-SAM Study

Evaluation of two vaginal uterus sparing surgical methods for pelvic organ reconstruction: the modified Manchester operation (MM) and sacrospinous hysteropexy (SSH)

Statistical Analysis Plan

EUDRA CT no. **Dutch Clinical trial registry no.**	NTR 6978
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Sponsor	Radboudumc
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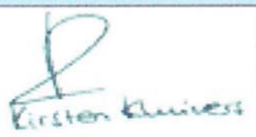
Principal investigator	Dr. Kirsten B. Kluivers, Department of Obstetrics and Gynaecology,, Radboud university medical center, Geert Grooteplein Zuid 10, 6525 GA, Nijmegen, The Netherlands		19-9-2022
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Revision history of statistical analysis plan

The revision history of the statistical analysis plan includes a version number, date of approval, summary of changes, justification of revision and timing of the revisions with respect to changes to the protocol, data safety monitoring board meetings, interim analyses and the final analyses. The revision history should be formally filed (for example in the trial master file). It does not need to contain all versions made in the internal process of producing a new filed version.

Updated statistical analysis plan version	Protocol version	Section number(s) changed	Description of and reason for changes	Date of approval
1.0				
2.0				
3.0				
…	…	…	…	…

Inhoud

1. List of abbreviations

- POP: pelvic organ prolapse
- POP-Q: pelvic organ prolapse quantification
- SSH: sacrospinous hysteropexy
- MM: modified Manchester operation
- ITT: intention to treat analysis
- PP: per protocol analysis
- SPSS: Statistical Package for the Social Sciences
- SD: standard deviation
- IQR: interquartile range
- PFDI-20: Pelvic Floor Distress Inventory-20, questionnaire
- POPDI-6: Pelvic Organ Prolaps Distress Inventory 6
- UDI-6: Urogenital Distress Inventory 6 questionnaire
- PFIQ-7: Pelvic Floor Impact Questionnaire-7, questionnaire
- PGI-I: Patient Global Impression of Improvement
- PISQ-IR: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire, IUGA-revised
- EQ5D5L: EuroQol quality of life questionnaire, 5 levels.

2. Introduction

2.1 Background

A detailed study background is provided in the published study protocol.(1)
Pelvic organ prolapse affects up to 40% of parous women which adversely affects the quality of life. During a life time, 20% of all women will undergo an operation. In general the guidelines advise a vaginal operation in case of an uterine descent: hysterectomy with uterosacral ligament plication, sacrospinous hysteropexy (SSH) or a modified Manchester operation (MM). Previous studies have shown the non-inferiority between SSH and vaginal hysterectomy. Whether or not SSH and MM are comparable concerning anatomical and functional outcome is still unknown. The practical application of both operations is at least in The Netherlands a known cause of practice pattern variation. To reveal any difference between both techniques the SAM study was designed.

2.2 Objective

The objective of this study is to compare the non-inferiority of SSH to MM in the treatment of uterine prolapse with POP-Q point D ≤ minus 1cm.

3. Endpoints

3.1 Primary endpoint

The primary outcome will be success after two years follow-up. Success is defined as:

- The absence of POP beyond the hymen in any compartment (POP-Q), and
- The absence of bulge symptoms (absence of bulge symptoms is defined as a negative response to the question, “Do you usually have a bulge or something falling out that you can see or feel in your vaginal area” (PFDI-20 POPDI-6 domain question 3; score: 0), and
- Absence of reoperation or pessary therapy for POP

3.2 Secondary endpoints

The secondary outcomes are listed below.

3.2.1 Perioperative data

3.2.1.1 Clinical parameters

a) Surgery time (minutes of operating time, to be found in operation report)
b) Hospitalisation time (time from day of operation to day of discharge)

3.2.1.2 Surgery related morbidity/complications

a) Menstrual problems
b) Hematometra
c) Any problems with uterine access (such as diagnostic cervical or endometrial sampling or Intra-uterine device insertion)
d) Infection needing antibiotics
e) Urinary retention (>200mL residual urine or prolonged catheterization (minimum of 24h after first removal of CAD)
f) Fever (>38, measured two times (minimal 12 hours apart))

3.2.2 Other endpoints

a) Subjective outcomes (patient reported outcomes)
    i) Presence or absence of vaginal bulge (PFDI-20 question 3).
    ii) Pain perception, e.g. buttock pain and dyspareunia (positive answer during follow-up consultation including Numeric Rating Scale (NRS)), or pain in other location with specification of that location.
    iii) Disease specific quality of life regarding symptoms and impact of symptoms (PFIQ-7, PFDI-20, PGI-I)
    iv) Sexual function (PISQ-IR)
    v) General quality of life (EQ5D-5L)
    vi) Clinical outcomes: lower urinary tract symptoms, stress urinary incontinence or bowel (PFDI-20)
b) Anatomical outcomes:
    i) Anatomy in all compartments using POP-Q
    ii) Anatomical failure (≥POP-Q IIb, i.e. prolapse beyond the hymen (>0 cm))
c) Further surgery:
    i) Repeat surgery for de novo POP (different site than index surgery)
    ii) Repeat surgery in the same compartment for POP symptom recurrence
    iii) Surgery for complications (pain, infection or haemorrhage)
    iv) Surgery for non-POP related conditions (i.e urinary or fecal incontinence)
d) Further treatments for POP or urinary incontinence (i.e. pelvic floor physiotherapy, pessary, consultation urology, extensive pelvic floor ultrasound or medication)
e) Abnormal cervical pathology after modified Manchester (pathology report)
f) Further treatments for related problems such as menstrual disorders, endometrial or cervical malignancies.
g) Costs

4. Study methods

4.1 Study design

The SAM study is a multicentre, non-inferiority, open label, randomized controlled trial. The study investigates the non-inferiority of SSH compared to MM in a 1:1 ratio. For detailed description of the interventions, see the study protocol (BMC Schulten 2019). (1)

4.2 Study population

Women aged 18 or older who are eligible for their first surgical treatment for symptomatic pelvic organ prolapse in any stage and with uterine descent and POP-Q point D at ≤ minus 1cm will be eligible for the study. In order to check eligibility for participation, the POP-Q will be performed at the outpatient clinic before counselling.

4.3 Inclusion criteria

The following criteria must be met to be included in the study:

- Women aged 18 or older
- Eligible for first surgical treatment for symptomatic pelvic organ prolapse in any stage
- With uterine descent and POP-Q point D at ≤ minus 1cm

4.4 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Previous prolapse or other pelvic floor surgery
- Need concomitant mid-urethral sling surgery
- Wish or need for uterus removal (In case indicated, a pap-smear and/or pipelle endometrial biopsy must be normal before inclusion.)
- Contraindication for uterus preservation (i.e. abnormal endometrial bleeding, endometrial or cervical malignancy)
- Future wish for childbearing
- Inadequate skills in the Dutch language or are not capable of filling in questionnaires

4.5 Treatment of subjects

The interventions for SAM study include two types of surgical correction.

4.5.1 Surgical procedures

- SSH: after opening the posterior vaginal wall, the pararectal space is explored at the right side and the sacrospinous ligament is identified. The posterior side of the cervix is attached to the sacrospinous ligament with two non-absorbable size 1 or 0 sutures at least 2 cm medial of the ischial spine. Either this procedure is performed open or using the Capio suturing device.
- MM: the procedure consists of extraperitoneal plication of the uterosacral ligaments (and cardinal ligaments where possible) with use of three or four absorbable size 1 sutures and amputation of the cervix. The most cranial suture is fixated through the posterior fornix of the vagina.

4.6 Blinding

Due to the nature of the investigational treatments, the patients and treating physician are not blinded to treatment allocation. The POP-Q at 12 and 24 months will be performed by a different researcher than the operating gynaecologist. All analyses will be performed in a blinded fashion.

4.7 Randomisation procedure

Randomization to treatment MM or treatment SSH will be executed in a ratio of 1:1 using dynamic randomization with blocks in variable block sizes 2, 4, 6 in online software Castor (version 2018.3.11, Castor Electronic Data Capture Amsterdam)). No stratification is applied in this study.

5. Sample-size

The sample size calculation was based on the expected comparability between the two techniques regarding the success composite of recurrent signs and symptoms of POP after two-years follow-up. A success rate of 89% for both SSH and MM, two years after the intervention, is expected. The actual treatment group proportion was set at 89% with a non-inferiority margin of 9%, assuming SSH to be below 80% under the null hypothesis of inferiority. Based on a power of 80% and the significance level of the test (α) targeted at 0.025, sample sizes of 193 per group need to be included in the study. With an expected loss to follow-up of 10%, a total of 430 women are needed.

6. Analysis considerations

6.1 Analysis populations

Definitions of analysis populations: Intention-to-treat and Per-protocol.

6.1.1 Full Analysis Population (ITT)

The intention-to-treat (ITT) population will consist of all patients who have given consent and have been allocated to one of the two treatments, irrespective of treatment received. This population consists of all patients of whom the primary outcome (POP-Q, questionnaire and information concerning reintervention for recurrent prolapse) is complete at 24 months of follow-up.

6.1.2 Per Protocol Population

A per-protocol (PP) analysis will be done complementary to the ITT analysis. This means that non-inferiority has to be demonstrated in both the ITT and PP analysis to declare non-inferiority. This will be done for the primary outcome and the two composite secondary outcomes (surgical failure of the apical compartment and overall surgical failure). In the PP population patients with the following characteristics will be excluded from the analysis:

- Major protocol deviations (see 6.1.3)

6.1.3 Definition of protocol violations

Randomized women who appear to fail inclusion and exclusion criteria (eligibility violations) during blinded data review after all follow-up visits are finalized and all data has been collected, will be excluded from the ITT and PP analysis. This will only be done for criteria that were present at the time of randomisation. Women who appear to fail the in-/exclusion criteria during the inclusion period will be replaced according to the same criteria as mentioned above.

(see chapter 5). Two clinicians will review the cases and where there are discrepancies, a third will be consulted.

Furthermore, the following protocol violations will be considered, of which major protocol violations will be excluded from PP analysis:

Major:

- Other intervention than randomized (e.g. other or no repair of apical compartment than randomized, only cervical amputation without plication of ligaments)
- Cervical amputation in SSH
- Concomitant sling or other urinary incontinence surgery
- Concomitant major other procedures during study procedure

Minor:

- Other type of device than Capio for SSH when closed procedure of SSH is performed
- >4 sacro-uterine stitches during MM procedure
- No cervical amputation in MM
- Concomitant minor other procedures during study procedure, such as laparoscopy

All major protocol violations mentioned in this section will be line-listed according to treatment group. In addition, the number and percentage of patients in each treatment group experiencing one or more protocol deviations will be presented.

6.2 Covariates and Subgroups

Subgroup analyses are planned to investigate the possible decreased or increased effects of the POP surgery with MM versus SSH in the following pre-specified subgroups in the ITT population:

- Age in years
- Menopausal status (yes vs. no)
- Usage of local estrogen (yes vs. no)
- Sexual activity (yes vs. no)
- POP-Q stage preoperative (stage II vs. stage III or IV)
- Cervical elongation (yes vs. no)
- Concomitant vaginal repair in anterior and posterior compartment (yes vs. no)
- Symptoms at 24m follow-up

Subgroup analyses will be conducted by adding an interaction term to the model and testing for the statistical significance of this interaction term. The results of the subgroup analyses will we presented regardless of the statistical significance (in the appendix, table 1).

6.3 Missing Data

Data on the primary outcome must be collected after 24 months follow-up, and missing data may be expected. However, drop-out has been allowed for in the sample size and complete case analysis is preferred. No imputation for the primary outcome will be used. Characteristics of complete and incomplete cases will be presented in an appendix (table 2).

6.4 Interim Analyses and Data Monitoring

No interim analyses are planned.

7. Efficacy analyses

7.1 Timing of final statistical analysis

The statistical analyses of the primary outcome and secondary outcomes (measured 24 months after surgery) will be performed after a minimum of 24 months have elapsed from the inclusion of the final patient in the study and data cleaning for these outcomes has been completed.

The statistical analysis of the secondary outcome sexual functioning will be performed after a minimum of 12 months have elapsed from the inclusion of the final patient in the study and data cleaning for these outcomes has been completed.

7.2 Primary endpoint analysis

Regarding the primary outcome, the null hypothesis entails that the success rate of SSH is inferior by a margin of 9% compared to MM. If the lower limit of the 95% confidence interval does not exceed the margin of -9%, the null hypothesis is rejected , and we will consider SSH to be non-inferior to MM. This is the main statistical analysis and will be performed both in the intention to treat (ITT) and per protocol (PP) population. This means that non-inferiority has to be demonstrated in both the ITT and PP analysis to declare non-inferiority of SHH compared to MM. The treatment effect will be expressed as relative risk and risk difference with a 95% confidence interval. Using the Farrington-Manning test, the non-inferiority hypothesis will be tested using the predetermined non-inferiority margin of 9% (risk difference). In the primary analysis no adjustments for covariates will be applied.

The analyses will be performed with IBM SPSS Statistics (version 25, Armonk, New York, United States) and SAS (version 9.4).

7.3 Secondary endpoint analyses

For other (secondary) outcomes, summaries of continuous data will be presented as mean ± standard deviation or median and (interquartile) range depending on their distribution. Categorical data will be presented as frequencies. When appropriate, differences between groups will be analysed using the Student's t test or Mann-Whitney test for continuous data. Mean differences and the corresponding 95% confidence intervals will be presented along with the p-value from the t-test (when applicable). For the comparison of not normal distributed data, the 95% confidence intervals corresponding with the median (and interquartile range) will be calculated. Comparisons with categorical data will be analysed using the Chi-square test or the Fisher's exact test or relative risks when applicable.

8. Safety analyses

8.1 Adverse events

Adverse event data will be analysed as allocated (intention-to-treat). Adverse events will be presented in a table per surgical procedure. Expected differences include: higher amount of patients with urinary retention after SSH.

8.1.1 Perioperative complications

1) Bladder lesion (yes/no)
2) Ureter lesion (yes/no)
3) Urethral lesion (yes/no)
4) Bowel lesion (yes/no)
5) Blood loss >500cc (yes/no)
6) Blood transfusion (yes/no)
7) Anesthestic event (yes/no)
8) Other (all complications that are not mentioned above with an explanation in the text)

8.1.2 Postoperative complications

All complications occurring within the first 6 weeks post-operative. Complications longer than 6 weeks post-operative will only be reported if evidently related to the surgical procedures of this study.

1) Urinary retention or residual urine (yes/no), > 200mL residual urine or prolonged catheterization (minimum of 24h after first removal of CAD)
2) Infection (yes/no)
    a) Temp>38, measured twice in 12 hours (yes/no)
    b) UTI within 6 weeks after the initial operation (yes/no)
    c) Pyelonephritis (yes/no)
    d) Wound infection/abcess (yes/no)
    e) Other (yes/no)
3) Delayed hemorrage (yes/no)
4) Blood transfusion (yes/no)
5) Hematoma (yes/no)

8.2 Deaths, Serious Adverse Events and other Significant Adverse Events

Serious adverse events will not be coded but will be described per allocation group.

1) Re-operation
2) Re-hospitalization
3) Death

9. Other analyses

We will do sensitivity analyses for secondary outcomes to evaluate the difference between imputed and non-imputed variables. A prognostic marker analysis will be performed to assess which baseline characteristics of the women have prognostic value and/or can be used as treatment selection markers.

Subgroup analysis mentioned in section 6.2 is seen as hypothesis generating.

10.Comparison to study protocol

The current analysis plan is largely based on the published SAM study protocol.(1) Slight changes were made and these are listed below:

- Bulge symptoms in the primary outcome will be defined as a negative response to the third question of the PFDI-20 ("Do you usually have a bulge or something falling out that you can see or feel in your vaginal area" (PFDI-20 question 3, POPDI-6 domain; score: 0) instead of "Do you feel or see a bulge in the vaginal area" of the UDI questionnaire.
- Subgroup analysis for patients who use local hormone therapy (yes vs. no)
- Composite outcome separate: anatomical failure, bulge symptoms, re-operation.
- Gynaecological examination as part of the primary outcome is specified: POP-Q will be sufficient to determine the primary outcome.
- The sample size calculation has been changed after the publication of the protocol due to recalculation of the expected loss to follow-up percentage. We have increased the sample size to 430 patients, instead of 424.
- Urinary retention or residual urine specified as : ≥200mL residual urine or prolonged catheterization (minimum of 24h after first removal of CAD)

11.Presentation of study results

11.1 Recruitment

The recruitment of study participants will be presented using the CONSORT flow diagram.

11.2 Protocol violations

All protocol violations mentioned in section 6.1.2 and this section will be line-listed according to allocation group. In addition, the number and percentage of patients in each allocation group experiencing one or more protocol deviations will be presented.

11.3 Baseline characterisations

The baseline characteristics will be presented for the total population as randomised (intention-to-treat), using the format of the mock table included in section 13.

Data will be presented using absolute numbers with percentages for discrete outcomes. Continuous outcomes will be presented as means with standard deviation, or medians with interquartile ranges.

11.4 Primary outcome

The primary outcome will be presented for the total population as randomised (intention-to-treat) and per protocol per allocation group. Data will be presented using absolute numbers with percentages for discrete outcomes. The risk difference will be presented together with 95% confidence interval.

11.5 Secondary outcome(s)

The secondary outcomes will be presented for the total population as randomised (intention-to-treat) per allocation group. The two composite outcome measures (overall surgical failure and

surgical failure of the apical compartment) will be analysed per protocol as well for comparison with SAVE-U trial and LAVA trial(2, 3). Data will be presented using absolute numbers with percentages for discrete outcomes. Relative Risk or mean difference will be presented together with 95% confidence interval and p-value.

12. Definitions of variables

12.1 Primary outcome

Composite success:

- The absence of POP beyond the hymen in any compartment (success is most descended POP-Q point smaller or equal to 0 cm,), and
- The absence of bulge symptoms (absence of bulge symptoms is defined as a negative response to the question, "Do you usually have a bulge or something falling out that you can see or feel in your vaginal area" (PFDI-20 POPDI-6 domain question 3; score: 0)), and
- Absence of reoperation or pessary therapy for POP

Numbers 1 to 3 will be computed into a composite variable. Only if all three criteria are met, this will be defined as 'success'=1. If one or more out of the three criteria is not met, this will be defined as 'no success'=0.

12.2 Secondary outcomes

- Surgical failure of the apical compartment: Recurrent apical prolapse stage ≥2 with bothersome symptoms or repeat surgery for apical prolapse
- Overall surgical failure: Prolapse POP-Q stage ≥2 (any compartment) or repeat surgery or pessary use.
- Anatomical failure: POP-Q C and/or Ba and/or Bp stage >2
  → If one or more out of the three criteria is met, this will be defined as 'anatomical failure' =1. No failure=0.
- Prolapse beyond the hymen: POP-Q C and/or Ba and/or Bp >0
  → If one or more out of the three criteria is met, this will be defined as 'anatomical failure' =1. No failure=0.
- Subjective recurrence: the presence of bulge symptoms (presence of bulge symptoms is defined as a positive response to the question from the PFDI-20 domain genital prolapse "Do you usually have a bulge or something falling out that you can see or feel in your vaginal area? in combination with a response 'somewhat bothered' to 'very much bothered' to the question 'how much does this bother you?')
- Repeat surgery in the same compartment for POP symptom recurrence
  - Anterior compartment: reoperation for POP recurrence in anterior compartment (anterior colporrhaphy) and previous operated anterior compartment
  - Apical compartment: reoperation for POP recurrence in apical compartment (defined as apical surgery or other surgery in CRF), all participants have undergone apical surgery (except the cases with a protocol violation and no surgery according to the

study protocol). Patients with an apical surgical technique but not according to the protocol will be included as well (according to the intention to treat analysis).
    - Posterior compartment: reoperation for POP recurrence in posterior compartment (posterior colporrhaphy) and previous operated posterior compartment
- Repeat surgery for de novo POP (different site than index surgery)
    - Anterior compartment: reoperation for POP in anterior compartment which is not previously operated.
    - Apical compartment: reoperation for POP in apical compartment which is not previously operated. This is limited to only the cases with a protocol violation (no operation according to study protocol = no apical surgery), since every other patients underwent apical surgery.
    - Posterior compartment: reoperation for POP in posterior compartment which is not previously operated.
- Surgery for complications
- Pessary use for POP complaints
- Duration of hospital stay (date of discharge minus date of admission)
- BMI: kg/m^2
- Cervical elongation: POP-Q point D minus POP-Q point C.

12.3 Other outcomes

- Patient reported outcomes based on questionnaires. Scores of the questionnaires will be calculated in line with the questionnaire instruction.

13. Tables

13.1 Baseline characteristics

***Table 1*. Baseline characteristics. Value are numbers (percentages) unless stated otherwise**

Characteristics	Sacrospinous hysteropexy (n=…)	Modified Manchester (n=…)
Age, median (range)	Median (IQR)	Median (IQR)
Highest educational level:		
Primary or secondary school	NNN (%)	NNN (%)
High school	NNN (%)	NNN (%)
Bachelor, master or academic degree	NNN (%)	NNN (%)
Comorbidity:		
Cardiovascular disease	NNN (%)	NNN (%)
Diabetes mellitus	NNN (%)	NNN (%)
Respiratory disease	NNN (%)	NNN (%)
Smoker	NNN (%)	NNN (%)
Postmenopausal	NNN (%)	NNN (%)
No of vaginal deliveries, median (range)	Median (IQR)	Median (IQR)
No of caesarean deliveries median (range)	Median (IQR)	Median (IQR)
No of assisted vaginal deliveries, median (range)	Median (IQR)	Median (IQR)
Positive family history for prolapse	NNN (%)	NNN (%)
Body mass index, mean (SD)	Mean (SD)	Mean (SD)
Caucasian	NNN (%)	NNN (%)
POP-Q stage uterine prolapse (point C)		
2	NNN (%)	NNN (%)
3	NNN (%)	NNN (%)
4	NNN (%)	NNN (%)
Prolapse beyond hymen		
Anterior (POP-Q Aa or Ba > 0)	NNN (%)	NNN (%)
Apical (POP-Q C > 0)	NNN (%)	NNN (%)
Posterior (POP-Q Ap or Bp > 0)	NNN (%)	NNN (%)
Overall POP-Q stage		
2	NNN (%)	NNN (%)
3	NNN (%)	NNN (%)
4	NNN (%)	NNN (%)

POP-Q=pelvic organ prolapse quantification.

13.2 Primary outcome

Table 2. **Outcomes for pelvic organ prolapse at 2year follow-up. Data are presented as numbers (percentages) stated otherwise.**

Outcomes	Sacrospinous hysteropexy	Modified Manchester	Risk difference (95% CI)
Composite outcome success*			
ITT analysis	NNN/nnn (%)	NNN (%)	X.X (95% CI)
Per protocol analysis	NNN (%)	NNN (%)	X.X (95% CI)
Surgical failure apical compartment§			
ITT analysis	NNN (%)	NNN (%)	X.X (95% CI)
Per protocol analysis	NNN (%)	NNN (%)	X.X (95% CI)
Overall surgical failure†			
ITT analysis	NNN (%)	NNN (%)	X.X (95% CI)
Per protocol analysis	NNN (%)	NNN (%)	X.X (95% CI)
Anatomical failure‡			
Overall anatomical failure	NNN (%)	NNN (%)	X.X (95% CI)
Anterior compartment	NNN (%)	NNN (%)	X.X (95% CI)
Apical compartment	NNN (%)	NNN (%)	X.X (95% CI)
Posterior compartment	NNN (%)	NNN (%)	X.X (95% CI)
Prolapse beyond the hymen			
Anterior (POP-Q Ba > 0)	NNN (%)	NNN (%)	X.X (95% CI)
Apical (POP-Q C > 0)	NNN (%)	NNN (%)	X.X (95% CI)
Posterior (POP-Q Bp > 0)	NNN (%)	NNN (%)	X.X (95% CI)
Bothersome bulge symptoms	NNN (%)	NNN (%)	X.X (95% CI)
Pessary therapy			
First year postoperative	NNN (%)	NNN (%)	X.X (95% CI)
Second year post-operative	NNN (%)	NNN (%)	X.X (95% CI)
Repeat surgery ††			
Repeat surgery in operated compartment	NNN (%)	NNN (%)	X.X (95% CI)
Anterior compartment	NNN (%)	NNN (%)	X.X (95% CI)
Apical compartment	NNN (%)	NNN (%)	X.X (95% CI)
Posterior compartment	NNN (%)	NNN (%)	X.X (95% CI)
Repeat surgery in non-operated compartment	NNN (%)	NNN (%)	X.X (95% CI)
Anterior compartment§§	NNN (%)	NNN (%)	X.X (95% CI)
Apical compartment	NNN (%)	NNN (%)	X.X (95% CI)
Posterior compartment	NNN (%)	NNN (%)	X.X (95% CI)
Surgery for non-prolapse conditions			
Urinary incontinence	NNN (%)	NNN (%)	X.X (95% CI)
Hysterectomy	NNN (%)	NNN (%)	X.X (95% CI)
Other‡‡	NNN (%)	NNN (%)	X.X (95% CI)

ITT=intention to treat; *the absence of POP beyond the hymen in any compartment, and the absence of bulge symptoms (absence of bulge symptoms is defined as a negative response to the question, “Do you usually have a bulge or something falling out that you can see or feel in your vaginal area” (PFDI-20, POPDI-6 domain question 3: 0)), and absence of reoperation or pessary therapy for POP

§Recurrent apical prolapse stage ≥2 with bothersome symptoms or repeat surgery for apical prolapse

†Prolapse POP-Q stage ≥2 (any compartment) or repeat surgery or pessary use.

‡POP-Q stage 2 or higher; POP-Q=pelvic organ prolapse quantification; Percentages were calculated using non-missing data.

‡POP-Q stage 2 or higher; POP-Q=pelvic organ prolapse quantification; Percentages were calculated using non-missing data

†† Repeat surgery for prolapse specified:

§§ Repeat surgery in non-operated compartment for patients who received non apical operation which was not according to randomization.

‡‡ Other operations (not prolapse related):

NA: not applicable.

13.3 Safety outcomes

13.4 Other secondary outcomes

Table 3. Anatomical outcomes according to POP-Q system preoperative and 2 years postoperative

		Sacrospinous hysteropexy				**Modified Manchester**				**Difference in POP-Q baseline versus 2 years postoperative**	
POP-Q point	N	pre-operative	N	2 years postoperative	N	pre-operative	N	2 years postoperative		SSH	MM
Aa	194	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
Ba		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
C		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
GH		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
Pb		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
TVL		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
Ap		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
Bp		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
D		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)

Mean (SD), Difference score is based on measurements pre-operative and with 24 months of follow-up.

Supplementary material

Table ... Anatomical outcomes according to POP-Q system preoperative and 1 year postoperative

		Sacrospinous hysteropexy				**Modified Manchester**				**Difference in POP-Q baseline versus 1 years postoperative**	
POP-Q point	N	pre-operative	N	1 year postoperative	N	pre-operative	N	1 year postoperative		SSH	MM
Aa	194	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
Ba		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
C		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
GH		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
Pb		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
TVL		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
Ap		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
Bp		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)
D		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	Mean (SD)

Mean (SD), Difference score is based on measurements pre-operative and with 12 months of follow-up.

480 ***Table 5 Patient reported outcomes***

	Before surgery				1 year				2 years				
		SSH (n=xxx)		MM (n =)		SSH (n=xxx)		MM (n = xxx)		SSH (n=xxx)		MM (n = xxx)	Sig.(p)** T0-T24
PFDI-20 (mean, SD/median IQR)	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**0.xx**
UDI-6	NNN	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD	0.xx
CRADI-8	etc	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD	0.xx
POPDI-6		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD	0.xx
PFIQ-7§ (mean, SD/median IQR)	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**0.xx**
UIQ-7	NNN	Mean ± SD		Mean ± SD	NNN	Mean ± SD		Mean ± SD	NNN	Mean ± SD		Mean ± SD	0.xx
CRAIQ-7	etc	Mean ± SD		Mean ± SD	etc	Mean ± SD		Mean ± SD	etc	Mean ± SD		Mean ± SD	0.xx
POPIQ-7		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD	0.xx
No complaints, n (%)													
PISQ-IR (mean, SD/median IQR)	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**etc**				**0.xx**
Sexually active	NNN	Mean ± SD		Mean ± SD	NNN	Mean ± SD		Mean ± SD					0.xx
Sexually inactive		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD					0.xx
EQ-5D-5L (mean, SD/median IQR)	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**			**NNN**	**Mean ± SD**			
Mobility	NNN	Mean ± SD	NNN	Mean ± SD	NNN	Mean ± SD			NNN	Mean ± SD			0.xx
Self-care		Mean ± SD		Mean ± SD		Mean ± SD				Mean ± SD			0.xx
Usual activities													0.xx
Pain													0.xx
Anxiety													0.xx
EQ-VAS													0.xx
PGI-I													0.xx
Very much better		-		-		N (%)		N (%)		N (%)		N (%)	0.xx
Much better		-		-									0.xx
Minimally better		-		-									0.xx
No change		-		-									0.xx
Minimally worse		-		-									0.xx
Much worse		-		-									0.xx
Very much worse		-		-									
PGI-I success*						SSH		MM		Risk ratio (95% CI)			Sig. (p)
12 months						N (%)		N (%)		RR (95%CI)			0.xx
24 months						N (%)		N (%)		RR (95%CI)			

PFDI-20: Pelvic Floor Disability Index-20, higher scores indicate more symptom distress.
PFIQ-7: Pelvic Floor Impact Questionnaire-7, higher scores indicate more impact on daily activity.
PISQ-IR: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire, IUGA-Revised, scores are total scores, not subdomains (score ranges from 1 (worse sexual experience) to 5 (better sexual experience)).
EQ5D-5L: EuroQol 5 dimensions-5 levels, index-scores calculated with EQ-5D value set for the Netherlands. EQ-VAS: EuroQol vertical visual analogue scale, patient's self-rated health (scale from 100 (worst to best health)).
PGI-I: patient global impression of improvement (only post-operative). *PGI-I success: very much better and much better compared to situation before operation.
*P-value represents the comparison between before surgery versus 2 years after surgery for both techniques (paired-samples t-test).

483 *Supplementary material. Table ..* **Patient reported outcomes (pre-operative and 6 months postoperative).**

		Before surgery				**6 months**		
		SSH (n=xxx)		MM (n =)		SSH (n=xxx)		MM (n = xxx)
PFDI-20 (mean, SD/median IQR)	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**
UDI-6	NNN	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD
CRADI-8	etc	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD
POPDI-6		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD
PFIQ-7§ ()	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**
UIQ-7	NNN	Mean ± SD		Mean ± SD	NNN	Mean ± SD		Mean ± SD
CRAIQ-7	etc	Mean ± SD		Mean ± SD	etc	Mean ± SD		Mean ± SD
POPIQ-7		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD
No complaints, n (%)								
PISQ-IR (median, IQR)	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**	**NNN**	**Mean ± SD**
Sexually active	NNN	Mean ± SD		Mean ± SD	NNN	Mean ± SD		Mean ± SD
Sexually inactive		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD
EQ-5D-5L (median, IQR)		Etc						
Mobility								
Self-care								
Usual activities								
Pain								
Anxiety								
EQ-VAS								
PGI-I								
Very much better		-		-		N (%)		N (%)
Much better		-		-				
Minimally better		-		-				
No change		-		-				
Minimally worse		-		-				
Much worse		-		-				
Very much worse		-		-				

PFDI-20: Pelvic Floor Disability Index-20, higher scores indicate more symptom distress.
PFIQ-7: Pelvic Floor Impact Questionnaire-7, higher scores indicate more impact on daily activity.
PISQ-IR: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire, IUGA-Revised, scores are total scores, not subdomains (score ranges from 1 (worse sexual experience) to 5 (better sexual experience)).
EQ5D-5L: EuroQol 5 dimensions-5 levels, index-scores calculated with EQ-5D value set for the Netherlands. EQ-VAS: EuroQol vertical visual analogue scale, patient's self-rated health (scale from 0-100 (worst to best health)).
PGI-I: patient global impression of improvement (only post-operative). *PGI-I success: very much better and much better compared to situation before operation.

13.5 Secondary outcome (surgery related morbidity/complications)

Table 4 Surgical procedures and perioperative outcomes Data are presented as numbers (percentages) unless stated otherwise

Characteristics	Sacrospinous hysteropexy (n=…)	Modified Manchester (n=…)	Risk difference (95% CI)
Operating time (min), median (IQR, 95%CI)	Median (IQR, 95% CI)	Median (IQR, 95% CI)	
Estimated blood loss (mL), median (IQR, 95%CI)	Median (IQR, 95% CI)	Median (IQR, 95% CI)	
Length of hospital stay (days), median (IQR, 95%CI)	Median (IQR, 95% CI)	Median (IQR, 95% CI)	
Concomitant surgery	NNN (%)	NNN (%)	difference (95% CI)
Anterior colporrhaphy	NNN (%)	NNN (%)	difference (95% CI)
Posterior colporrhaphy	NNN (%)	NNN (%)	difference (95% CI)
Anterior and posterior colporrhaphy	NNN (%)	NNN (%)	difference (95% CI)
Other	NNN (%)	NNN (%)	difference (95% CI)
Surgeon			
Gynaecologist	NNN (%)	NNN (%)	difference (95% CI)
Resident	NNN (%)	NNN (%)	difference (95% CI)
Type of SSH procedure		NA	
Open	NNN (%)	NA	
Device	NNN (%)	NA	
Histology of cervix after MM			
CIN 1	NA	N (%)	
CIN 2	NA	N (%)	
CIN 3	NA	N (%)	

Percentages were calculated using non-missing data. SD=standard deviation; CI=confidence interval; SSH=sacrospinous hysteropexy; MM=modified Manchester. Other: xxxxxx NA= not applicable.

491 ***Table 6. Adverse Events Related to the Surgical Outcome***
492

	Sacrospinous hysteropexy n=	**Modified Manchester n=**	**Sig. (p)**
Women with Serious Adverse Event (SAE), n (%)	N (%)	N (%)	
Death			
likely to be related to surgery*	N (%)	N (%)	
not related to surgery**	N (%)	N (%)	
Intraoperative period			
Injury to adjacent organs	N (%)	N (%)	
Blood loss >500 mL			
Blood transfusion			
Anesthetic incident‡			
Postoperative period			
Infection:			
temperature >38 measured twice in 12h	N (%)	N (%)	
urinary tract infection (<6w postop)			
wound infection			
other infections†			
Urinary retention* with following treatment:			
Foley catheter			
clean intermittent self-catheterization (CIC)			
Foley catheter and CIC			
number of days (median, IQR)			
Opiate use > 2 days after surgery			
Bleeding:			
delayed hemorrhage			
hematoma			
Reoperation other than POP‡; for reason:			
hemorrhage needing surgery			
suture removal			
Re-hospitalization other than POP‡; for reason:			
suture removal$			
urinary retention			
infection			
delayed hematoma (needing surgery)			
constipation			
Buttock pain and extra visit(s)			
Buttock pain; with treatment(s):			
suture removal			

	Sacrospinous hysteropexy n=	Modified Manchester n=	Sig. (p)
nerve block			
physical therapy			
Malignancy			
Cervical stenosis			
of whom had hematometra			

Data are presented as numbers (percentages) unless stated otherwise; POP= pelvic organ prolapse; N/A= not applicable; CI= Confidence Interval. *= cause of death: pulmonary embolism 5 weeks post-operative, which is possibly related to the surgery; **= cause of death: .. ; ‡= reoperation and rehospitalization for recurrence of POP are not included in table 6, but are shown in table 2; *= repetitive >150mL residual urine (according to local protocol) or prolonged catheterization (more than 24h after first removal of CAD; †=other infection consists of:… ; Sig (p) = p value as calculated with tests for significance as appropriate: a= Fischer exact test, b= Chi square test, c= Mann Whitney U.

501

502 ***Appendix table 1 Subgroup analysis***

Variable	Sacrospinous hysteropexy n=	Modified Manchester n=	Odds Ratio (95% CI)	P-value interaction
Age, *years*‡				
Menopausal status				
No	nn/NN (%)	nn/NN (%)	OR (xx to xx)	0.xx
Yes				
Local oestrogen use preoperative				
No				
Yes				
Sexual activity				
No				
Yes				
POP-Q stage preoperative (stage 2 versus stage 3 or 4)				
Stage 2				
Stage 3 or 4				
Cervical elongation*, cm* †‡				
Concomitant vaginal repair *(anterior or posterior or both)*				
No				
Yes				
Anterior vaginal repair				
No				
Yes				
Posterior vaginal repair				
No				
Yes				

Data present the number of women (%) in whom the treatment was a success as by the composite outcome of success; The composite outcome success defined as the absence of POP beyond the hymen in any compartment, and the absence of bulge symptoms and the absence of reoperation or pessary treatment for POP; Subgroup analyses were performed for the composite outcome of success by addition of the variables as interaction term; Odds ratio as assessed with logistic regression analysis; ‡ mean (SD); † Cervical elongation as measured by preoperative POP-Q point D minus preoperative POP-Q point C; p-value interaction represents the effect of the interaction term on the composite outcome of success.

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504 ***Appendix table 2 Description of loss to follow-up***

Characteristics	Complete follow-up (n=)		Incomplete follow-up (n=)	
	SSH	MM	SSH	MM
No of patients	nn (%)	nn (%)	nn (%)	nn (%)
Age in years, median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Highest educational level:				
Primary or secondary school				
High school				
Bachelor, master or academic degree				
Comorbidity:				
Cardiovascular disease				
Diabetes mellitus				
Respiratory disease				
Smoker				
Postmenopausal				
No of vaginal deliveries, median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
No of caesarean deliveries median (IQR)				
No of assisted vaginal deliveries, median (IQR)				
Positive family history for prolapse				
Body mass index, mean (SD)				
POP-Q stage cervix (point C) pre-operative				
2				
3				
4				
Prolapse beyond hymen pre-operative				
Anterior (POP-Q Aa or Ba > 0)				
Apical (POP-Q C > 0)				
Posterior (POP-Q Ap or Bp > 0)				
Overall POP-Q stage pre-operative				
2				
3				
4				

Data presented as numbers (percentages) unless stated otherwise; SD= standard deviation; IQR= interquartile range; POP-Q= pelvic organ prolapse quantification; POP= Pelvic organ prolapse; No= number; Stage POP-Q stage 2: most distal prolapse is between 1 cm above and 1 cm beyond hymen; stage 3: most distal prolapse is prolapsed >1 cm beyond hymen but no further than 2 cm less than total vaginal length; stage 4: total prolapse. Degree of prolapse of anterior vaginal wall (Aa and Ba), posterior vaginal wall (Ap and Bp), and uterus or vaginal vault (C) measured in centimeters both above or proximal to hymen (negative number) or beyond or distal to hymen (positive number), with plane of hymen defined as zero. A represents the descent of a measurement point 3 cm proximal to the hymen on the anterior (Aa) and posterior (Ap) vaginal wall. B is the most descended edge on the anterior (Ba) and posterior (Bp) vaginal wall.

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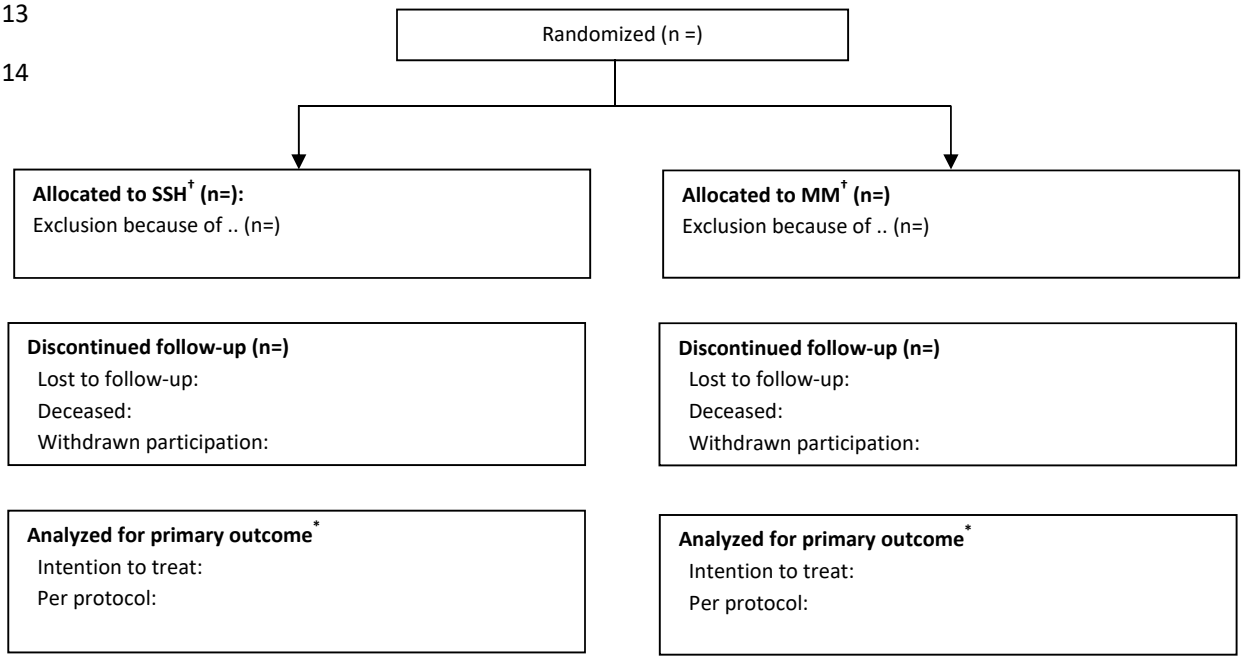
14.Figures

14.1 Flowchart of participants

A CONSORT flowchart including the type of choices should be included.

Illustrative example

The flow of study participants will be presented using the CONSORT flow-chart for clinical trial participants as shown below.



† SSH: sacrospinous hysteropexy, MM: modified Manchester, POP-Q: pelvic organ prolapse quantification.

* primary outcome: composite outcome of success.

15.References

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