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

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Manuscripts

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4 Is laparoscopic excision for superficial peritoneal endometriosis helpful or harmful? Protocol for
5 a double-blinded, randomized, placebo-controlled, three-armed surgical trial
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9 Henrik Marschall,¹ Axel Forman,² Sigrid Juhl Lunde,³ Ulrik Schiøler Kesmodel,⁴ Karina Ejgaard
10 Hansen⁵ & Lene Vase³
11
12

13
14 ¹Department of Psychology and Behavioural Sciences, School of Business and Social Sciences,
15 Aarhus University, Denmark .
16

17 ²Department of Obstetrics and Gynecology, Aarhus University Hospital, and Department of
18 Clinical Medicine, Aarhus University, Denmark.
19

20
21 ³Division for Psychology and Neuroscience, Department of Psychology and Behavioural Sciences,
22 School of Business and Social Sciences, Aarhus University, Denmark.
23

24 ⁴Department of Obstetrics and Gynaecology, Aalborg University Hospital, and Department of
25 Clinical Medicine, Aalborg University, Denmark.
26

27
28 ⁵Department of Public Health, Aarhus University, Denmark.
29
30

31
32
33 Corresponding author: Henrik Marschall

34 Department of Psychology and Behavioural Sciences

35 School of Business and Social Sciences

36 Bartholins Allé 11, DK-8000 Aarhus C, Denmark

37 E-mail: hmars@psy.au.dk

38 Tel. +4522394563
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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 post-surgical 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 randomized 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 and neuropathic pain symptoms. Contextual factors are also assessed. Assessments will be obtained at baseline and one, three and six months post-randomization. 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.

ARTICLE SUMMARY

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 post-surgical care, the trial should effectively be double-blinded.
- Quantitative sensory testing and risk factors of chronic post-surgical pain and neuropathic pain are used to examine risks more thoroughly than previous trials.
- 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 to 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 hypothesized therapeutic element(s).[1, 2] In these designs, the contribution of the hypothesized 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

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3 in placebo-controlled settings are largely unexplored, but may yield valuable insights into the
4 working mechanisms of elective surgical interventions.
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8 Despite the advantages that placebo-controlled designs may offer over observational
9 designs (e.g. blinding with results less prone to bias),[1, 16, 17] placebo-controlled designs are
10 not infallible[18, 19] and limitations exist. Firstly, there are two issues pertaining to blinding.
11 Blinding of patients, post-operative caregivers and outcome assessors is generally feasible,[20]
12 yet many studies employ only blinding of patients and/or outcome assessors, which may
13 introduce bias.[3, 19] The other issue is that it is often assumed that blinding is successful and
14 most studies do not test the extent to which this was the case.[3] Blinding is believed to be an
15 important eliminator of bias, where meta-analyses indicate that unblinded studies lean towards
16 greater pain relief when compared to blinded studies using similar treatments.[e.g. 17, 21]
17 Although a meta-epidemiological study indicated no link between blinding and treatment
18 effect,[22] potentially suggesting that blinding may not be as important for unbiased results as
19 presumed, the study included only two surgical trials. While not all procedures afford blinding of
20 the surgeon, double-blinding can effectively be maintained if the surgical staff is blinded to
21 treatment allocation in all their interactions prior to anesthesia, and if only blinded staff members
22 are responsible for the post-surgical care.
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34 A second limitation in placebo-controlled surgical trials for pain is that few studies
35 incorporated a no-surgery control group.[23, 24] As described above, by comparing an active
36 surgery condition to a sham surgery condition, an expression of the part of the total effect
37 attributable to the hypothesized therapeutic elements of the surgical intervention itself can be
38 computed. However, while the remaining effect in the sham surgery condition (the placebo
39 *response*) is indicative of contextual factors contributing to the observed effect, it is difficult to
40 ascertain the exact contribution without a no-surgery control group. Pain fluctuates over time,
41 and participants who report high pain levels upon inclusion may regress closer to the mean at
42 follow-up, regardless of treatment effectiveness.[1, 9, 25] This means that a reduction in
43 symptoms may be due to the treatment itself and/or contextual factors, but it may also be caused
44 by natural fluctuations in pain severity or regression to the mean. Hence, while the comparison
45 between active and sham surgery sheds light on how effective the hypothesized therapeutic
46 elements of surgery are at relieving symptoms, the comparison between sham surgery and no-
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3 surgery illuminates the contributions of contextual factors to the total treatment effect (the
4 placebo *effect*).^[9] Mapping out the placebo effect may yield valuable insights that can improve
5 clinical practice. For example, if an active surgery effect is significantly greater than a sham
6 surgery effect, and the comparison between sham surgery and no-surgery reveals that the
7 patient's expectations and alliance between surgeon and patient contribute greatly to the total
8 effect, then these contextual factors could be strengthened prior to surgery in an effort to
9 optimize the treatment effect further.

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16 Finally, while most studies test whether active surgery has an effect beyond sham surgery
17 or not, studies using tools like body maps and quantitative sensory testing to test the risks of
18 post-surgical pain and post-surgical neuropathic pain, respectively, are scarce. A recent twelve-
19 year follow-up on adhesiolysis for abdominal pain found that when compared to sham surgery,
20 patients in the active surgery group experienced more pain, worse quality of life and higher rates
21 of analgesic use and repeat-surgery due to persistent post-surgical pain.^[26, 27] Not only do
22 these results suggest that the benefit from sham surgery may be long lasting, they also suggest
23 that the active surgery procedure may have caused more harm than good. The higher rates of
24 persistent post-surgical pain in the active surgery group may have been caused by a number of
25 things, including increased sensory hypersensitivity, the development of widespread pain, nerve
26 damage and/or scar tissue formation, the development of neuropathic pain or something else
27 entirely. It can be difficult to disentangle precisely what has occurred from self-report measures
28 of pain alone. Previous studies have successfully detected and discerned adverse events
29 following surgery such as widespread pain using body maps from neuropathic pain using
30 quantitative sensory testing.^[28, 29] Without examinations of the potential pain-related adverse
31 events following surgery, it can be difficult to tell apart the continuation of pre-surgical pain
32 from the development of persistent post-surgical pain problems or post-surgical neuropathic
33 pain.^[29, 30] In other words, it can be hard to distinguish whether the intervention is ineffective
34 at providing pain relief, from whether the intervention *is* effective at providing pain relief, but is
35 associated with risks of post-surgical pain. This is an important distinction, as an effective
36 intervention can be further honed and have its risks mitigated, while ineffective treatments
37 should be reconsidered as treatment options.

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

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12 However, there is genuine doubt whether current surgical practice benefits these women,
13 as post-surgical pain and repeat surgeries are common. In 25% of repeated surgeries, there are no
14 indications of endometriosis, suggesting that the pain recurrence could be due to neuropathic or
15 widespread pain following repeated invasive interventions.[36-39] Previous research has not
16 adequately tested whether surgery is beneficial specifically for peritoneal endometriosis, but
17 suggests that the intervention may not be effective and the procedure is associated with risks of
18 persistent post-surgical pain and neuropathic pain.[29, 40-44] Although neuropathic pain has
19 scarcely been examined in this population, endometriosis-related pain may be associated with
20 central sensitization, which could increase risks of persistent pain and neuropathic pain following
21 surgery.[45] Accordingly, this three-armed, placebo-controlled surgical trial will examine the
22 risks of widespread pain and test changes in neuropathic pain symptoms, as it is currently
23 unknown if the intervention is helpful or harmful.

24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 **aims and hypotheses**

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

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

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51 *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 post-surgical 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 six months' follow-up, when compared to the sham surgery and no-surgery groups.

methods and materials

study design and context

Participants will be randomized 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 two and three will be offered active surgery if they so desire after completing six months' follow-up. Baseline data will be gathered one month prior to first randomization, and follow-up data will be gathered at one, three and six months following first randomization. Participants in the surgical groups will be unblinded after six months' follow-up has been completed.

The trial is a Danish multi-centre cooperation between Aarhus University Hospital and the Regional Hospitals in Herning, Randers, Viborg and Horsens. A multi-centre approach was deemed necessary to secure the best odds for recruiting the needed number of participants within a reasonable timeframe. Participants will be recruited by the surgeons, who will describe the study and hand out patient information material. After signing informed consent, participants

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3 will complete baseline data and be randomized in two steps to one of the study groups (see
4 “Treatment allocation”). The PI (HM) is responsible for overseeing recruitment and enrolment of
5 participants, coordinating interventions and analyzing data.
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9 The perioperative process has been standardized as much as possible in terms of anesthesia,
10 treatment of postoperative nausea, vomiting, pain and size of the laparoscopes used. The
11 equipment and medication used in the perioperative is noted by surgical staff which will make
12 any deviations from protocol visible. Any variations in the perioperative process between sites
13 will be reported and have their potential contribution to outcomes tested (see “Data analysis”).
14 See figure one for an overview of the surgical flow and data collection.
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19 20 **treatment allocation**

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22 Randomization will happen in two steps: in step one, participants are randomized to
23 either immediate surgery or no-surgery control (2:1 ratio), after completing baseline measures (4
24 weeks after giving informed consent). In step two, participants randomized to intervention are
25 randomized again to either active surgery or sham surgery in the operating room, after peritoneal
26 endometriosis has been diagnosed. Distant randomization will be used to allocate participants
27 and to conceal the randomization in step two. In both steps, block randomizations will be used
28 and randomizations will be stratified based on hospital site (5 strata). Block sizes will not be
29 revealed here to maintain blinding of surgical staff. For step one, a researcher outside the study
30 group will create the randomization list using R software and allocate participants.
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38 39 **blinding**

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41 *Patients* in the surgical groups will be blinded to treatment allocation, and blinding will
42 not be lifted until the six months’ follow-up has been completed. Because the incision and
43 closure procedures are identical in the active surgery group and the sham surgery group, patients
44 will have identical signs of incisions, which should retain blinding.
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49 *Healthcare personnel* will be blinded to treatment allocation as long as possible. The
50 result of the randomization will not be revealed to the surgical team until peritoneal
51 endometriosis has been visually diagnosed, in order to standardize pre-surgical preparations and
52 the diagnostic laparoscopy. After the intervention, no member of the surgical team will have
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3 further contact with the patient during the data collection period, and blinded personnel will be
4 responsible for post-surgical care.
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7 The success of blinding of patients and healthcare personnel will be tested by asking
8 which treatment they believe they have received/administered. Both parties will also be
9 presented with an open text field to describe their choice, and a 5-point Likert scale to measure
10 how certain they are in their judgement: “*completely uncertain*”, “*relatively uncertain*”, “*neither*
11 *uncertain nor certain*”, “*relatively certain*” or “*completely certain*”.
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16 The PI (*outcome assessor*) will also be blinded to treatment allocation, and blinding will
17 be retained until data analysis is complete. As a safeguard, patient IDs and group denominators
18 will be scrambled by a researcher outside of the research group once data collection has been
19 completed, but prior to data analysis.
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24 Parties will be unblinded only if a participant decides to drop out, if surgery shows no
25 indication of endometriosis, or if the clinical committee evaluates exclusion is in the best interest
26 of the patient. To monitor well-being and improving participant adherence, a specialized
27 endometriosis nurse, who is blinded to step two randomization, will consult participants by
28 telephone at approximately two weeks and three months post-surgery. This is done both to
29 monitor wellbeing of participants, and as a retention strategy.
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34 35 **participants and power**

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37 Inclusion criteria:

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- 40 - Adult women (≥ 18 years) with suspected superficial peritoneal endometriosis
 - 41 undergoing elective surgery for pain relief
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 - 43 - Pain intensity ≥ 5 on a Numeric Rating Scale (NRS) assessed by patient recall of average
 - 44 pain intensity in the four weeks prior to consenting to participation.
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47 Exclusion criteria:

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- 50 - Other known conditions that may cause pelvic pain
 - 51 - Personality disorder, schizophrenia or currently receiving anti-psychotic treatment
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 - 53 - Planning to become pregnant within study duration
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 - 55 - Inability to speak or read Danish
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Power:

Based on a recent meta-analysis and previous placebo-controlled trials for endometriosis, [35, 40-42] we estimated that 28 x 3 participants are needed. Assuming an approximate 15% attrition rate (some participants will drop out, some will show no signs of superficial peritoneal endometriosis at surgery), a total of 100 enrolled participants is deemed sufficient to achieve the 28 x 3 patients needed.

data collection

Data collection is structured in four blocks of four weeks: baseline (beginning after informed consent has been given), one month post-randomization, three months post-randomization and six months post-randomization. In weeks one to three 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 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 six months' follow-up. Overall pelvic pain intensity and unpleasantness will be measured using a 0-10 NRS.[46] Participants will rate their overall pelvic pain weekly with a NRS (0-10), with 0 labeled as "no pain" and 10 labeled as "worst pain imaginable". Weekly ratings will be in blocks of four 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

From baseline to six months' follow up.

Neuropathic pain symptoms will be measured using the validated painDETECT questionnaire [47, 48] 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 five centimeters laterally to the symphysis pubis on both sides.[49] 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 six 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 dysmenorrhea, 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 four weeks using NRS.[45]

contribution of contextual factors

Quality of the patient-doctor relationship will be measured using the validated "Care and Relational Empathy" questionnaire.[50] 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 a NRS.[9, 10]

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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 labeled as “no desire” and 10 labeled 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 discussed the trial with participants that could have been relevant to include. Discussions centered around the length of follow-up and the outcome measures. A feasibility trial was also conducted with two patients. Based on input from patients, we decided to shorten the follow-up period from 12 months to six months, and to use weekly recall of pelvic pain measures instead of daily.

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 analyzed 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 to determine if key differences exist. The newest version of R software will be used. All analyses will be two-tailed ($\alpha = .05$), with 95% confidence intervals reported when appropriate. Model assumptions will be investigated for all analyses, and alternative methods will be chosen if necessary. All outcome measures will be analyzed using mixed linear models, with time at level one nested within individuals at level two. The best model fit and function of

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3 time will be examined and reported. The main analysis is changes in pelvic pain intensity and
4 unpleasantness throughout the study period, and secondary analyses include all secondary
5 outcomes throughout the study period. The contribution of contextual factors and perceived
6 treatment allocation to pain relief will also be investigated using the principles described above.
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10 Sensitivity analyses

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12 Sensitivity analyses testing the relationship between differences in the perioperative process,
13 missing data and current medical treatment and pain relief will be performed. The aim is to
14 conduct all planned primary, secondary and sensitivity analyses blinded.
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18 **ETHICS AND DISSEMINATION**

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20 Only experienced, endometriosis-specialized surgeons will perform surgery. A clinical
21 committee of endometriosis-specialized healthcare professionals will oversee the wellbeing of
22 patients, and can exclude patients from further clinical assessment if needed. If participants
23 should experience harm from participating in the study, they are covered by the hospitals'
24 insurance policy.
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31 Personal information will be handled in accordance with Danish legislation and the
32 General Data Protection Regulation. The research group at Aarhus University will have access to
33 the final, raw trial dataset that contains personal information. Anonymous data and statistical
34 codes may be shared outside the group in a data repository.
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39 The results are expected to be published in high impact journals and presented at relevant
40 conferences, including the World Congress on Endometriosis and the World Congress on Pain.
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43 The authors that have contributed to the present protocol article will be invited to
44 contribute to future publications on data gathered in the planned study. Eligibility will be
45 determined based on the Vancouver criteria for authorship. There are no plans to involve
46 professional writers.
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50 **AUTHOR CONTRIBUTIONS**

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52 All authors contributed to the design of the study. HM wrote the first draft. LV and SJL
53 critically reviewed and commented on the first draft. HM revised the draft and LV, SJL, AF,
54 USK and KEH critically reviewed and commented on the revised draft.
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COMPETING INTERESTS STATEMENT

No competing interests to declare.

REFERENCES

- 1: Beard DJ, Campbell MK, Blazeby JM et al. Considerations and methods for placebo controls in surgical trials (ASPIRE guidelines). *Lancet* 2020;395(10226),828-838.
- 2: Beard DJ, Campbell MK, Blazeby JM et al. Placebo comparator group selection and use in surgical trials: the ASPIRE group project including expert workshop. *Health Technol Assess* 2021;53:1-52.
- 3: Wartolowska K, Judge A, Hopewell S et al. Use of placebo controls in the evaluation of surgery: systematic review. *BMJ* 2014;348:g3253.
- 4: Wartolowska KA, Feakins BG, Collins GS et al. The magnitude and temporal changes of response in the placebo arm of surgical randomized controlled trials: a systematic review and meta-analysis. *Trials* 2016;17(1):589.
- 5: Wartolowska KA, Gerry S, Feakins BG et al. A meta-analysis of temporal changes of response in the placebo arm of surgical randomized controlled trials: an update. *Trials* 2017;12:18(1):323.
- 6: Jonas WB, Crawford C, Colloca L et al. Are Invasive Procedures Effective for Chronic Pain? A Systematic Review. *Pain Med* 2019;1;20(7):1281-1293.
- 7: Gu AP, Gu CN, Ahmed AT et al. Sham surgical procedures for pain intervention result in significant improvement in pain: systematic review and meta-analysis. *J Clin Epidemiol* 2017;83:18-23.
- 8: Probst P, Grummich K, Harnoss JC et al. Placebo-Controlled Trials in Surgery: A Systematic Review and Meta-Analysis. *Medicine (Baltimore)*. 2016;95(17):e3516.
- 9: Benedetti F. Placebo Effects. Oxford University Press 2020.
- 10: Colloca L. The Placebo Effect in Pain Therapies. *Annu Rev Pharmacol Toxicol* 2019;59:191-211.

- 1
2
3 11: Petersen GL, Finnerup NB, Groesen K, Pilegaard HK, Tracey I, Benedetti F, Price DN, Jensen
4 TS & Vase L. Expectations and positive emotional feelings accompany reductions in ongoing
5 and evoked neuropathic pain following placebo interventions. *Pain* 2014;155: 2687-2698
6
7
8 12: Howick J, Moscrop A, Mebius A, Fanshawe TR, Lewith G, Bishop FL, Mistiaen P, Roberts
9 NW, Dieninyt  E, Hu X, Aveyard P & Onakpoya IJ. Effects of empathic and positive
10 communication in healthcare consultations: a systematic review and meta-analysis. *J R Soc Med*
11 2018;111(7):240-252.
12
13 13: Geurts JW, Willems PC, Lockwood C, van Kleef M, Kleijnen J & Dirksen C. Patient
14 expectations for management of chronic non-cancer pain: A systematic review. *Health Expect*
15 2017;20(6):1201-1217.
16
17
18 14: Cormier S, Lavigne GL, Choini re M & Rainville P. Expectations predict chronic pain
19 outcomes. *Pain* 2016;157(2):329-338.
20
21
22 15: Atlas LY & Wager TD. How expectations shape pain. *Neurosci Lett* 2012;520:140-148.
23
24
25 16: Hariton E & Locascio JJ. Randomised controlled trials – the gold standard for effectiveness
26 research. *BJOG* 2018;125(13):1716.
27
28
29 17: Hr bjartsson A, Emanuelsson F, Skou Thomsen AS et al. Bias due to lack of patient blinding
30 in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-
31 studies. *Int J Epidemiol* 2014;43(4):1272-83.
32
33
34 18: Cousins S, Blencowe NS, Tsang C et al. Reporting of key methodological issues in placebo-
35 controlled trials of surgery needs improvement: a systematic review. *J Clin Epidemiol*
36 2020;119:109-116.
37
38
39 19: Ciccozzi M, Menga R, Ricci G et al. Critical review of sham surgery clinical trials:
40 Confounding factors analysis. *Annals of medicine and surgery* 2016;12:21-26.
41
42
43 20: Wartolowska K, Beard DJ & Carr A. Blinding in trials of interventional procedures is
44 possible and worthwhile. *F1000Res* 2017;8:6:1663.
45
46
47 21: Hr bjartsson A, Boutron I. Blinding in randomized clinical trials: imposed impartiality. *Clin*
48 *Pharmacol Ther* 2011;90(5).
49
50
51 22: Moustgaard H, Clayton GL, Jones HE et al. Impact of blinding on estimated treatment effects
52 in randomised clinical trials: meta-epidemiological study. *BMJ* 2020;368:16802.
53
54
55 23: Beard DJ, Rees JL, Cook JA et al. Arthroscopic subacromial decompression for subacromial
56 shoulder pain (CSAW): a multicentre, pragmatic, parallel group, placebo-controlled, three-group,
57 randomised surgical trial. *Lancet* 2018;391:329-338.
58
59
60 24: Schwartz MP, Wellink H, Gooszen HG et al. Endoscopic gastroplication for the treatment of
gastro-oesophageal reflux disease: a randomised, sham-controlled trial. *Gut* 2007;56:20-28.

- 1
2
3
4 25: Fields HL & Levine JD. Placebo analgesia —a role for endorphins? *Trends Neurosci*
5 1984;7:271-3.
6
7
8 26: Swank DJ, Swank-Bordewijk SCG, Hop WCJ et al. Laparoscopic adhesiolysis in patients
9 with chronic abdominal pain: a blinded randomised controlled trial. *Lancet*
10 2003;12:361(9365):1247-51.
11
12 27: Molegraaf MJ, Torensma B, Lange CP et al. Twelve-year outcomes of laparoscopic
13 adhesiolysis in patients with chronic abdominal pain: A randomized clinical trial. *Surgery*
14 2017;161(2):415-421.
15
16
17 28: Lai H, Jemielita T, Sutcliffe S et al. Characterization of Whole Body Pain in Urologic
18 Chronic Pelvic Pain Syndrome at Baseline – A MAPP Research Network Study. *J Urol*
19 2017;198(3):622-631
20
21
22 29: Borsook D, Kussman BD, George E et al. Surgically-Induced Neuropathic Pain (SNPP):
23 Understanding the Perioperative Process. *Ann Surg* 2013;257(3):403-412.
24
25 30: Chapman CR & Vierck CJ. The transition of acute postoperative pain to chronic pain: an
26 integrative overview of research on mechanisms. *J Pain* 2017;18(4):359.e1-359.e38
27
28 31: Greene AD, Lang SA, Kendzioriski JA et al. Endometriosis: Where are We and Where are
29 We Going? *Reproduction* 2016;152(3):63-78.
30
31
32 32: American Society for Reproductive Medicine. Revised American Society for Reproductive
33 Medicine classification of endometriosis: *Fertil Steril* 1997;67(5):817-821.
34
35 33: Louis GMB, Hediger ML, Peterson CM et al. Incidence of endometriosis by study
36 population and diagnostic method: the ENDO study. *Fertil Steril* 2011;96(2):360-5.
37
38
39 34: Barra F, Grandi G, Tantari M et al. A comprehensive review of hormonal and biological
40 therapies for endometriosis: latest developments. *Expert Opin Biol Ther* 2019;19(4):343-360.
41
42 35: Leonardi M, Gibbons T, Armour M et al. When to Do and When Not to Do Surgery for
43 Endometriosis: A Systematic Review and Meta-analysis. *J Minim Invasive Gynecol*
44 2020;27(2):390-407.e3.
45
46
47 36: Horne AW, Daniels J, Hummelshøj L et al. Surgical removal of superficial peritoneal
48 endometriosis for managing women with chronic pelvic pain: time for a rethink? *BJOG*
49 2019;126(12):1414-1416.
50
51 37: Saraswat L, Ayansina D, Cooper KG et al. Impact of endometriosis on risk of further
52 gynaecological surgery and cancer: a national cohort study. *BJOG* 2018;125:64–7
53
54
55 38: Guo SW. Recurrence of endometriosis and its control. *Hum Reprod Update* 2009;15:441–61
56
57
58
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60

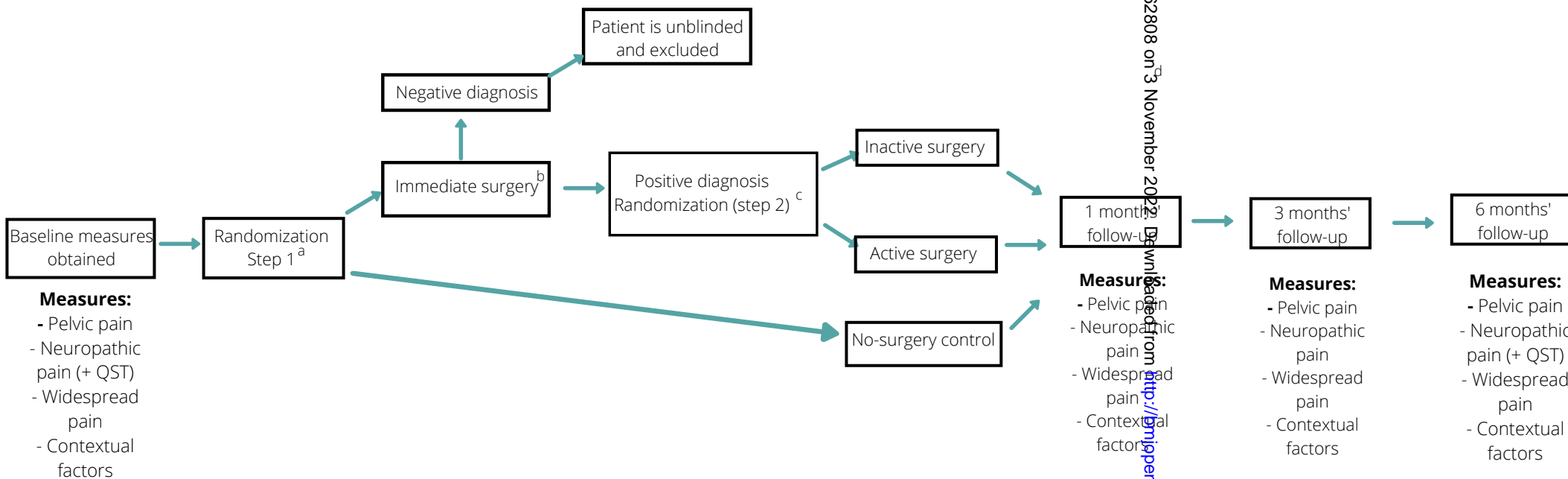
- 39: Ball E & Khan KS. Recent advances in understanding and managing chronic pelvic pain in women with special considerations to endometriosis. *F1000Res* 2020;9:83
- 40: Sutton CJG, Ewen SP, Whitelaw N et al. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. *Fertility and Sterility* 1994;62(4):696-700.
- 41: Abbott J, Hawe J, Hunter D et al. (2004). Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertil Steril* 2004;82(4):878-84.
- 42: Jarrell J, Mohindra R, Ross S et al. Laparoscopy and reported pain among patients with endometriosis. *J Obstet Gynaecol Can* 2005;27(5):477-85.
- 43: Althaus A, Hinrichs-Rocker A, Chapman R et al. Development of a risk index for the prediction of chronic post-surgical pain. *Eur J Pain* 2012;16(6):901-910.
- 44: Schug SA & Bruce J. Risk stratification for the development of chronic postsurgical pain. *Pain Reports* 2017;2(6):e627.
- 45: Zheng P, Zhang W, Leng J et al. Research on central sensitization of endometriosis-associated pain: a systematic review of the literature. *Journal of Pain Research* 2019;12:1447-1456.
- 46: Bourdel N, Alves J, Pickering G et al. Systematic review of endometriosis pain assessment: how to choose a scale? *Hum Reprod Update* 2015;21(1):136-52.
- 47: Freynhagen R, Baron R, Gockel U et al. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006;22(10):1911-20.
- 48: Whitaker LHR, Reid J, Choa A et al. An Exploratory Study into Objective and Reported Characteristics of Neuropathic Pain in Women with Chronic Pelvic Pain. *PLoS One* 2016;11(4):e0151950.
- 49: Grundström H, Gerdle B, Alehagen S et al. Reduced pain thresholds and signs of sensitization in women with persistent pelvic pain and suspected endometriosis. *Acta Obstet Gynecol Scand* 2019;98(3):327-336.
- 50: Mercer SW, Maxwell M, Heaney D et al. The consultation and relational empathy (CARE) measure: development and preliminary validation and reliability of an empathy-based consultation process measure. *Fam Pract* 2004;21(6):699-705.

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3 *Figure 1: design overview from recruitment to completion*
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8 *Description: ^a (step 1 randomization) = patients, surgeons, post-surgical staff and outcome*
9 *assessors are blinded to treatment allocation, ^b (positive endometriosis diagnosis) = patients,*
10 *surgeons, post-surgical staff and outcome assessors are blinded to treatment allocation, ^c (step 2*
11 *randomization) = patients, post-surgical staff and outcome assessors are blinded to treatment*
12 *allocation. QST = quantitative sensory testing.*
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1-14
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,14
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7-8

1 Introduction

2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	3-7
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	3-7
7				
8	Objectives	7	Specific objectives or hypotheses	6-7
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-8
12				
13				

14 Methods: Participants, interventions, and outcomes

15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	7-8
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	9
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	7-8
23			administered	
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	7,9
25			change in response to harms, participant request, or improving/worsening disease)	
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	7-8
27			(eg, drug tablet return, laboratory tests)	
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	10-12
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
32			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
33			efficacy and harm outcomes is strongly recommended	
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	7-8,10, figure 1
35			participants. A schematic diagram is highly recommended (see Figure)	
36				
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8
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7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9, figure 1
25				
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8-9
28				
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31	Methods: Data collection, management, and analysis			
32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-12
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39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
2				
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4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
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14	Methods: Monitoring			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
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32	Ethics and dissemination			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	N/A
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37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10,13
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
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16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	13
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
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29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by/4.0/)" license.

BMJ Open

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

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	SURGERY, PAIN MANAGEMENT, GYNAECOLOGY

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4 Is laparoscopic excision for superficial peritoneal endometriosis helpful or harmful? Protocol for
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10 Henrik Marschall,¹ Axel Forman,² Sigrid Juhl Lunde,³ Ulrik Schiøler Kesmodel,⁴ Karina Ejgaard
11 Hansen⁵ & Lene Vase³
12

13
14 ¹Department of Psychology and Behavioural Sciences, School of Business and Social Sciences,
15 Aarhus University, Denmark.
16

17 ²Department of Obstetrics and Gynaecology, Aarhus University Hospital, and Department of
18 Clinical Medicine, Aarhus University, Denmark.
19

20
21 ³Division for Psychology and Neuroscience, Department of Psychology and Behavioural Sciences,
22 School of Business and Social Sciences, Aarhus University, Denmark.
23

24 ⁴Department of Obstetrics and Gynaecology, Aalborg University Hospital, and Department of
25 Clinical Medicine, Aalborg University, Denmark.
26

27
28 ⁵Department of Public Health, Aarhus University, Denmark.
29
30

31
32
33 Corresponding author: Henrik Marschall

34 Department of Psychology and Behavioural Sciences

35 School of Business and Social Sciences

36 Bartholins Allé 11, DK-8000 Aarhus C, Denmark

37 E-mail: hmars@psy.au.dk

38 Tel. +4522394563
39

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52 **KEY WORDS:** endometriosis, placebo-controlled surgical trial, pain, contextual factors, quality
53 of life
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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 post-surgical 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 randomized 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 one, three and six months post-randomization. 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.

ARTICLE SUMMARY

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 post-surgical care, the trial should effectively be double-blinded.
- Quantitative sensory testing and risk factors of chronic post-surgical 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 to 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 hypothesized therapeutic element(s).[1, 2] Here, the contribution of the hypothesized 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

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3 relief, and psychological distress.[9-15] The contributions of these factors to surgical pain relief
4 in placebo-controlled settings are largely unexplored.
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8 Despite the advantages that placebo-controlled designs may offer over observational
9 designs (e.g. blinding with results less prone to bias),[1, 16, 17] placebo-controlled designs are
10 not infallible[18, 19] and limitations exist. Firstly, there are two issues pertaining to blinding.
11 Blinding of patients, post-operative caregivers and outcome assessors is generally feasible,[20]
12 yet many studies employ only blinding of patients and/or outcome assessors, which may
13 introduce bias.[3, 19] The other issue is that it is often assumed that blinding is successful and
14 most studies do not test the extent to which this was the case.[3] Blinding is believed to be an
15 important eliminator of bias, where meta-analyses indicate that unblinded studies lean towards
16 greater pain relief when compared to blinded studies using similar treatments.[e.g. 17, 21]
17 Although a meta-epidemiological study indicated no link between blinding and treatment
18 effect,[22] potentially suggesting that blinding may not be as important for unbiased results as
19 presumed, the study included only two surgical trials. While not all procedures afford blinding of
20 the surgeon, double-blinding can effectively be maintained if the surgical staff is blinded to
21 treatment allocation in all their interactions prior to anesthesia, and if only blinded staff members
22 are responsible for the post-surgical care.
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34 A second limitation in placebo-controlled surgical trials for pain is that few studies
35 incorporated a no-surgery control group.[23, 24] As described above, by comparing an active
36 surgery condition to a sham surgery condition, an expression of the part of the total effect
37 attributable to the hypothesized therapeutic elements of the surgical intervention itself can be
38 computed. However, while the remaining effect in the sham surgery condition (the placebo
39 *response*) is indicative of contextual factors contributing to the observed effect, it is difficult to
40 ascertain the contribution without a no-surgery control group. Pain fluctuates over time, and
41 participants who report high pain levels upon inclusion may regress closer to the mean at follow-
42 up, regardless of treatment effectiveness.[1, 9, 25] Thus, a reduction in symptoms may be due to
43 the treatment itself and/or contextual factors, but it may also be caused by natural fluctuations in
44 pain severity or regression to the mean. Hence, while the comparison between active and sham
45 surgery examines how effective the hypothesized therapeutic elements of surgery are at relieving
46 symptoms, the comparison between sham surgery and no-surgery illuminates the contributions of
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3 contextual factors to the total treatment effect (the placebo *effect*).[9] Mapping out the placebo
4 effect may yield valuable insights that can improve clinical practice, for example by enhancing
5 the quality of the patient-surgeon relationship, if it is revealed to be an important contributor to
6 treatment effect.
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11 Finally, while most studies test whether active surgery has an effect beyond sham surgery
12 or not, studies using tools like body maps and quantitative sensory testing to test the risks of
13 post-surgical pain and post-surgical neuropathic pain, respectively, are scarce. A twelve-year
14 follow-up on adhesiolysis for abdominal pain found that when compared to sham surgery,
15 patients in the active surgery group experienced more pain, worse quality of life and higher rates
16 of repeat-surgery due to persistent post-surgical pain.[26, 27] Not only do these results suggest
17 that the benefit from sham surgery may be long lasting, they also suggest that the active surgery
18 procedure may have caused more harm than good. Persistent post-surgical pain in the active
19 surgery group may have been caused by different factors, including increased sensory
20 hypersensitivity, the development of widespread pain, nerve damage and/or scar tissue
21 formation, the development of neuropathic pain or something else. Previous studies have
22 successfully detected and discerned adverse events following surgery such as widespread pain
23 using body maps from neuropathic pain using quantitative sensory testing.[28, 29] Without
24 examinations of the potential pain-related adverse events following surgery, it can be difficult to
25 tell apart the continuation of pre-surgical pain from the development of persistent post-surgical
26 pain problems or post-surgical neuropathic pain.[29, 30] In other words, it can be hard to
27 distinguish whether the intervention is ineffective at providing pain relief, from whether the
28 intervention *is* effective at providing pain relief, but is associated with risks of post-surgical pain.
29 This is an important distinction, as an effective intervention can be further honed and have its
30 risks mitigated, while ineffective treatments should be reconsidered as treatment options.
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46 For women suffering from peritoneal endometriosis, a three-armed, placebo-controlled
47 trial to evaluate the effectiveness and risks of surgery is needed. Endometriosis is a painful
48 gynaecological disease estimated to affect 5-10% of women, and it is characterized by the
49 presence and growth of endometrial-like tissue outside of the uterus.[31] In 70-80% of cases, the
50 endometrial tissue will attach itself superficially to the peritoneal lining and may cause chronic
51 pain.[32, 33] Approximately one third of women with endometriosis do not achieve adequate
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3 pain relief from medical treatment alone and may be offered surgery to manage their pain.[34,
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8 There is genuine doubt whether current surgical practice benefits these patients. In 25%
9 of repeated surgeries, there are no indications of endometriosis, suggesting that the pain
10 recurrence could be due to neuropathic or widespread pain following repeated invasive
11 interventions.[36-39] Previous research has not adequately tested whether surgery is beneficial
12 specifically for peritoneal endometriosis, but suggests that the intervention may not be effective
13 and the procedure is associated with risks of persistent post-surgical pain and neuropathic
14 pain.[29, 40-44] Endometriosis-related pain is associated with central sensitization, which could
15 increase risks of persistent pain and neuropathic pain following surgery.[45] Accordingly, this
16 three-armed, placebo-controlled surgical trial will examine the risks of widespread pain and test
17 changes in neuropathic pain symptoms, as it is currently unknown if the intervention is helpful or
18 harmful.
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26 27 **aims and hypotheses**

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29 *Aim 1:* To compare the effect of active surgery to sham surgery and no-surgery on pelvic
30 pain relief.
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34 *Hypothesis 1:* Both active and sham surgery will significantly reduce pelvic pain when
35 compared to the no-surgery control group. However, active surgery will *not* significantly reduce
36 pelvic pain when compared to sham surgery.
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40 *Aim 2:* To test the contribution of contextual factors to pelvic pain relief.
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43 *Hypothesis 2:* Quality of the patient-caregiver relationship, the patient's expectations of
44 treatment effectiveness, desire for symptom relief and degree of psychological distress will
45 significantly contribute to relief of chronic pain.
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48 *Aim 3:* To examine persistent post-surgical pain and to test whether participants develop
49 neuropathic pain components
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52 *Hypothesis 3:* Participants in the active surgery group will score higher on indications for
53 widespread pain and neuropathic pain symptoms at six months' follow-up, when compared to the
54 sham surgery and no-surgery groups.
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methods and materials

study design and context

Participants will be randomized 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 two and three will be offered active surgery after completing six months' follow-up. Baseline data will be gathered one month prior to first randomization, and follow-up data will be gathered at one, three and six months following first randomization. Participants in the surgical groups will be unblinded after six months' follow-up has been completed.

The trial is a Danish multi-centre cooperation between Aarhus University Hospital and the Regional Hospitals in Herning, Randers, Viborg and Horsens. A multi-centre 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 randomized in two steps to one of the study groups (see "Treatment allocation"). The PI (HM) is responsible for overseeing recruitment and enrolment of participants, coordinating interventions and analyzing data.

The perioperative process has been standardized 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 "*Data analysis*"). See figure one 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.

treatment allocation

Randomization will happen in two steps: in step one, participants are randomized to either immediate surgery or no-surgery control (2:1 ratio), after completing baseline measures (4 weeks after giving informed consent). In step two, participants randomized to intervention are randomized again to either active surgery or sham surgery in the operating room, after peritoneal endometriosis has been diagnosed. Distant randomization will be used to allocate participants in step two. In both steps, block randomizations will be used and randomizations will be stratified based on hospital site (5 strata). Block sizes will not be revealed here to maintain blinding of surgical staff. For step one, a researcher outside the study group will create the randomization 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 six 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 randomization.

Healthcare personnel will be blinded to treatment allocation as long as possible. The result of the randomization will not be revealed to the surgical team until peritoneal endometriosis has been visually diagnosed, in order to standardize pre-surgical preparations and the diagnostic laparoscopy. After the intervention, blinded personnel will be responsible for post-surgical 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 of 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 specialized endometriosis nurse, who is blinded to step two randomization, will consult participants by telephone at approximately two weeks and three months post-surgery.

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 (i.e. persistent or recurring pain for at least six months)
- All participants must have undergone first-line medical treatment (continuous oral contraceptives and/or levonorgestrel intrauterine device) for at least three months prior to inclusion.
- Pain intensity ≥ 5 on a Numeric Rating Scale (NRS) assessed by participant recall of average pain intensity in the four weeks prior to consenting to participation.

Exclusion criteria:

- Other known conditions that may cause pelvic pain (e.g. adenomyosis, IBS, interstitial cystitis)
- Personality disorder, schizophrenia or currently receiving anti-psychotic 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 (e.g. 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 six months' follow-up (no-surgery control group) = 5.25, $SD = 2.0$, Power ($1-\beta = .80$), $\alpha = .05$, 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 six 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 ($1-\beta = .80$), $\alpha = .05$, 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 randomized participants was deemed sufficient to reach 28 participants in each group.

data collection

Data collection is structured in four blocks of four weeks: baseline (beginning after informed consent has been given), one month post-randomization, three months post-randomization and six months post-randomization. In weeks one to three of each block, weekly

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3 pain measurements are assessed. In week four of a block, weekly pain measurements as well as
4 neuropathic pain symptoms, widespread pain, endometriosis-related symptoms, quality of life
5 and contextual factors (except quality of the patient-surgeon relationship, which is only
6 measured at baseline) are assessed. For participants who undergo surgery, success of blinding is
7 assessed at week four of each block. All data except quantitative sensory testing is assessed
8 online with RedCap surveys.
9

14 **outcomes**

16 The primary outcome is changes in

- 18 • Overall pelvic pain intensity and unpleasantness

20 from baseline to six months' follow-up. Overall pelvic pain intensity and unpleasantness will be
21 measured using a 0-10 NRS.[47] Participants will rate their overall pelvic pain weekly with a
22 NRS (0-10), with 0 labeled as “no pain” and 10 labeled as “worst pain imaginable”. Weekly
23 ratings will be in blocks of four weeks, corresponding to one menstrual cycle. The four pain
24 ratings of a block will be combined and used as one mean pain rating for the period.
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30 The secondary outcomes are changes in

- 32 • Neuropathic pain symptoms
- 33 • Widespread pain
- 34 • Worst pain intensity and unpleasantness
- 35 • Pain frequency
- 36 • Endometriosis-related symptoms
- 37 • Quality of life

38 From baseline to six months' follow up.

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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 five centimeters laterally to the symphysis pubis on
both sides.[50] Participants will complete the painDETECT at the end of each measurement

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3 block, and the quantitative sensory testing battery will be conducted at baseline and at the six
4 months' follow-up.
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7 Widespread pain will be measured using a body map, where participants mark all areas of
8 their body where they experience pain. Body maps have previously been used in this manner to
9 detect the development of widespread pain in patients suffering from pelvic pain.[28]
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13 Worst pain intensity and unpleasantness will be measured weekly similarly to overall
14 pelvic pain intensity and unpleasantness using NRS. Participants will be asked to rate how
15 intense or unpleasant their pelvic pain were in the past week, when the pain were at their worst.
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19 Pain frequency will be measured by asking participants how many days in the past week
20 they experienced pelvic pain, from 0 to 7 days.
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23 Endometriosis-related *symptoms* are dysmenorrhea, noncyclical pelvic pain, dyspareunia
24 during and after intercourse, dysuria and dyschezia. Participants will be asked to rate the
25 intensity of these symptoms for the past four weeks using NRS.[47]
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29 Quality of life will be assessed using the patient-generated and validated “Endometriosis
30 Health Profile-30”, designed to measure quality of life specifically for women with
31 endometriosis.[51] The questionnaire has been validated in Danish.[52]
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35 **contribution of contextual factors**

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37 Quality of the patient-doctor relationship will be measured using the validated “Care and
38 Relational Empathy” questionnaire.[53] Patients will be asked to complete the questionnaire at
39 baseline with the surgeon who recruited them in mind.
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43 Expectations of treatment efficacy will be measured by asking patients “*What do you*
44 *expect your pelvic pain [intensity/unpleasantness] to be in [2/3] months?*”, with the months
45 corresponding to the next measurement point. Ratings will be obtained with a NRS.[9, 10]
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49 Desire for symptom relief will be measured by asking patients “*How strong is your desire*
50 *for symptom relief?*” Ratings will be obtained with NRS: 0 labeled as “no desire” and 10 labeled
51 as “strongest desire imaginable”. [9, 10]
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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 centered around the length of follow-up and the outcome measures. Feasibility of blinding procedures was tested with two patients, and blinding of all relevant parties was successfully maintained for the full six months. Based on input from patients we decided to shorten the follow-up period from 12 months to six months, and to use weekly recall of pelvic pain measures instead of daily.

The decision to use six 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 to 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 six 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 DMC will not be established. There are no planned interim analyses.

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3 Data will be analyzed according to intention-to-treat principles, and missing data patterns will be
4 investigated and reported. Baseline data and demographics between the three groups will be
5 compared to determine if key differences exist. The newest version of R software will be used.
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7 All analyses will be two-tailed ($\alpha = .05$), with 95% confidence intervals reported when
8 appropriate. Model assumptions will be investigated for all analyses, and alternative methods
9 will be chosen if necessary. All outcome measures will be analyzed using mixed linear models,
10 with time at level one nested within individuals at level two. The best model fit and function of
11 time will be examined and reported. The main analyses are changes in pelvic pain intensity and
12 unpleasantness from baseline to six months' follow-up as the outcomes, and secondary analyses
13 include changes from baseline to six months' follow-up for all secondary outcomes. The three
14 groups will be compared in pairs. First, the two surgical groups will be viewed as one and
15 compared to the no-surgery group, based on the assumption that the two surgical groups will
16 provide roughly similar levels of pain relief. Then, the two surgical groups will be compared.
17 The contribution of contextual factors and blinding of patients and healthcare personnel to pain
18 relief will also be investigated and taken into account in the evaluation of the data using the
19 principles described above.
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31 Sensitivity analyses

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

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43 Only experienced, endometriosis-specialized surgeons will perform surgery. A committee
44 of endometriosis-specialized healthcare professionals will oversee the well-being of patients, and
45 can exclude patients from further clinical assessment. If participants should experience harm
46 from participating in the study, they are covered by the hospitals' insurance policy.
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51 Personal information will be handled in accordance with Danish legislation and the
52 General Data Protection Regulation. When participant inclusion has ended, data will be shared in
53 accordance with the ICJME guidelines, if relevant research objectives are provided. Data sharing
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3 will require approval from the Central Denmark Region and the Danish Data Protection Agency,
4 and the requesting party shall cover any data sharing fees. Requests for data can be addressed to
5 af@clin.au.dk.
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9 The results are expected to be published in high impact journals and presented at relevant
10 conferences.
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13 The authors that have contributed to the present protocol article will be invited to
14 contribute to future publications on data gathered in the planned study. Eligibility will be
15 determined based on the Vancouver criteria for authorship. There are no plans to involve
16 professional writers.
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19 **AUTHOR CONTRIBUTIONS**

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21 All authors contributed to the design of the study. HM wrote the first draft. LV and SJL
22 critically reviewed and commented on the first draft. HM revised the draft and LV, SJL, AF,
23 USK and KEH critically reviewed and commented on the revised draft.
24
25

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27
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30 involved in the design of the study, or will be involved in the reporting or publication of results
31 from the planned trial.
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34 **COMPETING INTERESTS STATEMENT**

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36 No competing interests to declare.
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39 **REFERENCES**

- 40
41
42
43
44 1: Beard DJ, Campbell MK, Blazeby JM et al. Considerations and methods for placebo controls
45 in surgical trials (ASPIRE guidelines). *Lancet* 2020;395(10226),828-838.
46
47 2: Beard DJ, Campbell MK, Blazeby JM et al. Placebo comparator group selection and use in
48 surgical trials: the ASPIRE group project including expert workshop. *Health Technol Assess*
49 2021;53:1-52.
50
51 3: Wartolowska K, Judge A, Hopewell S et al. Use of placebo controls in the evaluation of
52 surgery: systematic review. *BMJ* 2014;348:g3253.
53
54
55
56
57
58
59
60

- 4: Wartolowska KA, Feakins BG, Collins GS et al. The magnitude and temporal changes of response in the placebo arm of surgical randomized controlled trials: a systematic review and meta-analysis. *Trials* 2016;17(1):589.
- 5: Wartolowska KA, Gerry S, Feakins BG et al. A meta-analysis of temporal changes of response in the placebo arm of surgical randomized controlled trials: an update. *Trials* 2017;12:18(1):323.
- 6: Jonas WB, Crawford C, Colloca L et al. Are Invasive Procedures Effective for Chronic Pain? A Systematic Review. *Pain Med* 2019;1;20(7):1281-1293.
- 7: Gu AP, Gu CN, Ahmed AT et al. Sham surgical procedures for pain intervention result in significant improvement in pain: systematic review and meta-analysis. *J Clin Epidemiol* 2017;83:18-23.
- 8: Probst P, Grummich K, Harnoss JC et al. Placebo-Controlled Trials in Surgery: A Systematic Review and Meta-Analysis. *Medicine (Baltimore)*. 2016;95(17):e3516.
- 9: Benedetti F. Placebo Effects. Oxford University Press 2020.
- 10: Colloca L. The Placebo Effect in Pain Therapies. *Annu Rev Pharmacol Toxicol* 2019;59:191-211.
- 11: Petersen GL, Finnerup NB, Grosen K, Pilegaard HK, Tracey I, Benedetti F, Price DN, Jensen TS & Vase L. Expectations and positive emotional feelings accompany reductions in ongoing and evoked neuropathic pain following placebo interventions. *Pain* 2014;155: 2687-2698
- 12: Howick J, Moscrop A, Mebius A, Fanshawe TR, Lewith G, Bishop FL, Mistiaen P, Roberts NW, Dieninytė E, Hu X, Aveyard P & Onakpoya IJ. Effects of empathic and positive communication in healthcare consultations: a systematic review and meta-analysis. *J R Soc Med* 2018;111(7):240-252.
- 13: Geurts JW, Willems PC, Lockwood C, van Kleef M, Kleijnen J & Dirksen C. Patient expectations for management of chronic non-cancer pain: A systematic review. *Health Expect* 2017;20(6):1201-1217.
- 14: Cormier S, Lavigne GL, Choinière M & Rainville P. Expectations predict chronic pain outcomes. *Pain* 2016;157(2):329-338.
- 15: Atlas LY & Wager TD. How expectations shape pain. *Neurosci Lett* 2012;520:140-148.
- 16: Hariton E & Locascio JJ. Randomised controlled trials – the gold standard for effectiveness research. *BJOG* 2018;125(13):1716.
- 17: Hróbjartsson A, Emanuelsson F, Skou Thomsen AS et al. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. *Int J Epidemiol* 2014;43(4):1272-83.

- 1
2
3 18: Cousins S, Blencowe NS, Tsang C et al. Reporting of key methodological issues in placebo-
4 controlled trials of surgery needs improvement: a systematic review. *J Clin Epidemiol*
5 2020;119:109-116.
6
7
8 19: Ciccozzi M, Menga R, Ricci G et al. Critical review of sham surgery clinical trials:
9 Confounding factors analysis. *Annals of medicine and surgery* 2016;12:21-26.
10
11 20: Wartolowska K, Beard DJ & Carr A. Blinding in trials of interventional procedures is
12 possible and worthwhile. *F1000Res* 2017;8:6:1663.
13
14 21: Hróbjartsson A, Boutron I. Blinding in randomized clinical trials: imposed impartiality. *Clin*
15 *Pharmacol Ther* 2011;90(5).
16
17 22: Moustgaard H, Clayton GL, Jones HE et al. Impact of blinding on estimated treatment effects
18 in randomised clinical trials: meta-epidemiological study. *BMJ* 2020;368:16802.
19
20 23: Beard DJ, Rees JL, Cook JA et al. Arthroscopic subacromial decompression for subacromial
21 shoulder pain (CSAW): a multicentre, pragmatic, parallel group, placebo-controlled, three-group,
22 randomised surgical trial. *Lancet* 2018;391:329-338.
23
24 24: Schwartz MP, Wellink H, Gooszen HG et al. Endoscopic gastroplication for the treatment of
25 gastro-oesophageal reflux disease: a randomised, sham-controlled trial. *Gut* 2007;56:20-28.
26
27 25: Fields HL & Levine JD. Placebo analgesia —a role for endorphins? *Trends Neurosci*
28 1984;7:271-3.
29
30 26: Swank DJ, Swank-Bordewijk SCG, Hop WCJ et al. Laparoscopic adhesiolysis in patients
31 with chronic abdominal pain: a blinded randomised controlled trial. *Lancet*
32 2003;12:361(9365):1247-51.
33
34 27: Molegraaf MJ, Torensma B, Lange CP et al. Twelve-year outcomes of laparoscopic
35 adhesiolysis in patients with chronic abdominal pain: A randomized clinical trial. *Surgery*
36 2017;161(2):415-421.
37
38 28: Lai H, Jemielita T, Sutcliffe S et al. Characterization of Whole Body Pain in Urologic
39 Chronic Pelvic Pain Syndrome at Baseline – A MAPP Research Network Study. *J Urol*
40 2017;198(3):622-631
41
42 29: Borsook D, Kussman BD, George E et al. Surgically-Induced Neuropathic Pain (SNPP):
43 Understanding the Perioperative Process. *Ann Surg* 2013;257(3):403-412.
44
45 30: Chapman CR & Vierck CJ. The transition of acute postoperative pain to chronic pain: an
46 integrative overview of research on mechanisms. *J Pain* 2017;18(4):359.e1-359.e38
47
48 31: Greene AD, Lang SA, Kendzierski JA et al. Endometriosis: Where are We and Where are
49 We Going? *Reproduction* 2016;152(3),63-78.
50
51
52
53
54
55
56
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2
3
4
5
6
7
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41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- 32: American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: *Fertil Steril* 1997;67(5):817-821.
- 33: Louis GMB, Hediger ML, Peterson CM et al. Incidence of endometriosis by study population and diagnostic method: the ENDO study. *Fertil Steril* 2011;96(2):360-5.
- 34: Barra F, Grandi G, Tantari M et al. A comprehensive review of hormonal and biological therapies for endometriosis: latest developments. *Expert Opin Biol Ther* 2019;19(4):343-360.
- 35: Leonardi M, Gibbons T, Armour M et al. When to Do and When Not to Do Surgery for Endometriosis: A Systematic Review and Meta-analysis. *J Minim Invasive Gynecol* 2020;27(2):390-407.e3.
- 36: Horne AW, Daniels J, Hummelshøj L et al. Surgical removal of superficial peritoneal endometriosis for managing women with chronic pelvic pain: time for a rethink? *BJOG* 2019;126(12):1414-1416.
- 37: Saraswat L, Ayansina D, Cooper KG et al. Impact of endometriosis on risk of further gynaecological surgery and cancer: a national cohort study. *BJOG* 2018;125:64-7
- 38: Guo SW. Recurrence of endometriosis and its control. *Hum Reprod Update* 2009;15:441-61
- 39: Ball E & Khan KS. Recent advances in understanding and managing chronic pelvic pain in women with special considerations to endometriosis. *F1000Res* 2020;9:83
- 40: Sutton CJG, Ewen SP, Whitelaw N et al. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. *Fertility and Sterility* 1994;62(4):696-700.
- 41: Abbott J, Hawe J, Hunter D et al. (2004). Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertil Steril* 2004;82(4):878-84.
- 42: Jarrell J, Mohindra R, Ross S et al. Laparoscopy and reported pain among patients with endometriosis. *J Obstet Gynaecol Can* 2005;27(5):477-85.
- 43: Althaus A, Hinrichs-Rocker A, Chapman R et al. Development of a risk index for the prediction of chronic post-surgical pain. *Eur J Pain* 2012;16(6):901-910.
- 44: Schug SA & Bruce J. Risk stratification for the development of chronic postsurgical pain. *Pain Reports* 2017;2(6):e627.
- 45: Zheng P, Zhang W, Leng J et al. Research on central sensitization of endometriosis-associated pain: a systematic review of the literature. *Journal of Pain Research* 2019;12:1447-1456.

46: Wartolowska K, Collins GS, Hopewell S et al. Feasibility of surgical randomised controlled trials with a placebo arm: a systematic review. *BMJ Open* 2016;15:6(3):e010194.

47: Bourdel N, Alves J, Pickering G et al. Systematic review of endometriosis pain assessment: how to choose a scale? *Hum Reprod Update* 2015;21(1):136-52.

48: Freynhagen R, Baron R, Gockel U et al. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006;22(10):1911-20.

49: Whitaker LHR, Reid J, Choa A et al. An Exploratory Study into Objective and Reported Characteristics of Neuropathic Pain in Women with Chronic Pelvic Pain. *PLoS One* 2016;11(4):e0151950.

50: Grundström H, Gerdle B, Alehagen S et al. Reduced pain thresholds and signs of sensitization in women with persistent pelvic pain and suspected endometriosis. *Acta Obstet Gynecol Scand* 2019;98(3):327-336.

51: Jones G, Kennedy S, Barnard A et al. Development of an endometriosis quality-of-life instrument: The Endometriosis Health Profile-30. *Obstet Gynecol* 2001;98(2):258-264

52: Hansen KE, Lambek R, Røssaak K et al. Health-related quality of life in women with endometriosis: psychometric validation of the Endometriosis Health Profile 30 questionnaire using confirmatory factor analysis. *Human Reproduction Open* 2022;1:hoab042.

53: Mercer SW, Maxwell M, Heaney D et al. The consultation and relational empathy (CARE) measure: development and preliminary validation and reliability of an empathy-based consultation process measure. *Fam Pract* 2004;21(6):699-705.

Figure 1: design overview from recruitment to completion

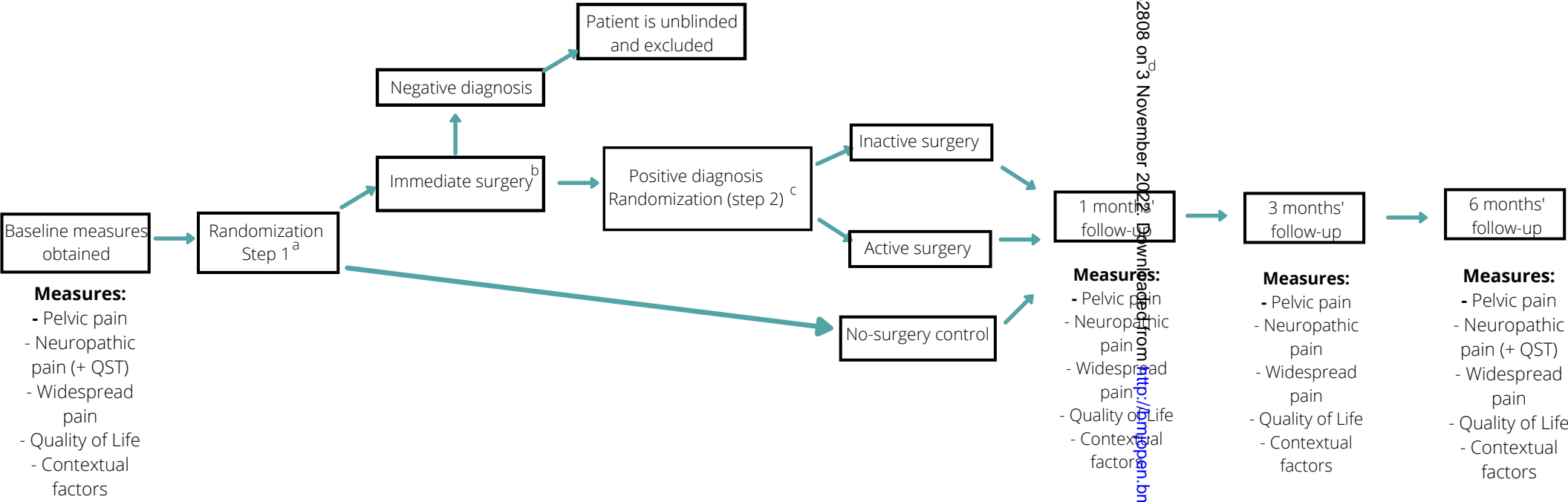
Description: ^a (step 1 randomization) = patients, surgeons, post-surgical staff and outcome assessors are blinded to treatment allocation, ^b (positive endometriosis diagnosis) = patients, surgeons, post-surgical staff and outcome assessors are blinded to treatment allocation, ^c (step 2 randomization) = patients, post-surgical staff and outcome assessors are blinded to treatment allocation. QST = quantitative sensory testing.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1-16
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,16
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7-8

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	3-7
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	3-7
7				
8	Objectives	7	Specific objectives or hypotheses	6-7
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-8
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	7-8
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	9-10
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	7-8
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	7,9
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	7-8
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	11-13
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	7-8,10-11, figure 1
39			participants. A schematic diagram is highly recommended (see Figure)	
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8
5				
6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
17				
18				
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
21				
22				
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9, figure 1
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8-9
28				
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31	Methods: Data collection, management, and analysis			
32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-13
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39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11, 15
2				
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5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
6				
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14-15
11				
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14	Methods: Monitoring			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
23				
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	N/A
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11,15
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
14				
15				
16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15-16
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	16
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A
35				
36				

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