

BMJ Open Is laparoscopic excision for superficial peritoneal endometriosis helpful or harmful? Protocol for a double-blinded, randomised, placebo-controlled, three-armed surgical trial

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ABSTRACT

Introduction Placebo-controlled surgical designs are recommended to ascertain treatment effects for elective surgeries when there is genuine doubt about the effectiveness of the surgery. Some elective surgeries for pain have been unable to show an effect beyond sham surgery, suggesting contributions from contextual factors. However, the nature of contextual factors in elective surgery is largely unexplored. Further, methodological difficulties in placebo-controlled surgical trials impact the ability to estimate the effectiveness of a surgical procedure. These include an overall lack of testing the success of blinding, absence of comparison to a no-surgery control group and dearth of test for neuropathic pain.

For women with peritoneal endometriosis, there is uncertainty regarding the pain-relieving effect of surgery. Surgery may put patients at risk of complications such as postsurgical neuropathic pain, without guarantees of sufficient pelvic pain relief. The planned placebo-controlled trial aims to examine the effect of surgery on pelvic pain, widespread pain and neuropathic pain symptoms in women with peritoneal endometriosis, and to test the contribution of contextual factors to pain relief.

Methods and analysis One hundred women with peritoneal endometriosis will be randomised to either diagnostic laparoscopy with excision of endometrial tissue (active surgery), purely diagnostic laparoscopy (sham surgery) or delayed surgery (no-surgery control group). Outcomes include pelvic pain relief, widespread pain, neuropathic pain symptoms and quality of life. Contextual factors are also assessed. Assessments will be obtained at baseline and 1, 3 and 6 months postrandomisation. Mixed linear models will be used to compare groups over time on all outcome variables.

Ethics and dissemination The trial is approved by the Regional Ethics Committee in the Central Denmark Region (1-10-72-152-20). The trial is funded by a PhD scholarship from Aarhus University, and supported by a grant from 'Helsefonden' (20-B-0448). Findings will be published in international peer-reviewed journals and disseminated at international conferences.

Trial registration number NCT05162794.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This trial employs a placebo-controlled surgical design with three arms, including a no-surgery control group.
- ⇒ This trial assesses contextual factors that are largely unexamined in placebo-surgical studies, but have been associated with pain relief in non-surgical trials.
- ⇒ By allocating patients between active and sham surgery in the operating room, and having blinded personnel responsible for postsurgical care, the trial should effectively be double-blinded.
- ⇒ Quantitative sensory testing and risk factors of chronic postsurgical pain and neuropathic pain are used to examine risks.
- ⇒ Limitations include a relatively short follow-up period and minor uncertainty in terms of the diagnosis of peritoneal endometriosis in the placebo arm, as biopsy confirmation would impede the validity of the sham procedure.

INTRODUCTION

When there is genuine doubt about the effectiveness of elective surgery, and the risks may outweigh the potential benefits, placebo-controlled testing should be performed.^{1 2} Some surgical interventions have been unable to demonstrate a significantly larger effect when compared with a sham surgical intervention.³⁻⁸ In surgical placebo-control designs, researchers compare active surgery to sham surgery, defined as a procedure that mimics the active surgery as closely as possible, while omitting only the hypothesised therapeutic element(s).^{1 2} Here, the contribution of the hypothesised therapeutic element(s) to the treatment effect can then be computed by subtracting the effect in the sham surgery condition from the effect in the active surgery condition.^{1 2} This affords



disentangling treatment-specific factors such as the surgical technique from potential confounders, including contextual factors. Contextual factors are defined as relational, cognitive and emotional factors embedded in the treatment context,⁹ in contrast to treatment-specific factors such as the removal of tissue. Known contextual factors that contribute to the effect of non-surgical treatments for pain include the quality of the patient–caregiver relationship, the patient’s expectations of treatment effectiveness, desire for symptom relief and psychological distress.^{9–15} The contributions of these factors to surgical pain relief in placebo-controlled settings are largely unexplored.

Despite the advantages that placebo-controlled designs may offer over observational designs (eg, blinding with results less prone to bias),^{116 17} placebo-controlled designs are not infallible^{18 19} and limitations exist. First, there are two issues pertaining to blinding. Blinding of patients, postoperative caregivers and outcome assessors is generally feasible,²⁰ yet many studies employ only blinding of patients and/or outcome assessors, which may introduce bias.^{3 19} The other issue is that it is often assumed that blinding is successful and most studies do not test the extent to which this was the case.³ Blinding is believed to be an important eliminator of bias, where meta-analyses indicate that unblinded studies lean towards greater pain relief when compared with blinded studies using similar treatments.^{17 21} Although a meta-epidemiological study indicated no link between blinding and treatment effect,²² potentially suggesting that blinding may not be as important for unbiased results as presumed, the study included only two surgical trials. While not all procedures afford blinding of the surgeon, double-blinding can effectively be maintained if the surgical staff is blinded to treatment allocation in all their interactions prior to anaesthesia, and if only blinded staff members are responsible for the postsurgical care.

A second limitation in placebo-controlled surgical trials for pain is that few studies incorporated a no-surgery control group.^{23 24} As described above, by comparing an active surgery condition to a sham surgery condition, an expression of the part of the total effect attributable to the hypothesised therapeutic elements of the surgical intervention itself can be computed. However, while the remaining effect in the sham surgery condition (the placebo response) is indicative of contextual factors contributing to the observed effect, it is difficult to ascertain the contribution without a no-surgery control group. Pain fluctuates over time, and participants who report high pain levels on inclusion may regress closer to the mean at follow-up, regardless of treatment effectiveness.^{1 9 25} Thus, a reduction in symptoms may be due to the treatment itself and/or contextual factors, but it may also be caused by natural fluctuations in pain severity or regression to the mean. Hence, while the comparison between active and sham surgery examines how effective the hypothesised therapeutic elements of surgery are at relieving symptoms, the comparison between sham

surgery and no-surgery illuminates the contributions of contextual factors to the total treatment effect (the placebo effect).⁹ Mapping out the placebo effect may yield valuable insights that can improve clinical practice, for example, by enhancing the quality of the patient–surgeon relationship, if it is revealed to be an important contributor to treatment effect.

Finally, while most studies test whether active surgery has an effect beyond sham surgery or not, studies using tools like body maps and quantitative sensory testing to test the risks of postsurgical pain and postsurgical neuropathic pain, respectively, are scarce. A 12-year follow-up on adhesiolysis for abdominal pain found that when compared with sham surgery, patients in the active surgery group experienced more pain, worse quality of life and higher rates of repeat-surgery due to persistent postsurgical pain.^{26 27} Not only do these results suggest that the benefit from sham surgery may be long-lasting, they also suggest that the active surgery procedure may have caused more harm than good. Persistent postsurgical pain in the active surgery group may have been caused by different factors, including increased sensory hypersensitivity, the development of widespread pain, nerve damage and/or scar tissue formation, the development of neuropathic pain or something else. Previous studies have successfully detected and discerned adverse events following surgery such as widespread pain using body maps from neuropathic pain using quantitative sensory testing.^{28 29} Without examinations of the potential pain-related adverse events following surgery, it can be difficult to tell apart the continuation of presurgical pain from the development of persistent postsurgical pain problems or postsurgical neuropathic pain.^{29 30} In other words, it can be hard to distinguish whether the intervention is ineffective at providing pain relief, from whether the intervention *is* effective at providing pain relief, but is associated with risks of postsurgical pain. This is an important distinction, as an effective intervention can be further honed and have its risks mitigated, while ineffective treatments should be reconsidered as treatment options.

For women suffering from peritoneal endometriosis, a three-armed, placebo-controlled trial to evaluate the effectiveness and risks of surgery is needed. Endometriosis is a painful gynaecological disease estimated to affect 5%–10% of women, and it is characterised by the presence and growth of endometrial-like tissue outside of the uterus.³¹ In 70%–80% of cases, the endometrial tissue will attach itself superficially to the peritoneal lining and may cause chronic pain.^{32 33} Approximately one-third of women with endometriosis do not achieve adequate pain relief from medical treatment alone and may be offered surgery to manage their pain.^{34 35}

There is genuine doubt whether current surgical practice benefits these patients. In 25% of repeated surgeries, there are no indications of endometriosis, suggesting that the pain recurrence could be due to neuropathic or widespread pain following repeated invasive interventions.^{36–39}

Previous research has not adequately tested whether surgery is beneficial specifically for peritoneal endometriosis, but suggests that the intervention may not be effective and the procedure is associated with risks of persistent postsurgical pain and neuropathic pain.^{29 40–44} Endometriosis-related pain is associated with central sensitisation, which could increase risks of persistent pain and neuropathic pain following surgery.⁴⁵ Accordingly, this three-armed, placebo-controlled surgical trial will examine the risks of widespread pain and test changes in neuropathic pain symptoms, as it is currently unknown if the intervention is helpful or harmful.

Aims and hypotheses

Aim 1: To compare the effect of active surgery to sham surgery and no-surgery on pelvic pain relief.

Hypothesis 1: Both active and sham surgery will significantly reduce pelvic pain when compared with the no-surgery control group. However, active surgery will not significantly reduce pelvic pain when compared with sham surgery.

Aim 2: To test the contribution of contextual factors to pelvic pain relief.

Hypothesis 2: Quality of the patient–caregiver relationship, the patient’s expectations of treatment effectiveness, desire for symptom relief and degree of psychological distress will significantly contribute to relief of chronic pain.

Aim 3: To examine persistent postsurgical pain and to test whether participants develop neuropathic pain components.

Hypothesis 3: Participants in the active surgery group will score higher on indications for widespread pain and neuropathic pain symptoms at 6 months’ follow-up, when compared with the sham surgery and no-surgery groups.

METHODS AND MATERIALS STUDY DESIGN AND CONTEXT

Participants will be randomised to one of three groups:

1. Active surgery, where peritoneal endometriosis is visually diagnosed by diagnostic laparoscopy, and the

tissue is excised. Histology will be performed in this group to confirm the diagnosis.

2. Sham surgery, where peritoneal endometriosis is visually diagnosed by diagnostic laparoscopy, but no tissue is excised and no histology is performed.

3. No-surgery control group, where medical treatment as usual is continued throughout the study period.

All groups continue their medical treatment as usual. Groups 2 and 3 will be offered active surgery after completing 6 months’ follow-up. Baseline data will be gathered 1 month prior to first randomisation, and follow-up data will be gathered at 1, 3 and 6 months following first randomisation. Participants in the surgical groups will be unblinded after 6 months’ follow-up has been completed.

The trial is a Danish multicentre cooperation between Aarhus University Hospital and the Regional Hospitals in Herning, Randers, Viborg and Horsens. A multicentre approach was deemed necessary to recruit the required number of participants. Participants will be recruited by the surgeons, who will describe the study and hand out patient information material. After signing informed consent, participants will complete baseline data and be randomised in two steps to one of the study groups (see the ‘Treatment allocation section’). The principal investigator (PI, HM) is responsible for overseeing recruitment and enrolment of participants, coordinating interventions and analysing data.

The perioperative process has been standardised as much as possible in terms of medical treatment and equipment, both of which are noted by surgical staff, which will make deviations from protocol visible. Any variations in the perioperative process between sites will be reported and have their potential contribution to outcomes tested (see the ‘Data analysis section’). See [figure 1](#) for an overview of the surgical flow and data collection.

To avoid patient collusion, eligible patients will have their appointments staggered and will not meet each other in the waiting room or when being informed about the study.

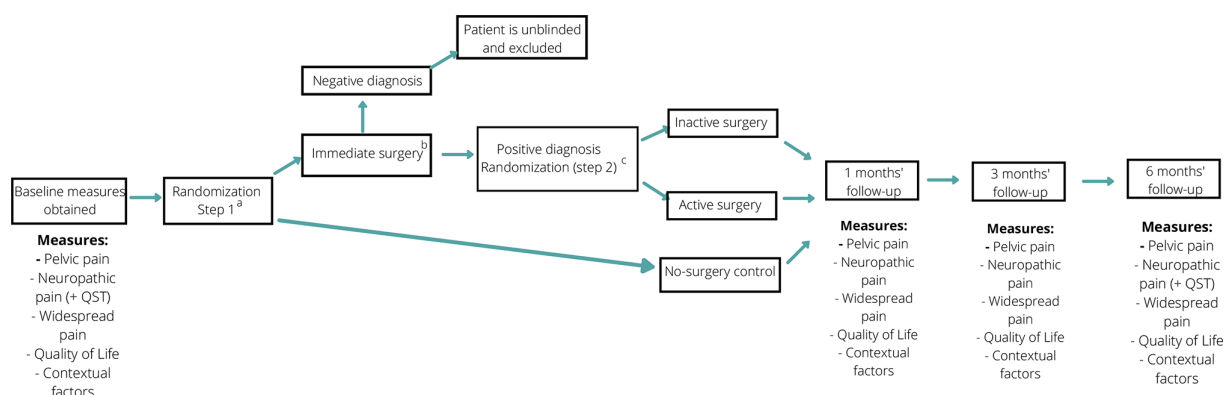


Figure 1 Design overview from recruitment to completion description: ^a(step 1 randomisation)=patients, surgeons, postsurgical staff and outcome assessors are blinded to treatment allocation, ^b(positive endometriosis diagnosis)=patients, surgeons, postsurgical staff and outcome assessors are blinded to treatment allocation, ^c(step two randomisation)=patients, postsurgical staff and outcome assessors are blinded to treatment allocation. QST, quantitative sensory testing.

Treatment allocation

Randomisation will happen in two steps: in step 1, participants are randomised to either immediate surgery or no-surgery control (2:1 ratio), after completing baseline measures (4 weeks after giving informed consent). In step 2, participants randomised to intervention are randomised again to either active surgery or sham surgery in the operating room, after peritoneal endometriosis has been diagnosed. Distant randomisation will be used to allocate participants in step 2. In both steps, block randomisations will be used and randomisations will be stratified based on hospital site (five strata). Block sizes will not be revealed here to maintain blinding of surgical staff. For step 1, a researcher outside the study group will create the randomisation list using R software and allocate participants.

Blinding

Patients in the surgical groups will be blinded to treatment allocation, and blinding will not be lifted until the 6 months' follow-up has been completed. Because the incision and closure procedures are identical in the active surgery group and the sham surgery group, patients will have identical signs of incisions, which should retain blinding. Participants in the no-surgery control group are blinded while completing baseline questionnaires, but unblinded at step 1 randomisation.

Healthcare personnel will be blinded to treatment allocation as long as possible. The result of the randomisation will not be revealed to the surgical team until peritoneal endometriosis has been visually diagnosed, in order to standardise presurgical preparations and the diagnostic laparoscopy. After the intervention, blinded personnel will be responsible for postsurgical care.

The success of blinding of patients and healthcare personnel will be tested by asking which treatment they believe they have received/administered. Both parties will also be presented with an open text field to describe their choice, and a 5-point Likert scale to measure how certain they are in their judgement: 'completely uncertain', 'relatively uncertain', 'neither uncertain nor certain', 'relatively certain' or 'completely certain'.

The PI (outcome assessor) will also be blinded to treatment allocation, and blinding will be retained until data analysis is complete. As a safeguard, patient IDs and group denominators will be scrambled by a researcher outside the research group once data collection has been completed, but prior to data analysis.

Parties will be unblinded only if a participant decides to drop out, if surgery shows no indication of endometriosis, or if the clinical committee evaluates exclusion is in the best interest of the patient. To monitor well-being and improving participant adherence, a specialised endometriosis nurse, who is blinded to step 2 randomisation, will consult participants by telephone at approximately 2 weeks and 3 months postsurgery.

Participants and power

Inclusion criteria:

- ▶ Adult women (≥ 18 years) with suspected superficial peritoneal endometriosis undergoing elective surgery for pain relief.
- ▶ All participants must suffer from chronic pelvic pain (ie, persistent or recurring pain for at least 6 months).
- ▶ All participants must have undergone first-line medical treatment (continuous oral contraceptives and/or levonorgestrel intrauterine device) for at least 3 months prior to inclusion.
- ▶ Pain intensity ≥ 5 on a Numeric Rating Scale (NRS) assessed by participant recall of average pain intensity in the 4 weeks prior to consenting to participation.

Exclusion criteria:

- ▶ Other known conditions that may cause pelvic pain (eg, adenomyosis, irritable bowel syndrome, interstitial cystitis).
- ▶ Personality disorder, schizophrenia or currently receiving antipsychotic treatment.
- ▶ Planning to become pregnant within study duration.
- ▶ Inability to speak or read Danish.

To assess the eligibility of potential participants, a physical examination as well as ultrasound and MRI imaging will be performed to detect other causes for pelvic pain. Invasive procedures (eg, cystoscopy to diagnose interstitial cystitis) will not be routinely performed as part of the trial, and conditions such as irritable bowel syndrome will be assessed via physical examination and evaluation of symptoms. The involved surgeons will perform the physical examination and ultrasound imaging.

Power:

Expected pain levels stem from a recent meta-analysis and previous placebo-controlled surgical trials.^{35 40–42} Using NRS, participants are estimated to score approximately 6.0 on pelvic pain intensity at baseline (SD=2.0). The calculations below were based on the smallest relevant expected differences, though actual differences may well be greater.

To test significant differences in pelvic pain intensity between the active and sham surgery groups (here viewed as one group, named intervention below, based on the assumption that the two interventions will provide approximately similar pain reduction) and the no-surgery control group, calculations were made with the following assumptions: mean pain intensity at 6 months' follow-up (intervention)=3.75, SD=2.0, mean pain intensity at 6 months' follow-up (no-surgery control group) = 5.25, SD=2.0, Power ($1-\beta = 0.80$), $\alpha=0.05$, two-sample test, two-sided test, a sample of 28 participants in each of the three groups is required.

To test if there are significant differences in pelvic pain intensity at 6 months' follow-up between the active and sham surgery groups, calculations were made with the following assumptions: mean pain intensity (active surgery group) = 3.0, SD=2.0, mean pain intensity (sham surgery group) = 4.5, SD=2.0, Power ($1-\beta = 0.80$), $\alpha=0.05$,

two-sample test, two-sided test, a sample of 28 participants in each group is required.

Assuming a 15% attrition rate (5% drop-out similar to other placebo-controlled trials,⁴⁶ and 10% negative laparoscopies), a total of 100 randomised participants was deemed sufficient to reach 28 participants in each group.

Data collection

Data collection is structured in four blocks of 4 weeks: baseline (beginning after informed consent has been given), 1-month postrandomisation, 3 months postrandomisation and 6 months postrandomisation. In weeks 1–3 of each block, weekly pain measurements are assessed. In week four of a block, weekly pain measurements as well as neuropathic pain symptoms, widespread pain, endometriosis-related symptoms, quality of life and contextual factors (except quality of the patient–surgeon relationship, which is only measured at baseline) are assessed. For participants who undergo surgery, success of blinding is assessed at week four of each block. All data except quantitative sensory testing is assessed online with REDCap surveys.

Outcomes

The primary outcome is changes in

- ▶ Overall pelvic pain intensity and unpleasantness from baseline to 6 months' follow-up. Overall pelvic pain intensity and unpleasantness will be measured using a 0–10 NRS.⁴⁷ Participants will rate their overall pelvic pain weekly with an NRS (0–10), with 0 labelled as 'no pain' and 10 labelled as 'worst pain imaginable'. Weekly ratings will be in blocks of 4 weeks, corresponding to one menstrual cycle. The four pain ratings of a block will be combined and used as one mean pain rating for the period.

The secondary outcomes are changes in

- ▶ Neuropathic pain symptoms.
- ▶ Widespread pain.
- ▶ Worst pain intensity and unpleasantness.
- ▶ Pain frequency.
- ▶ Endometriosis-related symptoms.
- ▶ Quality of life.

From baseline to 6 months' follow-up

Neuropathic pain symptoms will be measured using the validated painDETECT questionnaire^{48 49} and a quantitative sensory testing battery: A pressure algometer, brush and pinprick will be used to test symptoms of neuropathic pain below the fifth vertebra, 7 cm laterally to the umbilicus on both sides and 5 cm laterally to the symphysis pubis on both sides.⁵⁰ Participants will complete the painDETECT at the end of each measurement block, and the quantitative sensory testing battery will be conducted at baseline and at the 6 months' follow-up.

Widespread pain will be measured using a body map, where participants mark all areas of their body where they experience pain. Body maps have previously been used

in this manner to detect the development of widespread pain in patients suffering from pelvic pain.²⁸

Worst pain intensity and unpleasantness will be measured weekly similarly to overall pelvic pain intensity and unpleasantness using NRS. Participants will be asked to rate how intense or unpleasant their pelvic pain were in the past week, when the pain were at their worst.

Pain frequency will be measured by asking participants how many days in the past week they experienced pelvic pain, from 0 to 7 days.

Endometriosis-related symptoms are dysmenorrhoea, noncyclical pelvic pain, dyspareunia during and after intercourse, dysuria and dyschezia. Participants will be asked to rate the intensity of these symptoms for the past 4 weeks using NRS.⁴⁷

Quality of life will be assessed using the patient-generated and validated 'Endometriosis Health Profile-30', designed to measure quality of life specifically for women with endometriosis.⁵¹ The questionnaire has been validated in Danish.⁵² contribution of contextual factors

Quality of the patient–doctor relationship will be measured using the validated 'Care and Relational Empathy' questionnaire.⁵³ Patients will be asked to complete the questionnaire at baseline with the surgeon who recruited them in mind.

Expectations of treatment efficacy will be measured by asking patients 'What do you expect your pelvic pain (intensity/unpleasantness) to be in (2/3) months?', with the months corresponding to the next measurement point. Ratings will be obtained with an NRS.^{9 10}

Desire for symptom relief will be measured by asking patients 'How strong is your desire for symptom relief?' Ratings will be obtained with NRS: 0 labelled as 'no desire' and 10 labelled as 'strongest desire imaginable'.^{9 10}

Both expectations of treatment effectiveness and desire for symptom relief will be measured at all measurement points.

Adverse events

Information on adverse events from surgery will be gathered at all follow-up measurement points. Participants will be asked to mark which of a list of known adverse events they experienced, and an open text field to add any other adverse events they experienced. The study is audited annually by the Central Denmark Region Research Ethics Committee. The adverse events experienced by study participants will be reported in a future article.

patient and public involvement

While planning the study, the PI and physicians discussed the trial with eligible participants (N>20). Discussions centred around the length of follow-up and the outcome measures. The feasibility of blinding procedures was tested with two patients, and blinding of all relevant parties was successfully maintained for the full 6 months. Based on input from patients, we decided to shorten the



follow-up period from 12 months to 6 months, and to use weekly recall of pelvic pain measures instead of daily.

The decision to use 6 months' follow-up was to strike a balance between delaying surgical treatment for the no-surgery control group for as little as possible, while retaining a follow-up period that enables the assessment of whether active surgery for peritoneal endometriosis is helpful when compared with sham surgery. For active surgery to be considered effective it has to demonstrate a significantly larger effect than its sham comparison, including any placebo response that may still be ongoing at 6 months' follow-up.^{4 5} Hence, the follow-up period should not diminish the trial's capability to evaluate whether or not active surgery is helpful. However, the trial may be unable to detect changes in neuropathic pain symptoms, as neuropathic pain symptoms following surgery may have delayed onset of many months or even years.²⁹ data analysis

Due to the minimally invasive nature of the intervention and the relatively short follow-up period, a data monitoring committee will not be established. There are no planned interim analyses.

Data will be analysed according to intention-to-treat principles, and missing data patterns will be investigated and reported. Baseline data and demographics between the three groups will be compared with determine if key differences exist. The newest version of R software will be used. All analyses will be two tailed ($\alpha=0.05$), with 95% CIs reported when appropriate. Model assumptions will be investigated for all analyses, and alternative methods will be chosen if necessary. All outcome measures will be analysed using mixed linear models, with time at level 1 nested within individuals at level 2. The best model fit and function of time will be examined and reported. The main analyses are changes in pelvic pain intensity and unpleasantness from baseline to 6 months' follow-up as the outcomes, and secondary analyses include changes from baseline to 6 months' follow-up for all secondary outcomes. The three groups will be compared in pairs. First, the two surgical groups will be viewed as one and compared with the no-surgery group, based on the assumption that the two surgical groups will provide roughly similar levels of pain relief. Then, the two surgical groups will be compared. The contribution of contextual factors and blinding of patients and healthcare personnel to pain relief will also be investigated and taken into account in the evaluation of the data using the principles described above.

Sensitivity analyses

Sensitivity analyses testing the relationship between differences in the perioperative process (including medical treatment and timing of surgery), missing data and current medical treatment and pain relief will be performed. The aim is to conduct all planned primary, secondary and sensitivity analyses blinded.

Ethics and dissemination

Only experienced, endometriosis-specialised surgeons will perform surgery. A committee of endometriosis-specialised healthcare professionals will oversee the

well-being of patients, and can exclude patients from further clinical assessment. If participants should experience harm from participating in the study, they are covered by the hospitals' insurance policy.

Personal information will be handled in accordance with Danish legislation and the General Data Protection Regulation. When participant inclusion has ended, data will be shared in accordance with the ICJME guidelines, if relevant research objectives are provided. Data sharing will require approval from the Central Denmark Region and the Danish Data Protection Agency, and the requesting party shall cover any data sharing fees. Requests for data can be addressed to af@clin.au.dk.

The results are expected to be published in high impact journals and presented at relevant conferences.

The authors that have contributed to the present protocol article will be invited to contribute to future publications on data gathered in the planned study. Eligibility will be determined based on the Vancouver criteria for authorship. There are no plans to involve professional writers.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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