STATISTICAL ANALYSIS PLAN

Trial registration no:	NCT07006129
Study Name:	Effectiveness of perineorrhaphy in pelvic organ prolapse surgery
Study type:	Observational target trial emulation
Sponsor:	Lund University, Sweden
Statistical analysis plan date and version:	Version 1.0. June 5th, 2025
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SIGNATURE PAGE

Effectiveness of perineorrhaphy in pelvic organ prolapse surgery with native tissue repair

The primary and secondary outcome analyses of this emulated target trial in observational data have not been conducted prior to the registration of this analysis plan at clinicaltrials.gov. In addition, we have not been informed by any similar analysis of these outcomes in the data set during study planning.

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Version history

Version	Date	Changes from previous version
1.0	June 5, 2025	n/a

Abbreviations

ASA: American Society of Anaesthesiologists

ATT: Average effect in treated

BMI: Body mass index

GynOp: Swedish National Quality Register of Gynaecological Surgery

ICD: International classification of diseases

IPW: Inverse probability weighting

RMST: Restricted mean survival time

Summary

This is an observational registry-based study of long-term outcome after vaginal native tissue repair for pelvic organ prolapse designed to emulate a pragmatic open-label two-arm trial for which patients, in whom perineorrhaphy is not strictly indicated but clinically tenable, perioperatively are randomized to concomitant perineorrhaphy or not.

Hypothesis

The primary hypothesis is that concomitant perineorrhaphy during surgery for pelvic organ prolapse reduces the cumulative risk of reoperation at 5 years with non-inferior patient-reported outcomes at 1 year.

Intervention/Treatment

Primary pelvic organ prolapse surgery with vaginal native tissue repair, comparing those who have had concomitant perineorrhaphy or not.

Study start: January 1st 2007 (first eligible date of surgery)

Primary completion: December 31st 2022 (last date of follow-up)

Enrollment (estimated): 40 646 patients.

Study type: Observational

Specification and overview of target trial emulation

We seek to emulate a pragmatic open-label two-arm trial in patients undergoing native tissue repair surgery for pelvic organ prolapse, in which patients are randomized perioperatively to either concomitant perineorrhaphy or not. Our target population is the large group of patients for whom, at the discretion of the surgeon, this intervention is currently an option while not being strictly indicated.

Component	Target trial specification	Target trial emulation
Eligibility citeria	Pelvic organ prolapse eligible for pelvic organ prolapse surgery with vaginal native tissue repair No previous hysterectomy or pelvic organ prolapse surgery	Same
Participant selection	Exclusion criteria: primary surgery with colpocleisis, hysterectomy, use of mesh, laparoscopic or abdominal surgery, concomitant incontinence surgery (eg transvaginal tape). For patients meeting the inclusion criterion and no exclusion criterion, the gynaecologist surgeon perioperatively decides whether it is not strictly indicated but clinically tenable (clinical equipoise) to perform a perineorrhaphy and thus to randomize the patient to intervention or not.	Same exclusion criteria. Two different approaches are used to emulate randomization after the final inclusion of the patient in the trial based on the surgeon's discretion (clinical equipoise). In the primary analyses, inverse probability weighting following Sturmer trimming of propensity scores is used to estimate ATE. In the secondary analysis overlap weighting (mimicking clinical equipoise) is used instead of inverse probability weighting.
Treatment strategies	1) Vaginal pelvic organ prolapse surgery including perineorrhaphy 2) Vaginal pelvic organ prolapse surgery excluding perineorrhaphy	Same
Treatment assignments	Participants are randomly assigned perioperatively to either strategy and are postoperatively aware of the strategy to which they have been assigned.	We assumed that women were randomly assigned within levels of baseline co-variables: age, BMI, parity, lung disease, ASA-classification, constipation, hypermobility, prolapse in which vaginal compartment and if surgery is performed on it, year of primary surgery and region. Data was obtained from The Swedish National Quality Register of Gynaecological Surgery[1] (GynOp), the Swedish National Patient Register[2], the Swedish Medical Birth Register[3] and the Swedish Cause of Death Register.[4]

Start and end of follow-up	Follow-up starts at surgery, 2007 - Juli 31st 2021 and ends after 5 years, or December 31st 2022, whichever comes first.	Same
Outcome	Primary: Cumulative risk of reoperation within 5 years. Secondary: Symptoms of vaginal bulge and lack of patient-reported satisfaction at 1 year (non-inferiority absolute risk).	Same. Subjective results were obtained from the 1-year follow up questionnaire in GynOp-registry, reoperation was obtained from GynOp-registry and the Swedish National Patient Register.
Casual contrast(s) of interest	Primary outcome: Difference in cumulative reoperation risk at five years (intention to treat). Secondary outcomes: <10% non-inferiority absolute risk for respective outcome.	Same
Data analysis plan (SAP)	Cumulative risk of primary outcome (reoperation) reported as risk difference, with risks at five years of follow-up estimated using the Kaplan-Meier estimator. Absolute risk difference for each secondary (patient reported) outcome at 1 year follow-up with the non-inferiority margin set to 10% of the absolute risk in the comparison group. Additional analyses: Restricted mean survival time (RMST) will be calculated at five years of follow-up for the primary outcome.	Same, except that the observational analog of the analysis requires multiple imputation and adjustment for confounding through inverse probability weighting. In primary analysis: Inverse probability weighting with estimation of average treatment effect (ATE). Secondary analysis: The analysis of primary and secondary outcomes will be repeated but with overlap weights. Additional analyses: The sample will be re-weighted using IPW to estimate the average effect in treated (ATT). Bias analysis: Mortality during follow up for the primary outcome will be used as a negative control.

Primary analysis

Primary outcome

1. Reoperation for pelvic organ prolapse within 5 years after primary pelvic organ prolapse surgery, comparing those who have had concomitant perineorrhaphy or not.
   Reoperation is defined as subsequent prolapse surgery in any vaginal compartment either registered in GynOp or registered Swedish procedure coding system (KVÅ) "LEF" (prolapse surgery) in The Swedish National Patient Registry. For follow-up in the Swedish National Patient Registry only surgeries performed 29 days or more after the primary surgery was included to avoid registering the primary surgery as a subsequent surgery.

Secondary patient reported outcomes

1. Being unsatisfied at 1 year follow-up.
   Being unsatisfied defined as answered "dissatisfied"/"very dissatisfied" (4-5) to the question "Do you feel satisfied by the result of the procedure". The answer was scaled from 1 "very satisfied" to 5 "very dissatisfied" in the 1-year follow-up questionnaire in the GynOp-registry.

2. Vaginal bulging at 1 year follow-up.
   Reporting a vaginal bulge was defined as agreement to the question "Do you feel that something is bulging out from the vagina?" in the questionnaire answered to the GynOp-registry 1 year postoperative. The answers were dichotomized into yes ("1–3 times per week" or "daily") or no ("never", "almost never", "1–3 times per month").

Secondary analysis (using different weights)

Same outcomes as in primary analyses but with different set of weights (overlap weights).

Data sources

The Swedish National Quality Register of Gynaecological Surgery[1] (primary surgery, background variables, and reoperation), the Swedish National Patient Register[2] (co-morbidity and reoperation), the Swedish Medical Birth Register[3] (parity and birth related variables) and the Swedish Cause of Death Register (mortality).[4]

Study period

Primary vaginal pelvic organ prolapse surgery from January 1st 2007 to June 30th 2021. Follow-up during 5 years from primary surgery or December 31st 2022, whichever comes first. This means that all participants are followed so that they can reasonably report the patient-reported outcomes at 1 year.

Missing data and weighting

Prior to multiple imputation, propensity score weighting (on the intervention) using lasso is used to select covariables for the propensity score analyses, including interactions, among the subset of participants with complete data. Selected interactions are subsequently included in the multiple imputation step.

Imputation of missing data are performed using multiple chained equations through the SAS function PROC MI with n= 20 datasets. Outcome data are included in the imputation step. Following outcome analyses as described below, estimates from each dataset are pooled and appropriately summarized.

The primary and secondary analyses are based on propensity score weights calculated using logistic regression with perineorrhaphy as the outcome. Subsequent trimming of propensity scores is performed according to Sturmer et al. (i.e. asymmetrical trimming at fifth percentile propensity score of treated and 95th percentile propensity score of untreated).[5] Following trimming, the model for the propensity scores is refitted before used in weighting. In the primary analysis stabilized inverse probability weights[6] are used whereas overlap weights[7] are used for the secondary analysis. Standardized mean differences are used to inspect success of weighting with a margin of 0.1 considered sufficient.

Variables used for weighting

Body mass index: Based on data from GynOp and calculated after imputation of missing height and weight. Prior imputation of height and weight, these variables were set to missing if calculated BMI was outside range 15-60 kg/m2. Height outside range 131-197 centimeters and weight outside range 35-160 kg was set to missing.

In multiple imputation BMI was used as a categorical variable, for weighting BMI was grouped into five categories according to WHO definitions: (BMI < 18.5 kg/m^2, 18.5-24 kg/m^2, 25-29 kg/m^2, 30-34 kg/m^2, and ≥35 kg/m^2)

Age: Defined as a continuous variable based on information on date of surgery and date of birth collected from GynOp.

Parity: Categorized into five levels (0, 1, 2, 3, 4, or 5 or more deliveries).

The primary data source was self-reported parity in GynOp. If missing, the secondary data source was The Swedish Medical Birth Register, which started in 1973. Value of >15 was set to missing.

Constipation: Defined as "1-3 times a week" or "daily" (4-5). Data from GynOp, patient reported preoperative, variable "Do you sometimes have problems emptying your bowel", 5-grade scale, from "never" to "daily".

Severe lung disease: Defined as yes or no based on ICD-10 code J40-J47 before the primary surgery in the Swedish National Patient Register.

Hypermobility disease: Defined as yes or no based on ICD-10 code Q79.6 or M35.7, present during the study time in the Swedish National Patient Register.

ASA physical status classification: Defined as ASA 1, ASA 2, or ASA 3 to 4 based on data from GynOp.

Prolapse present preoperatively and vaginal compartment addressed at surgery: Coded through two binary variables (any prolapse present prior to surgery [yes or no] and surgery performed [yes or no]) describing each of the three vaginal compartments (anterior, posterior, apical), through their interactions. As a result, for each of the three vaginal compartments there are four categories, which are mutually exclusive within compartment but not between compartments ([prolapse present, surgery performed on the compartment], [prolapse present, surgery not performed on the compartment], [prolapse not present, surgery performed on the compartment], [prolapse not present, surgery not performed on the compartment]). Data from GynOp.

Year of primary surgery: Defined as a continuous variable based on data from GynOp.

Geographical region: Data from GynOp, registering clinic. Categorical variable with 25 categories.

Statistical analyses of outcomes

For the primary outcome, a weighted (see section above) Kaplan-Meier estimator[8] is used to estimate cumulative risk difference at 5 years of follow-up with censoring for death.

For the secondary outcomes, weighted risk differences (see section above) are used to estimate non-inferiority of each patient reported outcome at 1 year. The non-inferiority margin on the absolute risk scale is set to 10% of the absolute risk of outcome in the comparison group (i.e. in patients with no perineorrhaphy) for each secondary outcome.

In the primary analysis based on inverse probability weights it may be necessary to conduct ad-hoc Winsorization of weights, e.g., if the variability of results across imputations is considerable.

The statistical methods, excluding the weights, are identical in the primary and secondary analyses. All analyses are presented with two-sided 95% confidence intervals following bootstrapping.

Bias analysis

- As a negative control, incident mortality across five years of follow-up using weighted cumulative incidence curves will be used.

Pre-specified additional analyses

- Number needed to treat for the primary outcome will be calculated.

- The restricted mean survival time for the primary outcome will be calculated and reported.[9]
- The outcome analyses will be reweighted to estimate the average treatment effect on the treated (ATT).
- Stratified outcome analyses will be performed for each vaginal compartment targeted at surgery (anterior surgery, posterior surgery, apical surgery, respectively), age (<50 years or less, 51-70 years, and 71 years and older), BMI (24 kg/m2 or less, 25-29, 30 or higher) and year of primary procedure (2007-2011, 2012-2016, 2017-2021).

Statistical Software

The statistical analyses are tentatively to be conducted using SAS 9.4.

Tentative main display items

1. **Table 1** shows descriptive data of the study sample
2. **Figure 1** shows flowchart of study sample
3. **Figure 2** shows crude and adjusted cumulative incidence curves for the primary outcome
4. **Table 2** shows the results of the secondary patient-reported outcomes
5. **Table 3** shows the results of the restricted mean survival time analyses at five years

Tentative additional display items

- **Table** shows additional descriptive data following weighting
- **Figure** shows the result of the negative control bias analysis
- **Figure** shows the propensity score density plots
- **Figure** shows the adjusted cumulative incidence curves for the primary outcome when estimating the average treatment effect in treated (ATT)
- **Table** shows the results of the secondary patient-reported outcomes when estimating the average treatment effect in treated (ATT)

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