile clamp, to implantation of compression devices, such as bulking agents, fixed or dynamic slings, and sphincter prostheses [2]. Many of the publications on implants for male SUI, including studies with the current gold standard—the AMS800 artificial urinary sphincter (AUS) prosthesis, are retrospective. Moreover, they are often limited by their low number of patients, low generalisability due to selection criteria, and relatively short follow-up. Heterogeneous and low-quality studies with mostly out-of-date efficacy outcome criteria make a comparison between different studies difficult [3,4].

A randomised controlled trial (RCT) is the gold standard in evidence-based medicine. An example in male SUI is the MASTER trial [5]. The MASTER trial is a noninferiority RCT in 380 patients with male SUI. The trial randomised between a male sling and an AUS as treatment for postprostatectomy incontinence. Conclusions were made after 12 mo only. Firstly, using a strict definition of no urinary loss at all, urinary incontinence rates remained high, with no evidence of difference between male sling and AUS. Secondly, symptoms and quality of life improved significantly in both groups, and men were generally satisfied with both procedures. However, there are constraints such as complexity, costs, lack of external validity as results might not mimic the real-life treatment situation due to the highly selected patients, and the controlled trial design [6]. Therefore, the applicability of the results of this Master trial in daily practice has been questioned [7].

The European Association of Urology (EAU) Section of Female and Functional Urology is active in promoting best

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practices and evidence-based medicine for functional urological issues. It was decided to evaluate the long-term outcome of male SUI surgery on a European level, based on activities that best reflect clinical practice. A patient registry allows collection of data for evaluation, and can be a useful tool for observing the course of the disease and understanding variation in treatment and outcome. Moreover, it can avoid a selection bias and is not hampered by the lack of equipoise that is difficult to preserve in a surgical RCT. A well-designed and executed patient registry can provide a real-world view of clinical treatment practices and the resulting safety and effectiveness, especially if long-term follow-up is enabled. Our registry "surgery for male incontinence with artificial urinary sphincters and slings" (SATURN) was developed to include every certified implantable device for the surgical treatment of male SUI for the evaluation of short- and long-term efficacy and complications of these procedures along with their impact on quality of life.

The primary objective of this registry is to determine the real-world cure rate of surgical procedures with implantable devices for male SUI during follow-up. The cure rate is defined as urinary continence with no need for the use of pads or the need to use one light security pad.

The secondary objectives are to determine other outcomes of surgical treatment of male SUI for each of the devices, and to perform a prognostic factor analysis to identify clinical and surgical variables that correlate with (in)-continence or revisions for each of the device subtypes. A revision is defined as any urogenital surgical intervention that is related to the function, placement, or site reaction of the implanted device.

2. Design

The SATURN registry is a prospective, multicentre registry (prospective, observational cohort) in several European countries (Fig. 1). The study is registered at ClinicalTrials.gov with identifier NCT02757274. Data in this manuscript are reported as much as possible according to the STROBE statement where applicable [8,9].

Originally, the registry was designed to include 500 male patients with SUI opting for surgical treatment with follow-up up of 5 yr. However, rapid recruitment of patients raised the desired possibility of including more patients with longer follow-up. Therefore, recruitment was extended to include 1000 patients and the total study duration of 10 yr, allowing a maximum follow-up of 10 yr depending on the time of inclusion since the start of the first enrolment within the registry.

Participating centres have responded to multiple open invitations in the EAU European Urology Today newsletter. Ethical approval was obtained in all participating centres. Patients of all centres were contiguously included. Informed consent was obtained from each patient. Owing to restrictions for surgery during the COVID period, not all patients could be operated on. Therefore, over 1000 patients were allowed to enrol, and the date of May 1, 2022 was set to

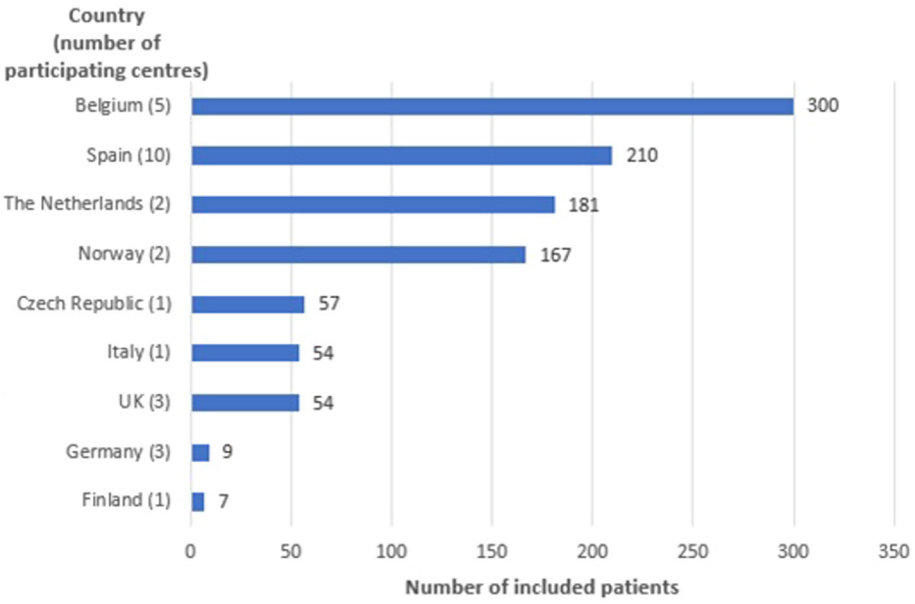

Fig. 1 – Twenty-eight centres included 1039 patients, who underwent surgery for male stress urinary incontinence. Belgium: University Hospitals Leuven (200 patients), Universitair Ziekenhuis Gent (14), Jessa Ziekenhuis Hasselt (64), AZ Groeninge Kortrijk (16), and Universitair Ziekenhuis Antwerpen (6). Spain: Hospital Universitario Puerta De Hierro-Majadahonda Madrid (31), Hospital Universitario 12 Octubre Madrid (57), Hospital Universitario de Canarias Tenerife (16), Hospital Universitario Virgen de las Nieves Granada (12), Hospital Universitari Germans Trias i Pujol Barcelona (20), Hospital General Universitario Gregorio Marañón Madrid (two), University Hospital La Fe Valencia (11), Hospital Universitario Ramón y Cajal Madrid (17), Hospital General Morales Meseguer Murcia (32), and Hospital La Paz Madrid (12). The Netherlands: Radboud University Medical Centre Nijmegen (133) and University Medical Centre Utrecht (48). Norway: Rikshoptitalet Oslo (148) and UNN Narvik (19). Czech Republic: Thomayer Hospital Prague (57). Italy: Fondazione Policlinico Universitario Agostino Gemelli IRCCS (54). UK: Royal National Orthopaedic Hospital (nine), CUH – Addenbrooke's Hospital Cambridge (26), and Guy's & Thomas' Hospital London (19). Germany: University Hospital Mainz (two), University Hospital Münster (four), and University Medical Center Hamburg Eppendorf (three). Finland: Helsinki University Central Hospital (seven).

close actual inclusion. Surgery should have been done by that date; otherwise, patients were excluded (Fig. 2).

2.1. Eligibility

A centre was allowed to participate in the study if the centre was familiar with one or more surgical procedures with implantable devices for male SUI and able to contribute consecutive patients (maximum of 200 patients per centre). The aim was to have a long-term collection of the dataset from as many centres as possible.

2.2. Patient inclusion criteria

1. Male patient undergoing surgery for SUI using medical devices such as an AUS or a male sling:
   (a) SUI of any cause
   (b) Inclusion of medical devices of any certified implantable device (therefore, procedures such as bulking agents and autologous slings were not included)
2. Participant is willing and able to give informed consent for participation in the study and is able to complete the questionnaires.

3. Protocol overview

The surgical procedure for the treatment of male SUI was according to the standard practice. Patients scheduled for these types of interventions were asked to participate in the SATURN registry. At screening, patients were informed and received written information about the SATURN registry prior to surgery. Informed consent was obtained. Figure 3 and Table 1 show an overview of the registry outline for a patient. The Supplementary material provides the electronic case report form.

At baseline, preoperative characteristics were registered, including:

1. Age
2. Weight
3. Length
4. Prostatectomy date
5. Type of other previous treatments, specifically urological surgeries and other surgery in the pelvic area, and high-intensity focused ultrasound
6. Radiotherapeutic treatment of the prostate (date of first session and total Gray delivered)
7. Presence of diabetes mellitus
8. Presence of stricture disease and type of stricture treatment
9. Use of anticoagulants
10. Charlson Comorbidity Index
11. 24-h pad weight test
12. Urodynamic results (if available from regular health care)
13. Presence of urinary tract infections
14. Cystoscopy results (if available from regular health care)
15. Physical examination results
16. Data about the use of antiseptic washings and whether patients received preoperative antibiotics
17. The International Consultation on Incontinence Questionnaire—Urinary Incontinence Short Form (ICIQ-UI SF) questionnaire
18. European Quality of Life 5 Dimensions 5 Level (EQ-5D-5L) questionnaire

Table 2 shows the main baseline characteristics. Pad test outcomes at baseline per device are shown in Figure 4.

Perioperative data concerned the type of device preferred by the patient and urologist preoperatively and implanted during surgery. Patients were treated according to the standard of care in their centre. For AUS, the date and time of surgery, surgeon ID, time of shaving, presence of skin wounds, type of prosthesis, cuff location, cuff size, pressure of regulating balloon (cmH_2O), presence of double cuff, type of intraoperative antibiotics, type of associated procedures (eg, penile prosthesis), use of suprapubic or transurethral catheter or drain, and complications of sur-

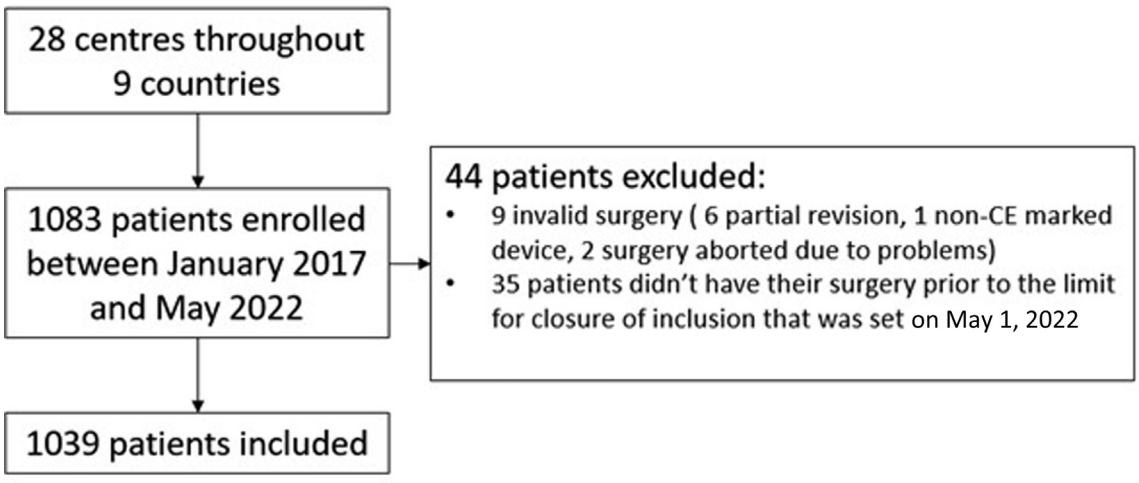

Fig. 2 – Flowchart showing the study inclusion and exclusion criteria.

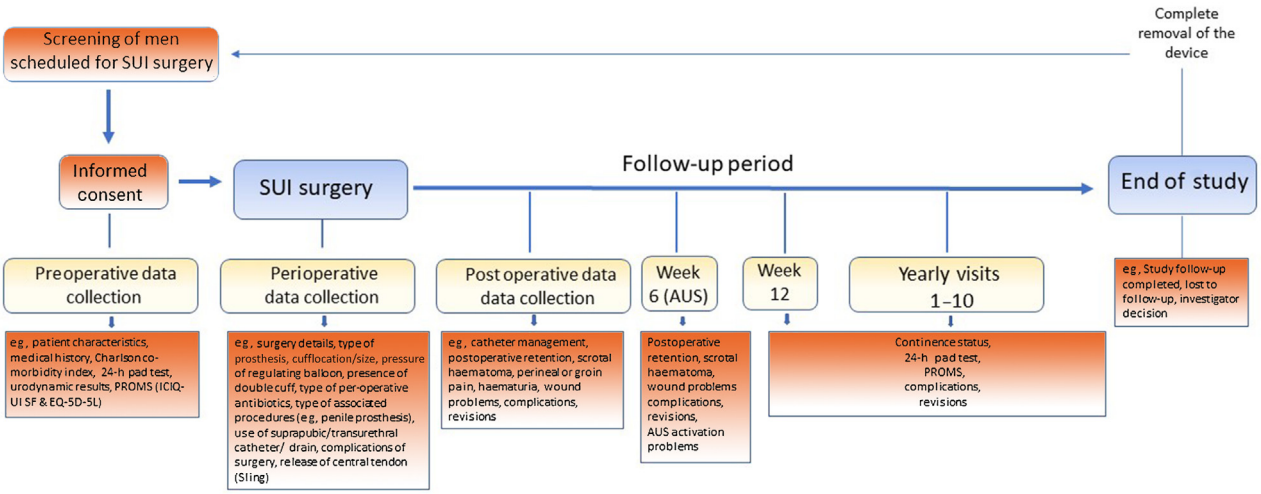

Fig. 3 – The flowchart shows the moments in follow-up with a maximum of 10 yr when patients are contacted by questionnaires regarding continence, 24-h pad weight test, and PROMS (EQ-5D-5L and ICIQ-UI SF), or data are derived from patients' files during the interval concerning complications and revisions. AUS = artificial urinary sphincter; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level; ICIQ-UI SF = International Consultation on Incontinence Questionnaire—Urinary Incontinence Short Form; PROMS = patient-reported outcome measures; SUI = stress urinary incontinence.

Table 1 – Overview of the registry outline for a patient

	Baseline	Surgery	Week 6[a]	Week 12	Yearly[b]
Informed consent	×				
Weight and length	×				
Medical history, Charlson Comorbidity Index	×				
Medication use (anticoagulation, antibiotics) and use of antiseptic washing	×				
24-h pad test[c]	×			×	×
Urodynamic investigation (if applicable)	×				
Cystoscopy	×				
Surgery		×[d]			
Activation of AUS			×		
Questionnaires (ICIQ-UI SF and EQ-5D-5L)	×			×	×
Complications		×	×	×	×
Revisions			×	×	×

AUS = artificial urinary sphincter; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level; ICIQ-UI SF = International Consultation on Incontinence Questionnaire—Urinary Incontinence Short Form.

[a] In case of AUS surgery.

[b] Yearly follow-up up to a maximum of 10 yr.

[c] Moreover, the date of becoming continent and, if applicable, the date of becoming incontinent again will be reported.

[d] For AUS, the date and time of surgery, surgeon ID, use of specific centre protocol, time of shaving, presence of skin wounds, type of prosthesis, cuff location, cuff size, pressure of regulation balloon (cmH_2O), presence of double cuff, type of intraoperative antibiotics, type of associated procedures (eg, penile prosthesis), and use of suprapubic or transurethral catheter or drain be reported. For slings, similar data will be reported (except for AUS device–specific items), including the type of sling and if there was a release of central tendon.

gery will be reported. For slings, similar data will be reported, including the type of sling and if there was a release of central tendon.

Directly postoperatively, the use and duration of a suprapubic or transurethral catheter (in days), use of antibiotics, and complications (urinary retention, scrotal haematoma, perineal or groin pain, haematuria, swelling or other wound, or other problems) will be reported. During further postoperative follow-up, data regarding complications (associated symptoms, type, date, and revision required), revisions (including a change of cuff/balloon/pump in case of an AUS), and other local conditions (eg, bladder neck sclerosis/stenosis) and local treatments (possibly) affecting (in)continence and/or complications/revision (eg, Botulinumtoxine and urethrotomy) will be collected after 6 wk (for devices that require activation) and 12 wk, and yearly thereafter up to 10 yr. Moreover, as shown in Table 1, a 24-h pad weight leakage, whether a patient is dry, the date of becoming continent, and, if applicable, the date of becoming incontinent again will be registered. The ICIQ-UI SF and EQ-5D-5L questionnaires will be asked at 12 wk after surgery and then yearly up to the end of the study period.

In the registry, besides data on recurrence of incontinence, complications, and revisions, as mentioned in the previous paragraph, information on formal (serious) adverse events or adverse device effects will not be recorded in the electronic case report form. (Serious) adverse events or adverse device effects will be collected in the way the physician routinely does in daily standard of care. It is the responsibility of the physician to report

Table 2 – Main baseline characteristics

		Mean (SD)
Age (yr)		69.6 (7.7)
BMI (kg/m^2)		27.4 (4.1)
Age adjusted CCI		4.4 (1.9)
		Percentage (of patients)
Diabetes mellitus		16.7
Anticoagulants	None	69.4
	Vitamin K inhibitor	2.4
	Platelet inhibitor	19.5
	Low molecular weight heparin	0.7
	Direct oral anticoagulant	6.7
	Other	1.3
Radiotherapy only		2.2
Both prostatectomy and radiotherapy		27.8
Prostatectomy only		61.3
No prostatectomy, no radiotherapy[a]		8.7
Type of prostatectomy	Robot-assisted laparoscopic	51.3
	Open	26.9
	Laparoscopic	19.7
	Other/unknown[b]	2.2
Previous stricture treatment		15.7
Main cause of SUI	Prostatectomy	83.3
	Radiotherapy	4.6
	Minimally invasive treatment of bladder outlet obstruction	9.6
	Neurological	1.0
	Trauma	0.2
	Other[c]	1.3
Number of previous SUI surgical treatments[d]	None	80.1
	1	14.7
	2–3	4.6
	>3	0.61
Preoperative	Urodynamic investigation	65.8
	Cystoscopy	79.7
	UTI screening	68.9
	24-h pad weight test	64.3
	ICIQ-UI SF	92.7
	EQ-5D-5L	92.2
Type of implant[e]	AMS 800	65.4
	Advance XP	19.9
	ATOMS	6.1
	Victo or Victo Plus	3.2
	ProACT	2.9
	Argus	1.2
	Virtue	0.7
	ZSI 375	0.5
	Remeex	0.1
	Tiloop	0.1

BMI = body mass index; CCI = Charlson Comorbidity Index; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level; HIFU = high-intensity focused ultrasound; ICIQ-UI SF = International Consultation on Incontinence Questionnaire—Urinary Incontinence Short Form; SD = standard deviation; SUI = stress urinary incontinence; TURP = transurethral resection of the prostate; UTI = urinary tract infections.
The mean age, age-adjusted CCI score, and BMI did not differ significantly per implant type.
[a] Other minimally invasive treatment of the prostate (eg, TURP, HIFU, cryotherapy, and laser treatment), and neurological or traumatic cause of SUI without prior prostate treatment.
[b] Transurethral resection of the prostate, transurethral resection, unknown type.
[c] Other: transurethral resection of a bladder tumour (three), penile implant (two), other pelvic urological surgery (one), other pelvic nonurological surgery (three), other nonpelvic nonurological surgery (two), pelvic floor weakness (one), and unknown (one).
[d] The 15% of patients who had one prior SUI surgery had a failed AMS800 sphincter prosthesis (51%), Advance XP sling (20%), bulking agents (6%), ProACT (5%), or other type of sphincter prosthesis or sling.
[e] There was no association between the implant type and age or BMI. One, two, and three or more different implant types per centre were shown from the database to be used in, respectively, nine, 11, and eight centres. Victo (plus), ProACT, Argus, TILOOP, and Remeex were used only at one participating centre.

unanticipated and/or serious adverse device effects to the relevant marketing authorisation holder according to local guidelines.

4. Statistical analysis

Patient characteristics, perioperative data, and follow-up data will be summarised using descriptive statistics. The number of patients with nonmissing data, mean, standard deviation, median, minimum, and maximum will be presented for continuous outcomes. The number and percentage of patients in each category will be presented for categorical outcomes. A subgroup analysis by device type will be carried out.

Cure rate is the main endpoint of the study, and is defined as urinary continence with no need for the use of pads or the need to use one light security pad. The cure rate

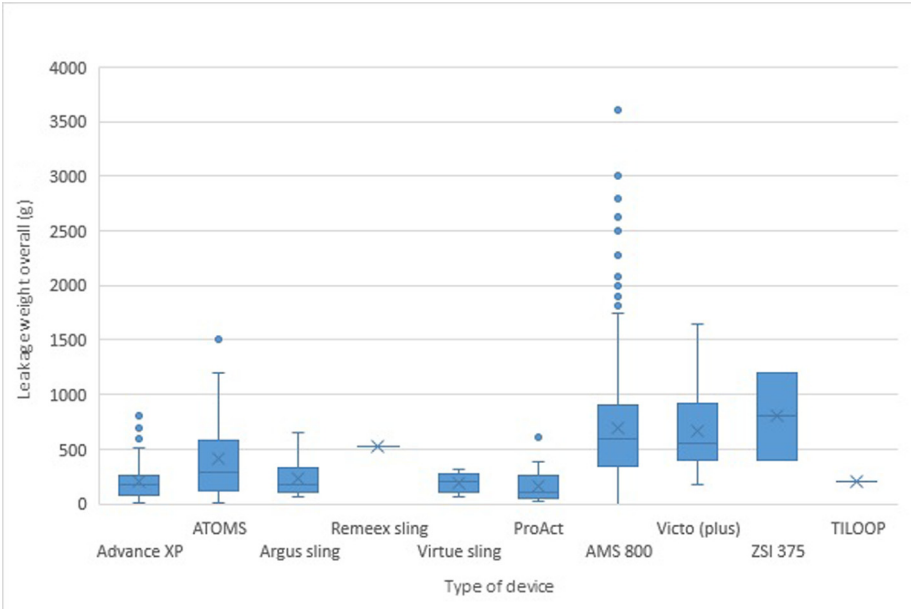

Fig. 4 – Twenty-four-hour pad test: a mean and median of, respectively, 523 and 400 g/24 h, taking all devices into account. The distribution of the pad test per device is shown in here. Patients receiving an artificial urinary sphincter prosthesis (AMS800, Victo [plus] or ZSI 375) had a clinically relevant higher leakage weight compared to other devices.

during study follow-up will be calculated together with its 95% confidence interval, for the total patient group as well as for each device subtype.

Secondary endpoints that will be evaluated are the following:

1. Time being incontinence free, which is defined as the interval being continent from after surgery to the date of incontinence recurrence
2. Time being revision free, which is defined as the interval from the date of surgery to the date of revision
3. Revision-free rate during study follow-up

Patients who die will be censored at the time of death. Both the time being incontinence free and the time being revision free will be presented using the Kaplan-Meier curve, for the total patient group as well as for each device subtype:

1. The change incontinence questionnaire and quality of life questionnaire scores compared with baseline over time
2. Postoperative general events related to the surgical procedure or the device, for example, urinary retention, scrotal haematoma, perineal pain, haematuria, or other general problems
3. Postoperative specific events related to the surgical procedure or the device, for example, pump/reservoir/cuff failure, and erosion of the device through the skin or urethra

The results of questionnaires ICIQ-UI SF and EQ-5D-5L will be analysed comparing baseline with 12 wk after surgery, and the yearly follow-up results for the whole group and for the device subgroups. Further, complications, pain, and symptoms during and postsurgery and other postoperative data will be evaluated in the device subgroups.

Univariable and multivariable analyses will be carried out to identify clinical and surgical variables that correlate with (in)continence or revisions for each of the device subtypes.

5. Summary

SATURN is a prospective, multicentre registry (prospective, observational cohort) for male SUI surgery to collect prospective data from multiple European centres and surgeons, to evaluate the short- and long-term success along with an evaluation of the impact on quality of life. Twenty-eight centres in nine European countries included 1039 patients who underwent surgery for male SUI consecutively. The surgical procedure is chosen and carried out according to the standard practice. The primary objective is the cure rate of surgical procedures for male SUI. The cure rate is defined as urinary continence with no need for use of pads or the need to use one light security pad. Preoperative characteristics and work-up peri- and postoperative data (including complications, revision surgery, and quality of life questionnaires) were and will be collected. Inclusion was closed as the maximum number of patients needed to be included had been reached. All patients have had their implant surgery, and the process of collecting follow-up data is on-going. Over a period of time, a large database from multiple European centres will be available to compare the outcomes and complication profiles of these procedures, and also to direct clinical research in this field to improve patient outcome.

Author contributions: Frank Martens had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Heesakkers, Van der Aa, Thiruchelvam, Hamid.
Acquisition of data: Martens, Heesakkers, Van der Aa, Thiruchelvam, Hamid, Everaert, Van Renterghem, Van Bruwaene, De Wachter, Zachoval, Hüsch, Queissert, Fisch, Martinez-Salamanca, Romero-Otero, Castro Diaz, Puche-Sanz, Gago, Lledó, Landis, Fraile Poblador, Romero Hoyela, Gómez de Vicente, Tikkinen, Sahai, Sacco, De Kort, Nilsen, Pedersen.
Analysis and interpretation of data: Martens, Heesakkers, Van der Aa, Thiruchelvam, Hamid.
Drafting of the manuscript: Martens.
Critical revision of the manuscript for important intellectual content: Heesakkers, Van der Aa, Thiruchelvam, Witjes, Caris, Kats.
Statistical analysis: Caris, Kats.
Obtaining funding: Heesakkers, Witjes.
Administrative, technical, or material support: Witjes, Caris, Kats.
Supervision: None.
Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.09.011.

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