Version 1.0 – 2025-09-11

Trial Title

A register-based randomized controlled multicenter trial of laparo-endoscopic bilateral inguinal hernia repairs with an asymptomatic contralateral hernia

---

Trial Code

BILAP-HERNIA trial

Trial Registration Number

ClinicalTrials.gov Identifier: Not yet registered

BILAP HERNIA Trial – Statistical Analysis Plan (SAP)

Randomization

Patient will be allocated through the ECRF-system using pre-generated randomization lists via the Swedish Hernia Register (SHR). The randomization will be conducted using a block randomization with 1:1 relationship to the two procedures. Total concealment of the allocation will be achieved with 4 or 6 block random sequence generation.

Analysis

- **ITT – Intention to treat and PP – Per Protocol analysis**

All analysis will primally be made using an intention to treat procedure. Corresponding per-protocol analysis and completed case analysis will be made and results from this analysis will be attached as a supplement in the final publication.

- **Primary endpoint**

Patient-reported chronic pain postoperatively (PROM) [Time Frame: 1 year after surgery]

To compare chronic pain 1 year after surgery between laparo-endoscopic bilateral inguinal hernia repair with an asymptomatic contralateral inguinal hernia (bilateral arm) versus a laparoscopic unilateral inguinal hernia repair (unilateral arm) without repairing the asymptomatic contralateral inguinal hernia in bilateral groin hernias in adults.

The chronic pain rate 1 year after surgery in previous hand-full studies are ranging from 10-15% and up to 18% for women following groin hernia repair. We hypothesize that there is no significant difference in chronic pain rate 1 year after surgery between bilateral repair and unilateral repair as a non-inferiority analysis. We assume a 12% chronic pain rate in both groups. If there is truly no difference between the standard and the intervention group for the binary primary outcome, then 2074 patients are required to be 80% sure that the upper limit of a one-sided 97.5% confidence interval (CI) (or equivalently a 95% two-sided CI) will exclude a difference in favor of the standard group of more than 4% (non-inferiority margin). In any case, the number of patients in each group must be increased by 10% to cover the expected patient drop off of the primary outcome of patient-reported chronic pain (this number has been decreased from earlier cohort studies of 30% to 10% due to that this trial will have reminders to the patients of the PROM questionnaire and an assumption of being included in a trial can increase the response rate). The estimated total amount of patients would be 2200.
Approximately 16,000 groin hernia repairs are performed annually in Sweden and approximately 3700 endo-laparoscopic repairs (25 surgical units of total 85) are being performed annually in surgical units that perform > 50 endo-laparoscopic groin hernia repairs per year (medium to high volume centra). The prevalence of an asymptomatic contralateral groin hernia in patients with symptomatic unilateral groin hernia has been estimated to be around 15%. This gives the trial approximately 555 patients to include annually and with some not meeting the inclusion criteria, we estimate an inclusion of approximately 450 patients annually. To include 2200 patients, the estimated inclusion period will be 4,8 years.

The analysis will be simple t-tests and a logistic regression analysis with odds ratio to estimate the difference of the risk of chronic pain 1 year after surgery between the two groups. Descriptive rates will be presented. All time depended outcomes as time to reoperation for recurrence will be analyzed using the Cox regression model, while an unadjusted Kaplan-Meier curve with log-rank test will also be presented.

Missing data

In earlier reports of patient reported chronic pain rate through the PROM questionnaire via the SHR, response rate has been approximately 70% with a lost-to follow up of approximately 30%. This number has been decreased to 10% lost-to follow up in this trial due to that reminders of the PROM questionnaire will be sent out to the patients and an assumption of that when patients are being included in a randomized trial with digital PROM questionnaires it can increase the response rate. In this trial reminders of the questionnaire will be sent out twice. Primary outcome will be analyzed using fully conditional multiple imputations to handle missing data.

- **Secondary endpoints**

To compare the two arms with regard to;

- **Risk of reoperation of the hernia repair** [Time Frame: within 2, 5 and 10 years]
    - Descriptive rate and differences in risk with cox proportional regression analysis with hazards ratio
- **Perioperative complications (safety)** [Time Frame: Intraoperatively]
    - Descriptive rate and difference in risk with logistic regression analysis (odds ratio) and simple statistical tests
- **Postoperative complications (safety)** [Time Frame: 30 days after surgery]
    - Descriptive rate and difference in risk with logistic regression analysis (odds ratio) and simple statistical tests
- **Rate of future elective hernia repair of the unrepaired asymptomatic contralateral inguinal hernia** [Time Frame: within 1, 2, 5 and 10 years]
    - Descriptive rate
- **Rate of future emergency hernia repair of the unrepaired asymptomatic contralateral inguinal hernia** [Time Frame: within 2 years]
    - Descriptive rate
- **Comparting <u>all women</u> in the study population to the men according to above outcomes** [Time Frame: different for outcomes]
    - Descriptive rate and risk differences with cox proportional regression analysis with hazard ratios (reoperation) and logistic regression analysis with odds ratio (chronic pain, patient satisfaction, peri-and post op complications)
- **Rate and characteristics of found femoral hernias in the total study population** [Time Frame: Intraoperatively]
    - Descriptive rate
- **Time of surgery** [Time Frame: Intraoperatively]
    - Descriptive rate and difference with simple statistical tests (variable in Table 1)
- **Patient satisfaction** [Time Frame: 1 after surgery]

- Descriptive rate and difference in risk with logistic regression analysis (odds ratio)

DSMB (Data safety monitoring board)

Consisting of independent researchers or at least one statistician from the Swedish Hernia register.

After half of the recruitment has been completed, independent researchers or at least one statistician from the Swedish Hernia register are to extract data from the study database and check one or more of the outcomes.

If the intervention group (bilateral repair) is markedly worse with respect to the chosen outcome of the primary binary outcome of chronic pain (> 16% (12%+4% limit margin), then it would be reasonable to stop the recruitment.

If the standard group of women (unilateral repair), whereas the asymptomatic inguinal hernia is left without surgery, has a markedly worse and higher rate of emergency repair (> 5%) compared to the standard group of men (unilateral repair), then it would be reasonable to stop the recruitment of women.