BMJ Open

Determining the effectiveness of cognitive behavioural therapy in improving quality of life in patients undergoing endometriosis surgery: a study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054896
Article Type:	Protocol
Date Submitted by the Author:	25-Jun-2021
Complete List of Authors:	Boersen, Zoë; Hospital Rijnstate Arnhem, Obstetrics and Gynaecology Oosterman, Joukje; Radboud University Donders Institute for Brain Cognition and Behaviour Hameleers, Esther; Hospital Rijnstate Arnhem, Medical psychology Delcliseur, Heidi; Ziekenhuis Rijnstate Arnhem, Medical psychology Lutters, Cobie; Medisch Centrum Haaglanden, Endometriose in Balans IJssel de Schepper, Alicia; Radboudumc, Medical Psychology Braat, Didi; Radboudumc Department of Obstetrics and Gynecology Verhaak, Christianne; Radboudumc, Medical Psychology Nap, Annemiek; Radboudumc Department of Obstetrics and Gynecology
Keywords:	SURGERY, GYNAECOLOGY, PAIN MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Determining the effectiveness of cognitive behavioural therapy in improving quality of life in patients undergoing endometriosis surgery: a study protocol for a randomized controlled trial

Z. Boersen[1]* (MD), J.M. Oosterman[2] (PhD), E.G. Hameleers[3] (MSc), H.S.M.J Delcliseur[3] (MSc), C.E.T. Lutters[4] (MSc), K.A. IJssel de Schepper[5] (MSc), D.D.M. Braat[6] (MD; PhD), C.M. Verhaak[5] (PhD), A.W. Nap[6] (MD; PhD)

[1]Department of Gynaecology and Obstetrics, Rijnstate, Arnhem, The Netherlands

[2]Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands

[3]Department of Medical Psychology, Rijnstate, Arnhem, The Netherlands

[4]Endometriose in Balans, Haaglanden Medisch Centrum, Den Haag, The Netherlands

[5]Department of Medical Psychology, Radboud University Medical Centre, Nijmegen, The Netherlands

[6]Department of Obstetrics and Gynaecology, Radboud University Medical Centre, Radboud University, Nijmegen, The Netherlands

*Corresponding author. E-mail address: zboersen@rijnstate.nl

Word count: 4862

Abstract

Introduction: Endometriosis can cause chronic pain and subfertility thereby negatively affecting Quality of Life (QoL). Surgical removal of endometriosis lesions leads to improved Health Related QoL, although not to the level of QoL of healthy controls. Pain intensity and cognitions regarding pain can play a crucial role in this Health Related QoL following surgical treatment. Cognitive behavioural therapy (CBT) is a psychological treatment. In patients with chronic pain caused by a variety of medical conditions, CBT is effective in improving QoL. We designed a research protocol to investigate the effect of CBT on QoL in patients with endometriosis-associated chronic pain who are undergoing surgery.

Methods and analysis: This is a study protocol for a randomized controlled trial in which 100 patients, undergoing endometriosis removal surgery due to endometriosis-associated chronic pain, will be randomized between post-surgery usual care with CBT and post-surgery usual care only. Participants in the CBT group will additionally receive seven sessions of CBT, focused on expectancy management, cognitions regarding pain, and emotional and behavioural impact of pain. To determine the primary outcome Quality of life, both groups will complete questionnaires assessing QoL. The secondary outcomes pain intensity, pain cognitions, fatigue and perceived stress are also measured using questionnaires. Additionally, a marker for stress (cortisol extracted from a hair sample) will be assessed at T0 (baseline assessment), T1 (post-intervention; two weeks after completion of all CBT sessions) and T2 (follow-up; 14 weeks after T1). Statistical analysis will be performed using SPSS software.

Ethics and dissemination: The study protocol has been approved by the Medical Ethical Committee of the region Arnhem-Nijmegen from the Radboud University Medical Centre on September 2nd 2020. The findings of this study will be published in scientific journals and will be presented at scientific conferences.

Article summary

Strengths and limitations of this study

- A cognitive behavioural therapy protocol was developed specifically for this patient group to be used as intervention.
- Patients are treated with cognitive behavioural therapy in addition to endometriosis reduction surgery.
- There is a difference in contact time between therapists and patients in the intervention versus the control group.
- Treatment blinding is not possible due to used intervention which could lead to bias.

Introduction

Endometriosis, the presence of functioning endometrium-like tissue outside the uterine cavity, is one of the most prevalent benign gynaecologic conditions[1]. It can cause chronic pain and subfertility and can lead to impaired Quality of Life (QoL). Although medical therapy can halt disease activity, surgical removal of endometriosis is often required. Unfortunately, pain symptoms remain present in approximately 50 percent of the patients after surgery[2]. Moreover, the level of Health Related QoL remains lower compared to the QoL of healthy controls[3]. Van Aken et al[4]. showed that pain intensity and pain cognitions including pain anxiety, catastrophizing and hypervigilance towards pain are all independent factors contributing to Health Related QoL in patients diagnosed with endometriosis. This indicates that modifying these cognitions via psychological intervention might improve QoL in endometriosis patients. Cognitive behavioural therapy (CBT) is an evidence-based psychological treatment and is increasingly being recognized as an effective treatment to improve QoL in patients with various medical conditions[5]. CBT focuses on supporting positive cognitions, healthy coping behaviours and emotional regulation targeting current problems that affect QoL. To date, there are no studies available that describe the efficacy of post-surgical CBT to improve QoL in patients diagnosed with endometriosis. CBT has been used and proven effective in improving QoL and decreasing perceived pain intensity in other chronic pain conditions[6-8]. We have recently shown that patients undergoing endometriosis surgery believe that CBT could be a valuable asset to their treatment, in order to improve QoL[9]. We designed this research protocol for a randomized controlled trial to investigate the efficacy of CBT on improving QoL in patients with endometriosis-associated pain in addition to endometriosis removal surgery.

Methods

Participants, interventions, outcomes and intervention allocation

Study design

This is a research protocol for a randomized, controlled, prospective, single-blind (assessor) clinical trial in which patients undergoing surgery for endometriosis-related pain will be randomly allocated to surgery and usual care (control group) or to surgery and usual care plus CBT (CBT group). The participants and the psychologists delivering the intervention cannot be blinded due to the used intervention. Figure 1 shows an overview of patient flow throughout the study. This protocol was developed in accordance with the SPIRIT reporting guidelines[10].

Patient involvement

In 2019 and 2020, prior to developing this study protocol, we conducted a focus group study with patients who underwent endometriosis surgery to investigate if they were interested in psychological therapy in order to improve QoL in addition to endometriosis surgery and why[9]. We furthermore explored how they would design such a psychological treatment. The information acquired in these focus groups was taken into account when designing the intervention used in this research protocol.

Sample size calculation

The calculation for the required sample size was performed for the primary endpoint QoL. There was no study available describing the effect size of CBT on QoL after endometriosis surgery which could be used in the sample size calculation. Therefore, we used a study in which the authors examine a cognitive behavioural intervention to improve QoL in patients undergoing surgery due to chronic back pain[11]. Based on this article we expect to find medium to large effect sizes (Cohen's *d*) of 0.75 and 1.35 (measured with the physical and mental component scales of the 12-Item Short-Form

Health Survey) of postoperative CBT compared to usual care-only on QoL regarding physical and mental health, respectively. Based on literature we expect the dropout rate to be 15 to 16 percent[12, 13]. However, due to the intensity of the intended intervention combined with surgery we anticipating patient dropout to be higher: 19 percent. Therefore, a total of 100 patients should be included to detect significant effects ($\alpha = 0.05$, power $(1-\beta) = 0.85$).

Study population and recruitment

At the start of the study, subjects will be recruited in Rijnstate Hospital, Radboud University Medical Center and Catharina Hospital, all located in the Netherlands. In all hospitals, a multi-disciplinary centre for diagnosis and treatment of endometriosis is present, in which gynaecologists, surgeons and psychologists with extensive experience in treating women with endometriosis are involved. All centres are located in urban areas. All patients undergoing endometriosis removal surgery due to endometriosis-associated chronic pain will be referred by their gynaecologist to a researcher who will check whether they meet the inclusion criteria. Patients are eligible for this study when they are 18 to 50 years of age, diagnosed with endometriosis (proven by ultrasound, MRI or surgery) and have an indication for endometriosis surgery due to endometriosis-related chronic pain. An indication for surgery is present when hormonal and/or analgesic therapy failed in suppressing pain symptoms, is contra indicated due to comorbidity or has unacceptable side effects. Chronic pain is defined as pain existing longer than three months (in accordance with the ICD-11 formulated by the World Health Organization[14]), with an average Numerical Rating Scale (NRS) of four or higher in the month prior to inclusion (which will be asked at inclusion). Furthermore, participants should be able to read and write Dutch in order to be able to complete the questionnaires.

Because certain conditions require a different psychological approach[4, 15-17], and therefore could influence the efficacy of the intervention used in this study, we exclude patients suffering from endometriosis-related infertility without pain, chronic pain that can be allocated to other diseases or syndromes, patients that are diagnosed with a mood, anxiety or personality disorder (as defined by the DSM-V[18]), are undergoing psychological therapy or use psychopharmacologic medication aimed at altering mood at the moment of inclusion. Because we will also assess cortisol levels in scalp hair, patients will also be excluded if they have scalp hair shorter than four centimeters.

Patients eligible for inclusion will be provided with detailed written and verbal information. Informed consent will be obtained by an authorized researcher if patients are willing to participate and all questions have been resolved. Patients can contact an independent researcher if they wish to discuss the study with someone who is not directly involved in the project but has knowledge about all aspects of this study. Participants can withdraw consent at any time without providing a reason.

Randomization

Computerized randomization will be conducted after inclusion and baseline assessment. Participants will be allocated to the control or intervention group by an authorized investigator. No stratification factors will be used. This study is single blinded (the assessor is blinded for treatment allocation). Participants and psychological therapists cannot be blinded due to the used intervention. The randomization code will be broken when a patient's health is at risk or when investigation is required by the sponsor, the Medical Ethics Committee (METC) or the monitor, for example to verify if the study is executed in accordance with the study protocol and national and international regulations.

Variables

Demographic variables will be recorded, including age, length, weight, BMI, marital status, educational attainment, occupation, the method used to diagnose endometriosis, year of diagnosis, r-ASRM classification, type of endometriosis, use of contraception, use of analgesics, use of other

medications, presence of subfertility, parity, history of DSM-V diagnosis and if patients underwent psychological treatment prior to inclusion in this study. An overview of these variables, including their corresponding values, is provided in table 1.

The primary endpoint in this study is QoL. In our opinion evaluating this outcome, that reflects an improvement that patients themselves experience in their daily lives, should have priority over other measurements (for example pain score, lab results or absence of endometriosis lesions) that do not. QoL will be measured by two questionnaires: a general QoL questionnaire, the Dutch version of the Short Form 36 (RAND-36), and an endometriosis disease specific questionnaire, the Endometriosis Health Profile 30 (EHP-30). Both questionnaires measure QoL but do so differently. The EHP-30 is a disease-specific QoL questionnaire which is validated for use in endometriosis patients[19, 20] and measures the impact of the disease on physical, mental and social aspects of life. The questionnaire is divided into two parts. The core questionnaire consists of five subscales: pain, control and powerlessness, emotional well-being, social support, and self-image. The second part consists of six subscales: work, relationship with children, sexual intercourse, infertility, medical profession and treatment. Raw scores are transformed to a scale ranging from 0 to 100, and a higher score corresponds with worse QoL. The validated[21] questionnaire RAND-36 is used to measure general QoL. It is a multipurpose, general health survey which is applied to measure QoL on nine different domains: physical functioning, social functioning, role limitations due to physical health, role limitations due to emotional problems, emotional well-being, vitality, pain, general health, and health change. Raw scores are transformed to a scale ranging from 0 to 100, and a higher score corresponds with better QoL. The EHP-30 is a sensitive tool which is responsive to changes in Health Related QoL in this specific patient group[20] while the RAND-36 provides a complete QoL assessment which can be compared more easily with QoL of patients with other illnesses or healthy people.

Secondary endpoints are pain intensity, fatigue, pain related cognitions including anxiety and catastrophizing, perceived stress, and cortisol level as a marker for stress. Pain related cognitions have shown to be independent factors contributing to the Health Related QoL of endometriosis patients[4], therefore it interesting to determine whether CBT influences these cognitions as well. Pain intensity is measured by the NRS, pain anxiety by the Pain Anxiety Symptom Scale (PASS), catastrophizing by the Pain Catastrophizing Scale (PCS). Additionally, fatigue is measured using the Checklist Individual Strength (CIS). Indicators for stress will be measured in two ways. First, perceived stress is measured by the Perceived Stress Scale (PSS) questionnaire which measures self-reported stress levels in patients. In addition to perceived stress, stress can also trigger a response leading to an activation of the hypothalamus-pituitary-adrenal axis. Activation of this axis leads to the secretion of cortisol by the adrenal cortex. Cortisol modulates the immune system[22] and is therefore essential for proper body and brain function in response to stress. Cortisol levels can be used as an indicator for the amount of stress. To date, cortisol levels are measured in saliva, serum or urine, representing a dynamic reflection of cortisol concentrations and stress reactivity at one single point in time. These types of measurements are easily affected by short term changes of cortisol including the circadian rhythm or situational stress and are therefore less reliable to use as an indicator for chronic stress, which is present in patients with chronic pain including endometriosis. In order to use cortisol as a marker for chronic stress, it should be measured in another body specimen. Since recently, cortisol can be extracted from hair. Hair has an average growth rate of 1 cm/month and evidence of long term stress exposure can be analyzed in a string of hair. This makes hair cortisol a useful biomarker for chronic stress. In an earlier prospective follow-up study, researchers showed that hair cortisol levels are higher in endometriosis patients as compared to healthy controls, and that hair cortisol levels correlate with QoL[23].

All primary and secondary outcomes will be measured at baseline (T0) between two and four weeks prior to surgery, post-intervention (T1) approximately two weeks after completion of all CBT sessions and at follow-up (T2) approximately 14 weeks after T1. An overview of all outcome variables is provided in table 2. All questionnaires will be sent and returned through a web-based platform. The collection of the hair sample for cortisol measurements will be conducted by authorized and trained researchers. Analysis of the hair samples will be performed by a certified laboratory experienced in extracting cortisol from hair samples.

Intervention

Control group

The control group will receive usual care. Usual care consists of pre-surgical counseling by the participant's gynaecologist about the intended surgical procedure, possible complications and expected results. When indicated, patients will consult a gastro-intestinal surgeon and/or a urologist from the endometriosis team. Surgery will be carried out, following medical standards, by members of a team of gynaecologists and, if indicated, together with gastro-intestinal surgeons and/or urologists. Before and after surgery, patients will take their usual hormonal therapy to minimize menstrual cycle effects. Patients are allowed to use analgesics if necessary, but are asked to refrain from seeking (additional) psychological treatment when participating in this study. Patients will receive medical check-ups after approximately six weeks, three and six months post-surgery, consisting of history taking (in which symptoms and postoperative recovery will be assessed) and physical examination. They can contact the endometriosis nurse by e-mail or phone at any time.

CBT group

In addition to the usual care as described above, patients in the intervention group will also undergo seven sessions of CBT. Therefore, a CBT protocol was developed by members of the research team consisting of gynaecologists experienced in treating women with endometriosis and of psychologists with experience in CBT, chronic pain and/or treating patients diagnosed with endometriosis. In order to develop a CBT protocol, we first performed a focus group study. In this focus group study we showed that patients who had been surgically treated for endometriosis expect that CBT could improve QoL and reduce pain[9]. Patients in this study were exclusively interested in face-to-face sessions (either in-person or using a videoconference) instead of web-based therapy without personal contact. Patients noted however, that web-based sessions could positively contribute to face-to-face CBT by providing a detailed overview of all the information already introduced in the face-to-face sessions. They also noted that the psychologist administering the CBT sessions should have knowledge about endometriosis and the problems that are experienced by patients in their daily lives. There was no clear consensus among participants of the focus groups about other aspects such as the amount and duration of CBT sessions. Patients did stress however that their symptoms should be taken seriously. They did acknowledge that living with endometriosis might eventually negatively affect mental wellbeing but emphasised that those problems are a result of the physical aspects of endometriosis.

Taking these findings into account, we developed a CBT protocol specifically aimed at improving QoL in patients undergoing surgical treatment due to endometriosis-associated pain. Patients will receive one pre-surgery and six post-surgery individual face-to-face sessions of CBT. Face-to-face therapy can be in-person therapy or therapy using a videoconference. The used method depends on the participants' choice or current restriction due to the COVID-19 pandemic. The pre-surgery session is always in-person and will take place approximately two weeks prior to surgery. The post-surgery sessions will start four weeks after surgery and take place every two weeks. All sessions will be coordinated by registered psychotherapists who are experienced in CBT and have knowledge about

endometriosis. The CBT protocol contains standardized information divided into separate sessions. Content of the CBT protocol is based on standard CBT interventions for chronic pain, supplemented with interventions aimed at specific issues present in endometriosis patients, as described below. In the pre-surgery session, the therapy is introduced and the influence of endometriosis complaints on the patient's life is assessed. To improve treatment compliance and cognitions with respect to complaints after surgery, expectations towards the psychological treatment and the operation will be managed. Furthermore, general psycho-education about pain is provided. In the six post-surgery sessions, psycho-education concerning the biological link between endometriosis-related pain and behaviour, as well as relaxation, relationship between emotions, thoughts and behavior, ways to change thoughts and regulate emotions and hypervigilance will be addressed. Additionally, one session is dedicated to discuss possible issues concerning intimacy and sexuality, which are often affected in patients diagnosed with endometriosis. In the final session patients will evaluate the therapy together with the psychologist. Relapse prevention will be discussed too. An overview of each session is provided in table 3.

All sessions have a fixed layout: each session begins with a brief introduction of the session. Next, the homework assignments from the previous session are discussed (except in the first session). Then the themes of that particular session are explained. Together, the patient and psychologist will execute assignments to support positive coping skills. Finally, the patient and psychologist will decide on one or more homework assignments that should be carried out in preparation for the next session before concluding the session by a brief evaluation. To assist the executing psychologists, each session in the CBT protocol provides examples of (homework) assignments that psychologists can complete together with patients. All sessions have a duration of 45 minutes, except the pre-surgical session which will take one hour. In addition to the sessions provided by a psychologist, an online module CBT is available containing general information about chronic pain. Patients in the CBT-group can use this online module freely to re-explore information already explained in the face-to-face sessions.

Data collection, management, analysis and monitoring

Data handling, storage and archiving

All information obtained is considered to be confidential information and will not be distributed to third parties. The research data will be stored pseudo-anonymously in a database. Each subject will be given a code, consisting of letters and a number (e.g. RST-ARNH-00001). The key linking this code to patient identity will be stored in a separate and secured file. Personal data will be handled in accordance with the Dutch General Data Protection Regulation. The research data will be stored for 15 years after finalization of the project. The data required for the trial will be entered by the investigation sites into electronic Case Report Forms. Detailed edit checks will ensure high quality standard of the data entered in the database. The principal investigator of each participating study site will assure that queries are resolved by the site on an ongoing basis. In the case of missing data, a comparison with the original source data will be performed in order to locate missing data. If we are unable to retrieve missing data, this will be represented by a symbol.

Statistical analysis

Statistical analysis will be performed, using SPSS software (version 27), after all data of each participant has been collected. The significance level has been established at 0.05. Descriptive statistics will be calculated for both groups. An interim analysis will not be performed.

To answer the primary question, whether adding CBT to usual post-surgery care significantly improves QoL, multivariate repeated measures MANOVA will be conducted with time (baseline

versus T1 and T2) as within-subjects variable, group (CBT versus usual care) as between-subjects variable and the QoL measures as dependent variables. If variability between subjects is larger than expected (for example due to missing data, non-normal residuals or a temporarily study halt because of the COVID-19 pandemic), a linear mixed model will be used instead of repeated measures MANOVA. An intention-to-treat analysis will be followed in the case of follow-up losses. Participants that have withdrawn from treatment will receive the same follow up as described above: they will be asked to fill in questionnaires and a hair sample will be collected at T1 and at T2.

Secondary endpoints will be analysed with computed mediation models using validated methods (using Hayes macro[24]). Briefly, regression models are calculated with the change in QoL as dependent variables (difference in QoL at baseline and T2), group (CBT versus usual care) as independent predictor, and pain cognition, pain intensity, fatigue and stress measurements as mediators. Here, we can answer the question to what extent improvements in pain cognitions, pain intensity, fatigue and stress levels underlie the anticipated positive effect of CBT on improvement in QoL in patients undergoing endometriosis surgery.

Data monitoring

A certified on-site monitor will conduct periodic monitoring visits with adequate frequency to ensure that obligations of participating sites are being fulfilled and that the facilities continue to be acceptable. All Serious Adverse Events (SAEs) will be reported to the METC after obtaining knowledge of the events. All Adverse Events (AEs) will be followed until they have abated, or until a stable situation has been reached. A summary of the progress of the trial will be submitted to the accredited METC once a year.

Premature termination of the study

The study can be terminated prematurely if there is evidence of an unacceptable risk for trial subjects, if there is reason to conclude that it is not feasible to collect the data necessary to reach the study objectives and it is therefore not ethical to continue, and in case of failure of the investigator and/or staff to follow either good clinical practice standards or to adhere to protocol requirements. The decision to end the trial prematurely will be made by de coordinating investigators in close collaboration with the principal investigator.

Ethics and dissemination

Ethics approval

The study protocol has been approved by the METC of the region Arnhem-Nijmegen from the Radboud University Medical Centre on September 2nd 2020. It has been registered on ClinicalTrails.gov with number NCT04448366 on June 3th 2020. Amendments, changes made to the research protocol after a primary favourable opinion by the accredited METC has been given, will be notified to the METC that gave the primary favourable opinion. After an amendment is approved, informed consent will be obtained from participants after receiving sufficient verbal and written information about the protocol amendments, when this is required by the METC. Participants will be asked consent to use collected data in ancillary studies.

Disclosure of interest

The authors have no conflict of interest to disclose.

Data access

Project Principal Investigators will have direct access to their own site's data sets, and will have access to other sites data by request. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

Ancillary and post-trial care

Patients that are enrolled in the study are covered by indemnity for negligent harm through the standard health insurance. Due to the used intervention the METC did not require the sponsor to take out additional insurance to cover non-negligent harm associated with the protocol. If patients wish to continue or start psychological treatment after the study had finished, they may be covered through the standard health insurance, depending on their health care assurance.

Public disclosure and publication policy

The findings of this study will be published in scientific journals and will be presented at scientific conferences. Authors that substantially contributed to the results of this study will be granted authorship. The research protocol, original dataset and statistical code will be available on request in accordance with the conditions of ethics approval. If participants wish, they will be notified of the findings when they are available.

Discussion

Patients suffering from endometriosis often have impaired QoL and severe chronic pain. Non-medical therapies including cognitive behavioural interventions have been widely used and proven effective in suppressing pain and pain-related problems in several chronic pain syndromes[6-8, 11, 25, 26]. In this study we aim to determine the efficacy of CBT to improve QoL in patients undergoing endometriosis surgery due to endometriosis-associated chronic pain. To our knowledge, this is the first research project investigating this.

To determine whether CBT is effective in improving QoL, participants will be randomized into two groups. The control group will receive surgery and care as usual, and the intervention group will additionally receive seven sessions of CBT.

Strengths and limitations

For this study a CBT protocol was developed by members of the research team consisting of gynaecologists experienced in treating women with endometriosis and of psychologists with experience in CBT, chronic pain and/or treating patients diagnosed with endometriosis. Importantly, patients' opinions on CBT were taken into account during development of the CBT protocol. By involving patients in the development of the CBT protocol we believe that the CBT protocol better meets the needs of this specific patient group. Using a fixed CBT protocol ensures that the intervention can be carried out congruently across all participating sites and by all executing psychologists. This minimizes differences in therapy. Moreover, frequent sessions of intervision between all executing psychologists will take place in order to address possible issues and queries in the execution of the CBT protocol. This will ensure in-between centre consistency and reduce variability even further. At the same time, room for individual adjustments is facilitated in the design of the CBT protocol in order to meet specific needs of individual patients.

It is important to note that CBT will be given to patients who will undergo another treatment for endometriosis: reduction surgery. One session of CBT will be scheduled before the surgical procedure, the other six will take place after surgery. Prior to surgery, patients with endometriosis-associated chronic pain have a physical explanation for the pain they experience since the endometriosis is still present at that time. After surgery, the endometriosis as cause for their pain will be removed but they may still suffer from chronic pain symptoms. At that moment, CBT may be effective in treating the psychological aspects of their chronic pain symptoms. Parrish et al.[27] showed in a recent systematic review and meta-analysis that CBT combined with lumbar-spine surgery improves QoL compared to usual care or an alternative therapy. Combining CBT with surgical

treatment will stress the importance of a combined intervention targeting both physical and psychological determinants of pain as well as its interaction and will support the idea that gynaecologists, psychologists and researchers take patients' symptoms seriously. In our opinion, this is an important strength of our study. Another strength is that we measure two indicators for stress: an assessment of self-reported stress measured by a questionnaire as well as an indicator for stress measured via cortisol extracted from hair. The scalpel hair cortisol measurement enables us to objectively quantify if CBT contributes to chronic stress present in participants.

The most important limitation of this study protocol is the difference in attention given by health care professionals to patients in the intervention and the control group. Because women in the intervention group will undergo seven sessions of CBT, they will get more attention from a health care professional as compared to women in the control group. More attention because of more contact time might lead to better QoL on itself. To compensate for this, we ideally would have added a third group of patients who would receive endometriosis-reduction surgery and seven non-therapeutic appointments with for example a nurse. However, this would have greatly increased the required number of participants, thereby increasing the costs of the study as well as the required time period for the inclusions. Because we aimed to compare usual care with the CBT intervention, we chose to investigate the two groups described in this protocol. It is important to stress that women in both the intervention as well as in the control group may contact their endometriosis nurse as often as they need for support or for answering questions.

Another limitation is that due to the used intervention, we are only able to blind accessors and gynaecologists performing the operation for treatment allocation. Psychologists performing the intervention and, more importantly, participants cannot be blinded which can introduce bias.

Finally, presence or absence of motivation to undergo CBT may bias the results of this study. From motivational interviewing[28] it is known that motivation to undergo psychological therapy can influence treatment results. In our study, prior to randomization we will measure patients' motivation to undergo psychological treatment. After finishing the treatment, we will analyse whether there were in-between group differences with respect to group allocation preference and disappointment as well as motivation to undergo cognitive behavioural treatment.

Clinical implications

Depending on the outcome of our study, advice will be provided whether CBT should be added to the treatment of patients undergoing endometriosis reduction surgery. If this study shows a positive result, patients may have an additional treatment options to improve the quality of their daily lives. Results of this study could moreover pave the road to fund more clinical trials and cost-effectiveness studies on the use of CBT in patients diagnosed with endometriosis specifically and chronic pain conditions in general.

Administrative information

Trial acronym

COGENS

Trial registration

ClinicalTrials.gov NCT04448366. Registered on June 3th, 2020.

Current protocol version

8 (1-6-2021)

Trial sponsor
Rijnstate Hospital
Address: Wagnerlaan 55, 6815 AD, Arnhem, The Netherlands
Telephone: +31 088 005 8888
Website: www.rijnstate.nl

Funding
This work was supported by the Radboudumc-Rijnstate PhD funding, grant number W.000003.1. This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Author contributions
AN conceived the study. CV, DB, JO and AN initiated the study design and ZB helped with implementation. CV and AN are grant holders. JO provided statistical expertise in the clinical trial design. EH, HD, CL and AS helped develop the CBT protocol. All authors contributed to refinement of the study protocol, revised different versions of the manuscript and approved the final manuscript.

Roles and responsibilities
Principal investigator and research physician:

- Design and conduct of COGENS
- Preparation of protocols and revisions
- Preparation of CRFs
- Reviewing progress of study and if necessary agreeing changes to the protocol to facilitate the smooth running of the study
- (S)AEs reporting to Medical Ethical Committee
- Responsible for trial master file
- Budget administration and contractual issues with individual centres
- Data verification

Lead investigators:
In each participating centre a lead investigator will be identified, to be responsible for identification, recruitment, randomisation, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol.

Acknowledgements
Not applicable.

Availability of data and materials
Not applicable.

References

1. Giudice LC, Kao LC. Endometriosis. Lancet. 2004;364(9447):1789-99.
2. Vercellini P, Crosignani PG, Abbiati A, Somigliana E, Viganò P, Fedele L. The effect of surgery for symptomatic endometriosis: the other side of the story. Hum Reprod Update. 2009;15(2):177-88.
3. van Aken M, Oosterman J, van Rijn T, Kozicz T, Aalders K, Witteman B, et al. The effect of endometriosis surgery on biopsychosocial correlates of pain. Submitted. 2019.
4. van Aken MAW, Oosterman JM, van Rijn CM, Ferdek MA, Ruigt GSF, Peeters B, et al. Pain cognition versus pain intensity in patients with endometriosis: toward personalized treatment. Fertil Steril. 2017;108(4):679-86.

5. Olatunji B, Hollon S. Preface: The Current Status of Cognitive Behavioral Therapy for Psychiatric Disorders. The Psychiatric clinics of North America. 2010;33:xiii-xix.
6. Richmond H, Hall AM, Copsey B, Hansen Z, Williamson E, Hoxey-Thomas N, et al. The Effectiveness of Cognitive Behavioural Treatment for Non-Specific Low Back Pain: A Systematic Review and Meta-Analysis. PLoS One. 2015;10(8):e0134192.
7. Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. Am Psychol. 2014;69(2):153-66.
8. Wang L, Chang Y, Kennedy SA, Hong PJ, Chow N, Couban RJ, et al. Perioperative psychotherapy for persistent post-surgical pain and physical impairment: a meta-analysis of randomised trials. Br J Anaesth. 2018;120(6):1304-14.
9. Boersen Z, de Kok LM, van der Zanden M, Oosterman JM, Nap AW. Patients' perspective on cognitive behavioural therapy after surgical treatment of endometriosis: a qualitative study. Reprod Biomed Online. 2021.
10. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. 2013;346:e7586.
11. Archer KR, Devin CJ, Vanston SW, Koyama T, Phillips SE, Mathis SL, et al. Cognitive-Behavioral-Based Physical Therapy for Patients With Chronic Pain Undergoing Lumbar Spine Surgery: A Randomized Controlled Trial. J Pain. 2016;17(1):76-89.
12. Karekla M, Konstantinou P, Ioannou M, Kareklas I, Gloster AT. The Phenomenon of Treatment Dropout, Reasons and Moderators in Acceptance and Commitment Therapy and Other Active Treatments: A Meta-Analytic Review. Clinical Psychology in Europe. 2019;1(3):1-36.
13. Fernandez E, Salem D, Swift J, Ramtahal N. Meta-Analysis of Dropout From Cognitive Behavioral Therapy: Magnitude, Timing, and Moderators. J Consult Clin Psychol. 2015;83.
14. Organization WH. International Statistical Classification of Diseases and Related Health Problems (ICD) World Health Organization2020 [Available from: https://www.who.int/classifications/classification-of-diseases.
15. Hart VA. Infertility and the role of psychotherapy. Issues Ment Health Nurs. 2002;23(1):31-41.
16. Chachamovich JR, Chachamovich E, Ezer H, Fleck MP, Knauth D, Passos EP. Investigating quality of life and health-related quality of life in infertility: a systematic review. Journal of Psychosomatic Obstetrics & Gynecology. 2010;31(2):101-10.
17. Rapaport MH, Clary C, Fayyad R, Endicott J. Quality-of-Life Impairment in Depressive and Anxiety Disorders. 2005;162(6):1171-8.
18. Association AP. Diagnostic and Statistical Manual of Mental Disorders: Dsm-5: Amer Psychiatric Pub Incorporated; 2013.
19. van de Burgt TJ, Hendriks JC, Kluivers KB. Quality of life in endometriosis: evaluation of the Dutch-version Endometriosis Health Profile-30 (EHP-30). Fertil Steril. 2011;95(5):1863-5.
20. Jones G, Jenkinson C, Kennedy S. Evaluating the responsiveness of the Endometriosis Health Profile Questionnaire: the EHP-30. Qual Life Res. 2004;13(3):705-13.
21. van der Zee K, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36. Noordelijk Centrum voor Gezondheidsvraagstukken, reeks meetinstrumenten. 1993;3:1-28.
22. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull. 2004;130(4):601-30.
23. van Aken M, Oosterman J, van Rijn T, Ferdek M, Ruigt G, Kozicz T, et al. Hair cortisol and the relationship with chronic pain and quality of life in endometriosis patients. Psychoneuroendocrinology. 2018;89:216-22.
24. Hayes AF. Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. New York, NY, US: Guilford Press; 2013. xvii, 507-xvii, p.
25. Evans S, Fernandez S, Olive L, Payne LA, Mikocka-Walus A. Psychological and mind-body interventions for endometriosis: A systematic review. J Psychosom Res. 2019;124:109756.

26. Till SR, Wahl HN, As-Sanie S. The role of nonpharmacologic therapies in management of chronic pelvic pain: what to do when surgery fails. Current opinion in obstetrics & gynecology. 2017;29(4):231-9.

27. Parrish JM, Jenkins NW, Parrish MS, Cha EDK, Lynch CP, Massel DH, et al. The influence of cognitive behavioral therapy on lumbar spine surgery outcomes: a systematic review and meta-analysis. Eur Spine J. 2021.

28. Miller WR, Rollnick S. Motivational interviewing: Helping people change: Guilford press; 2012.

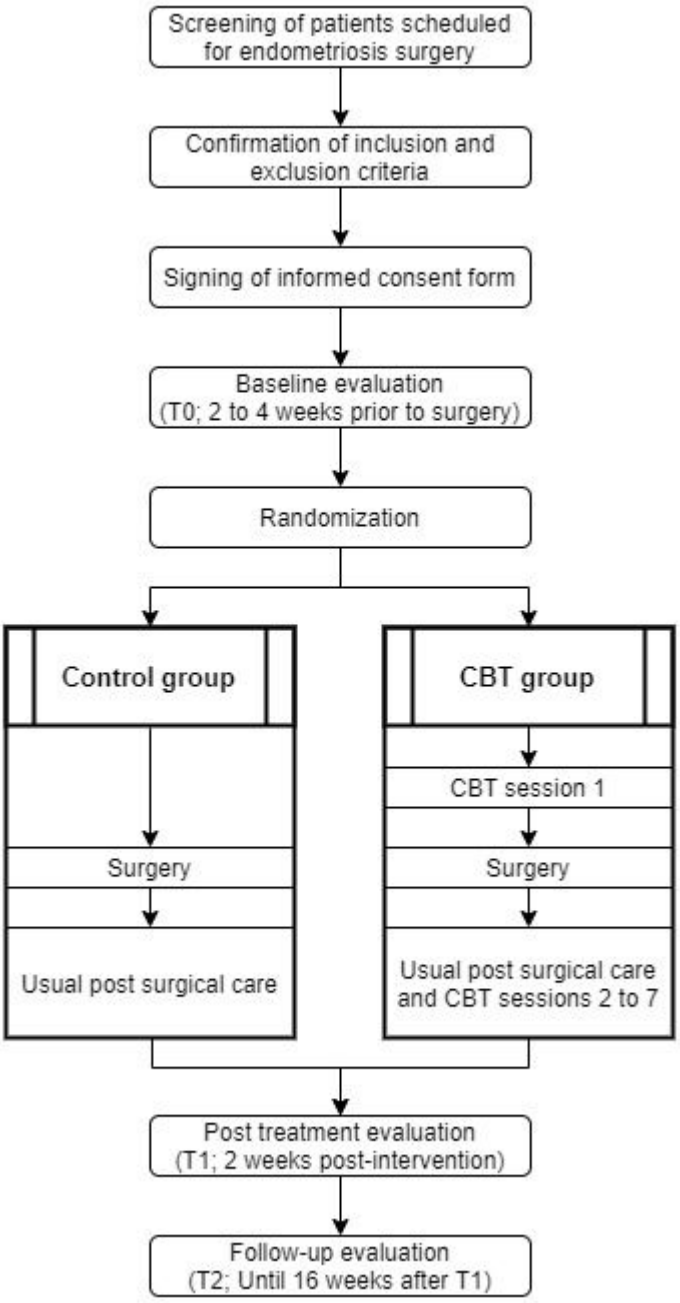


Figure 1: Patient flow throughout the study

Variable	Values
Age	Years
Length	Centimetres
Weight	Kilograms
BMI	Kg/m^2
Marital status	Single/Married or living with partner/Widow/Separated
Educational attainment	Non-categorical text
Occupation	Student/Employee/Housewife/Unable to work/Unemployed
Method used to diagnose endometriosis	Ultrasound/MRI/Surgery
Year of diagnosis	Year
r-ASRM classification	I - IV
Type of endometriosis	Ovarian/Peritoneal/Deep
Use of analgesics	Yes (specify)/No
Contraception use	Yes (specify)/No
Use of other medications	Yes (specify)/No
Subfertility	Yes/No
Parity	Numerical
History of DSM-V diagnosis	Yes (specify)/No
Underwent psychological treatment prior to inclusion	Yes (specify)/No

Table 1: Sociodemographic variables. BMI=Body Mass Index; r-ASRM = revised American Society for Reproductive Medicine; DSM-V = Diagnostic and Statistical Manual of Mental Disorders V.

Outcome variable	Evaluation period			Measuring instrument
	T0	T1	T2	
QoL[1]	×	×	×	EHP-30 and RAND-36
Pain intensity[2]	×	×	×	NRS
Pain anxiety[2]	×	×	×	PASS
Catastrophizing[2]	×	×	×	PCS
Fatigue[2]	×	×	×	CIS
Subjective stress[2]	×	×	×	PSS
Marker for physiological stress[2]	×	×	×	Hair cortisol analysis

Table 1: Outcome variables. [1]Primary endpoint; [2]Secondary endpoint. QoL = Quality of Life; EHP-30 = Endometriosis Health Profile 30; RAND-36 = Short form 36; NRS = Numerical Rating Scale; PASS = Pain Anxiety Symptom Scale; PCS = Pain Catastrophizing Scale; CIS = Checklist Individual Strength ; PSS = Perceived Stress Scale

Session	Themes to be discussed	**Time period related to surgery** (weeks)	**Duration of sessions** (min)
1	- Therapeutic compliance and expectation towards therapy - Effects of endometriosis on patient's life - Expectations towards effect of surgery - General pain-education	-2	60
2	- Setting goals for therapy - The biological link between pain and behaviour - Relaxation	4	45
3	- The biological link between pain and emotion	6	45
4	- The biological link between pain and thoughts - Negative automatic thoughts	8	45
5	- Hypervigilance towards pain	10	45
6	- Intimacy and sexuality	12	45
7	- Evaluation of therapy - Relapse prevention	14	45

Table 1: Overview of cognitive behavioural therapy content

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	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,	9

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	9
Protocol version	#3	Date and version identifier	9
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	9
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	9
Roles and responsibilities: sponsor and funder	#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	9
Roles and responsibilities: committees	#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)	9 and 10

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	3, 4 and 7

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5 and 6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5 and 6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4 and 5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	3

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	3
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	3, 4
Methods: Assignment of interventions (for controlled trials)			
Allocation: 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	4
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	4
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4
Methods: Data collection, management, and analysis			
Data collection plan	#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	7 and 9
Data collection plan: retention	#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	6
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	6

		(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	
Statistics: outcomes	#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	6 and 7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6 and 7
Statistics: analysis population and missing data	#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)	6 and 7
Methods: Monitoring			
Data monitoring: formal committee	#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	7
Data monitoring: interim analysis	#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	6
Harms	#22	Plans for collecting, assessing, reporting, and managing	7

		solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
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)	7
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	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	6

		trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
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	7
Dissemination policy: trial results	#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	8
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a

	biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

BMJ Open

Determining the effectiveness of cognitive behavioural therapy in improving quality of life in patients undergoing endometriosis surgery: a study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054896.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Nov-2021
Complete List of Authors:	Boersen, Zoë; Hospital Rijnstate Arnhem, Department of Obstetrics and Gynaecology Oosterman, Joukje; Radboud University Donders Institute for Brain Cognition and Behaviour Hameleers, Esther; Hospital Rijnstate Arnhem, Department of Medical Psychology Delcliseur, Heidi; Ziekenhuis Rijnstate Arnhem, Department of Medical Psychology Lutters, Cobie; Medisch Centrum Haaglanden, Endometriose in Balans IJssel de Schepper, Alicia; Radboudumc, Department of Medical Psychology Braat, Didi; Radboudumc Department of Obstetrics and Gynecology Verhaak, Christianne; Radboudumc, Department of Medical Psychology Nap, Annemiek; Radboudumc Department of Obstetrics and Gynecology
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Surgery
Keywords:	SURGERY, GYNAECOLOGY, PAIN MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Determining the effectiveness of cognitive behavioural therapy in improving quality of life in patients undergoing endometriosis surgery: a study protocol for a randomized controlled trial

Z. Boersen[1]* (MD), J.M. Oosterman[2] (PhD), E.G. Hameleers[3] (MSc), H.S.M.J Delcliseur[3] (MSc), C.E.T. Lutters[4] (MSc), K.A. IJssel de Schepper[5] (MSc), D.D.M. Braat[6] (MD; PhD), C.M. Verhaak[5] (PhD), A.W. Nap[6] (MD; PhD)

[1]Department of Gynaecology and Obstetrics, Rijnstate, Arnhem, The Netherlands

[2]Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands

[3]Department of Medical Psychology, Rijnstate, Arnhem, The Netherlands

[4]Endometriose in Balans, Haaglanden Medisch Centrum, Den Haag, The Netherlands

[5]Department of Medical Psychology, Radboud University Medical Centre, Nijmegen, The Netherlands

[6]Department of Obstetrics and Gynaecology, Radboud University Medical Centre, Radboud University, Nijmegen, The Netherlands

*Corresponding author:
Zoë Boersen
Wagnerlaan 55, 6815 AD Arnhem.
Gelderland, The Netherlands
zboersen@rijnstate.nl

Word count: 4883

Abstract

Introduction: Endometriosis can cause chronic pain and subfertility thereby negatively affecting Quality of Life (QoL). Surgical removal of endometriosis lesions leads to improved Health Related QoL, although not to the level of QoL of healthy controls. Pain intensity and cognitions regarding pain can play a crucial role in this Health Related QoL following surgical treatment. Cognitive behavioural therapy (CBT) is a psychological treatment. In patients with chronic pain caused by a variety of medical conditions, CBT is effective in improving QoL. We designed a research protocol to investigate the effect of CBT on QoL in patients with endometriosis-associated chronic pain who are undergoing surgery.

Methods and analysis: This is a study protocol for a randomized controlled trial in which 100 patients, undergoing endometriosis removal surgery due to endometriosis-associated chronic pain, will be randomized between post-surgery usual care with CBT and post-surgery usual care only. Participants in the CBT group will additionally receive seven sessions of CBT, focused on expectancy management, cognitions regarding pain, and emotional and behavioural impact of pain. To determine the primary outcome Quality of life, both groups will complete questionnaires assessing QoL. The secondary outcomes pain intensity, pain cognitions, fatigue and perceived stress are also measured using questionnaires. Additionally, a marker for stress (cortisol extracted from a hair sample) will be assessed at T0 (baseline assessment), T1 (post-intervention; two weeks after completion of all CBT sessions) and T2 (follow-up; 14 weeks after T1). Statistical analysis will be performed using SPSS software.

Ethics and dissemination: The study protocol has been approved by the Medical Ethical Committee of the region Arnhem-Nijmegen from the Radboud University Medical Centre on September 2nd 2020. The findings of this study will be published in scientific journals and will be presented at scientific conferences.

Article summary

Strengths and limitations of this study

- A cognitive behavioural therapy protocol was developed specifically for this patient group to be used as intervention.
- Patients are treated with cognitive behavioural therapy in addition to endometriosis reduction surgery.
- There is a difference in contact time between therapists and patients in the intervention versus the control group.
- Participants are not blinded for group allocation which could lead to bias.

Keywords: surgery, gynaecology, pain management

INTRODUCTION

Endometriosis, the presence of functioning endometrium-like tissue outside the uterine cavity, is one of the most prevalent benign gynaecologic conditions[1]. It can cause chronic pain and subfertility and can lead to impaired Quality of Life (QoL). Although medical therapy can halt disease activity, surgical removal of endometriosis is often required. Unfortunately, pain symptoms remain present in approximately 50 percent of the patients after surgery[2]. Moreover, the level of Health Related QoL remains lower compared to the QoL of healthy controls[3]. Van Aken et al[4]. showed that pain intensity and pain cognitions including pain anxiety, catastrophizing and hypervigilance towards pain are all independent factors contributing to Health Related QoL in patients diagnosed with endometriosis. This indicates that modifying these cognitions via psychological intervention might improve QoL in endometriosis patients. Cognitive behavioural therapy (CBT) is an evidence-based psychological treatment and is increasingly being recognized as an effective treatment to improve QoL in patients with various medical conditions[5]. CBT uses a process called cognitive restructuring: a technique designed to teach patients how to identify, evaluate and relabel maladaptive thoughts, evaluations or beliefs that are suspected to be the root cause of one's psychological disturbance[6, 7]. Cognitive restructuring should result in a more rational, realistic and balanced view of those unhelpful thoughts, evaluations or beliefs. The patient is furthermore expected to contribute to her own treatment process. This can be done by questioning maladaptive thoughts and behaviours about situations and by exposing herself to those situations to evaluate whether those thoughts and beliefs have come true. The therapist helps the patient to achieve treatment goals by sharing his expertise and support. This approach is named collaborative empiricism and is a key feature of CBT. It aims to result in the patient attributing her behavioural change to her own efforts leading to better and more persistent outcomes[6, 7]. To date, there are no studies available that describe the efficacy of post-surgical CBT to improve QoL in patients diagnosed with endometriosis. CBT has been used and proven effective in improving QoL and decreasing perceived pain intensity in other chronic pain conditions[8-10]. We have recently shown that patients undergoing endometriosis surgery believe that CBT could be a valuable asset to their treatment, in order to improve QoL[11]. We designed this research protocol for a randomized controlled trial to investigate the efficacy of CBT on improving QoL in patients with endometriosis-associated pain in addition to endometriosis removal surgery.

METHODS

Participants, interventions, outcomes and intervention allocation

Study design

This is a research protocol for a randomized, controlled, prospective, single-blind (assessor) clinical trial in which patients undergoing surgery for endometriosis-related pain will be randomly allocated to surgery and usual care (control group) or to surgery and usual care plus CBT (CBT group). The participants and the psychologists delivering the intervention cannot be blinded due to the used intervention. Figure 1 shows an overview of patient flow throughout the study. This protocol was developed in accordance with the SPIRIT reporting guidelines[12].

Patient involvement

In 2019 and 2020, prior to developing this study protocol, we conducted a focus group study with patients who underwent endometriosis surgery to investigate if they were interested in psychological therapy in order to improve QoL in addition to endometriosis surgery and why[11]. We furthermore explored how they would design such a psychological treatment. The information acquired in these focus groups was taken into account when designing the intervention used in this research protocol.

Sample size calculation

The calculation for the required sample size was performed for the primary endpoint QoL. There was no study available describing the effect size of CBT on QoL after endometriosis surgery which could be used in the sample size calculation. Therefore, we used a study in which the authors examine a cognitive behavioural intervention to improve QoL in patients undergoing surgery due to chronic back pain[13]. Based on this article we expect to find medium to large effect sizes (Cohen's *d*) of 0.75 and 1.35 (measured with the physical and mental component scales of the 12-Item Short-Form Health Survey) of postoperative CBT compared to usual care-only on QoL regarding physical and mental health, respectively. Based on literature we expect the dropout rate to be 15 to 16 percent[14, 15]. However, due to the intensity of the intended intervention combined with surgery we anticipating patient dropout to be higher: 19 percent. Therefore, a total of 100 patients should be included to detect significant effects ($\alpha = 0.05$, power $(1-\beta) = 0.85$).

Study population and recruitment

At the start of the study, subjects will be recruited in Rijnstate Hospital, Radboud University Medical Center and Catharina Hospital, all located in the Netherlands. In all hospitals, a multi-disciplinary centre for diagnosis and treatment of endometriosis is present, in which gynaecologists, surgeons and psychologists with extensive experience in treating women with endometriosis are involved. All centres are located in urban areas. All patients undergoing endometriosis removal surgery due to endometriosis-associated chronic pain will be referred by their gynaecologist to a researcher who will check whether they meet the inclusion criteria. Patients are eligible for this study when they are 18 to 50 years of age, diagnosed with endometriosis (proven by ultrasound, MRI or surgery) and have an indication for endometriosis surgery due to endometriosis-related chronic pain. An indication for surgery is present when hormonal and/or analgesic therapy failed in suppressing pain symptoms, is contra indicated due to comorbidity or has unacceptable side effects. Chronic pain is defined as pain existing longer than three months (in accordance with the ICD-11 formulated by the World Health Organization[16]), with an average Numerical Rating Scale (NRS) of four or higher in the month prior to inclusion (which will be asked at inclusion). Furthermore, participants should be able to read and write Dutch in order to be able to complete the questionnaires.

Because certain conditions require a different psychological approach[4, 17-19], and therefore could influence the efficacy of the intervention used in this study, we exclude patients suffering from endometriosis-related infertility without pain, chronic pain that can be attributed to other diseases or syndromes, patients that are diagnosed by a psychiatrist or psychologist with a mood, anxiety or personality disorder (as defined by the DSM-V[20]), are undergoing psychological therapy or use psychopharmacologic medication aimed at altering mood (according to either patient or their physician) at the moment of inclusion. Because we will also assess cortisol levels in scalp hair, patients will also be excluded if they have scalp hair shorter than four centimeters.

Patients eligible for inclusion will be provided with detailed written and verbal information. Informed consent will be obtained by an authorized researcher if patients are willing to participate and all questions have been resolved. Patients can contact an independent researcher if they wish to discuss the study with someone who is not directly involved in the project but has knowledge about all aspects of this study. Participants can withdraw consent at any time without providing a reason.

Randomization

Computerized randomization will be conducted after inclusion and baseline assessment. Only an authorized researcher will be able to perform randomization and have insight in randomization results. No stratification factors will be used. This study is single blinded (the assessor is blinded for treatment allocation). Participants and psychological therapists cannot be blinded due to the used intervention. The randomization code will be broken when a patient's health is at risk or when investigation is required by the sponsor, the Medical Ethics Committee (METC) or the monitor, for example to verify if the study is executed in accordance with the study protocol and national and international regulations.

Variables

Demographic variables will be recorded, including age, length, weight, BMI, marital status, educational attainment, occupation, the method used to diagnose endometriosis, year of diagnosis, r-ASRM classification, type of endometriosis, use of contraception, use of analgesics, use of other medications, presence of subfertility, parity, history of DSM-V diagnosis and if patients underwent psychological treatment prior to inclusion in this study. An overview of these variables, including their corresponding values, is provided in table 1.

Variable	Values
Age	Years
Length	Centimetres
Weight	Kilograms
BMI	Kg/m^2
Marital status	Single/Married or living with partner/Widow/Separated
Educational attainment	Non-categorical text
Occupation	Student/Employee/Housewife/Unable to work/Unemployed
Method used to diagnose endometriosis	Ultrasound/MRI/Surgery
Year of diagnosis	Year
r-ASRM classification	I - IV
Type of endometriosis	Ovarian/Peritoneal/Deep

Use of analgesics	Yes (specify)/No
Contraception use	Yes (specify)/No
Use of other medications	Yes (specify)/No
Subfertility	Yes/No
Parity	Numerical
History of DSM-V diagnosis	Yes (specify)/No
Underwent psychological treatment prior to inclusion	Yes (specify)/No

Table 1: Sociodemographic variables. BMI=Body Mass Index; r-ASRM = revised American Society for Reproductive Medicine; DSM-V = Diagnostic and Statistical Manual of Mental Disorders V

The primary endpoint in this study is QoL. In our opinion evaluating this outcome, that reflects an improvement that patients themselves experience in their daily lives, should have priority over other measurements (for example pain score, lab results or absence of endometriosis lesions) that do not. QoL will be measured by two questionnaires: a general QoL questionnaire, the Dutch version of the Short Form 36 (RAND-36), and an endometriosis disease specific questionnaire, the Endometriosis Health Profile 30 (EHP-30). Both questionnaires measure QoL but do so differently. The EHP-30 is a disease-specific QoL questionnaire which is validated for use in endometriosis patients[21, 22] and measures the impact of the disease on physical, mental and social aspects of life. The questionnaire is divided into two parts. The core questionnaire consists of five subscales: pain, control and powerlessness, emotional well-being, social support, and self-image. The second part consists of six subscales: work, relationship with children, sexual intercourse, infertility, medical profession and treatment. Raw scores are transformed to a scale ranging from 0 to 100, and a higher score corresponds with worse QoL. The validated[23] questionnaire RAND-36 is used to measure general QoL. It is a multipurpose, general health survey which is applied to measure QoL on nine different domains: physical functioning, social functioning, role limitations due to physical health, role limitations due to emotional problems, emotional well-being, vitality, pain, general health, and health change. Raw scores are transformed to a scale ranging from 0 to 100, and a higher score corresponds with better QoL. The EHP-30 is a sensitive tool which is responsive to changes in Health Related QoL in this specific patient group[22] while the RAND-36 provides a complete QoL assessment which can be compared more easily with QoL of patients with other illnesses or healthy people.

Secondary endpoints are pain intensity, fatigue, pain related cognitions including anxiety and catastrophizing, perceived stress, and cortisol level as a marker for stress. Pain related cognitions have shown to be independent factors contributing to the Health Related QoL of endometriosis patients[4], therefore it interesting to determine whether CBT influences these cognitions as well. Pain intensity is measured by the NRS, pain anxiety by the Pain Anxiety Symptom Scale (PASS), catastrophizing by the Pain Catastrophizing Scale (PCS). Additionally, fatigue is measured using the Checklist Individual Strength (CIS). Indicators for stress will be measured in two ways. First, perceived stress is measured by the Perceived Stress Scale (PSS) questionnaire which measures self-reported stress levels in patients. In addition to perceived stress, stress can also trigger a response leading to an activation of the hypothalamus-pituitary-adrenal axis. Activation of this axis leads to the secretion of cortisol by the

adrenal cortex. Cortisol modulates the immune system[24] and is therefore essential for proper body and brain function in response to stress. Cortisol levels can be used as an indicator for the amount of stress. To date, cortisol levels are measured in saliva, serum or urine, representing a dynamic reflection of cortisol concentrations and stress reactivity at one single point in time. These types of measurements are easily affected by short term changes of cortisol including the circadian rhythm or situational stress and are therefore less reliable to use as an indicator for chronic stress, which is present in patients with chronic pain including endometriosis. In order to use cortisol as a marker for chronic stress, it should be measured in another body specimen. Since recently, cortisol can be extracted from hair. Hair has an average growth rate of 1 cm/month and evidence of long term stress exposure can be analyzed in a string of hair. This makes hair cortisol a useful biomarker for chronic stress. In an earlier prospective follow-up study, researchers showed that hair cortisol levels are higher in endometriosis patients as compared to healthy controls, and that hair cortisol levels correlate with QoL[25].

All primary and secondary outcomes will be measured at baseline (T0) between two and four weeks prior to surgery, post-intervention (T1) approximately two weeks after completion of all CBT sessions and at follow-up (T2) approximately 14 weeks after T1. An overview of all outcome variables is provided in table 2. All questionnaires will be sent and returned through a web-based platform. The collection of the hair sample for cortisol measurements will be conducted by authorized and trained researchers. Analysis of the hair samples will be performed by a certified laboratory experienced in extracting cortisol from hair samples.

Outcome variable	Evaluation period			Measuring instrument
	T0	T1	T2	
QoL[1]	×	×	×	EHP-30 and RAND-36
Pain intensity[2]	×	×	×	NRS
Pain anxiety[2]	×	×	×	PASS
Catastrophizing[2]	×	×	×	PCS
Fatigue[2]	×	×	×	CIS
Subjective stress[2]	×	×	×	PSS
Marker for physiological stress[2]	×	×	×	Hair cortisol analysis

Table 2: Outcome variables. [1]Primary endpoint; [2]Secondary endpoint. QoL = Quality of Life; EHP-30 = Endometriosis Health Profile 30; RAND-36 = Short form 36; NRS = Numerical Rating Scale; PASS = Pain Anxiety Symptom Scale; PCS = Pain Catastrophizing Scale; CIS = Checklist Individual Strength ; PSS = Perceived Stress Scale

Intervention

Control group

The control group will receive usual care. Usual care consists of pre-surgical counseling by the participant's gynaecologist about the intended surgical procedure, possible complications and expected results. When indicated, patients will consult a gastro-intestinal surgeon and/or a urologist from the endometriosis team. Surgery will be carried out, following medical standards, by members of a team of gynaecologists and, if indicated, together with gastro-intestinal surgeons and/or urologists. Before and

after surgery, patients will take their usual hormonal therapy to minimize menstrual cycle effects. Patients are allowed to use analgesics if necessary, but are asked to refrain from seeking (additional) psychological treatment when participating in this study. Patients will receive medical check-ups after approximately six weeks, three and six months post-surgery, consisting of history taking (in which symptoms and postoperative recovery will be assessed) and physical examination. They can contact the endometriosis nurse by e-mail or phone at any time.

CBT group

In addition to the usual care as described above, patients in the intervention group will also undergo seven sessions of CBT. Therefore, a CBT protocol was developed by members of the research team consisting of gynaecologists experienced in treating women with endometriosis and of psychologists with experience in CBT, chronic pain and/or treating patients diagnosed with endometriosis. In order to develop a CBT protocol, we first performed a focus group study. In this focus group study we showed that patients who had been surgically treated for endometriosis expect that CBT could improve QoL and reduce pain[11]. Patients in this study were exclusively interested in face-to-face sessions (either in-person or using a videoconference) instead of web-based therapy without personal contact. Patients noted however, that web-based sessions could positively contribute to face-to-face CBT by providing a detailed overview of all the information already introduced in the face-to-face sessions. They also noted that the psychologist administering the CBT sessions should have knowledge about endometriosis and the problems that are experienced by patients in their daily lives. There was no clear consensus among participants of the focus groups about other aspects such as the amount and duration of CBT sessions. Patients did stress however that their symptoms should be taken seriously. They did acknowledge that living with endometriosis might eventually negatively affect mental wellbeing but emphasised that those problems are a result of the physical aspects of endometriosis.

Taking these findings into account, we developed a CBT protocol specifically aimed at improving QoL in patients undergoing surgical treatment due to endometriosis-associated pain. Patients will receive one pre-surgery and six post-surgery individual face-to-face sessions of CBT. Face-to-face therapy can be in-person therapy or therapy using a videoconference. The used method depends on the participants' choice or current restriction due to the COVID-19 pandemic. The pre-surgery session is always in-person and will take place approximately two weeks prior to surgery. The post-surgery sessions will start four weeks after surgery and take place every two weeks. All sessions will be coordinated by registered psychologist (meaning at least two years additional post master education) who are experienced in CBT and have knowledge about endometriosis. The CBT protocol contains standardized information divided into separate sessions. Content of the CBT protocol is based on standard CBT interventions for chronic pain, supplemented with interventions aimed at specific issues present in endometriosis patients, as described below. In the pre-surgery session, the therapy is introduced and the influence of endometriosis complaints on the patient's life is assessed. To improve treatment compliance and cognitions with respect to complaints after surgery, expectations towards the psychological treatment and the operation will be managed. Furthermore, general psycho-education about pain is provided. In the six post-surgery sessions, psycho-education concerning the biological link between endometriosis-related pain and behaviour, as well as relaxation, relationship between emotions, thoughts and behavior, ways to change thoughts and regulate emotions and hypervigilance will be addressed. Additionally, one session is dedicated to discuss possible issues concerning intimacy and sexuality, which are often affected in patients diagnosed with endometriosis. In the final session patients will evaluate

the therapy together with the psychologist. Relapse prevention will be discussed too. An overview of each session is provided in table 3.

Session	Themes to be discussed	Time period related to surgery (weeks)	Duration of sessions (min)
1	- Therapeutic compliance and expectation towards therapy - Effects of endometriosis on patient's life - Expectations towards effect of surgery - General pain-education	-2	60
2	- Setting goals for therapy - The biological link between pain and behaviour - Relaxation	4	45
3	- The biological link between pain and emotion	6	45
4	- The biological link between pain and thoughts - Negative automatic thoughts	8	45
5	- Hypervigilance towards pain	10	45
6	- Intimacy and sexuality	12	45
7	- Evaluation of therapy - Relapse prevention	14	45

Table 2: Overview of cognitive behavioural therapy content

All sessions have a fixed layout: each session begins with a brief introduction of the session. Next, the homework assignments from the previous session are discussed (except in the first session). Then the themes of that particular session are explained. Together, the patient and psychologist will execute assignments to support positive coping skills. Finally, the patient and psychologist will decide on one or more homework assignments that should be carried out in preparation for the next session before concluding the session by a brief evaluation. To assist the executing psychologists, each session in the CBT protocol provides examples of (homework) assignments that psychologists can complete together with patients. All sessions have a duration of 45 minutes, except the pre-surgical session which will take one hour. In addition to the sessions provided by a psychologist, an online module CBT is available containing psycho-education about general chronic pain. It furthermore has chapters on pain and behavior, emotion, thoughts and attention. There are also assignments that participants can complete. Patients in the CBT-group can use this online module freely to re-explore information already explained in the face-to-face sessions.

Data collection, management, analysis and monitoring

Data handling, storage and archiving

All information obtained is considered to be confidential information and will not be distributed to third parties. The research data will be stored pseudo-anonymously in a database. Each subject will be given a code, consisting of letters and a number (e.g. RST-ARNH-00001). The key linking this code to patient identity will be stored in a separate and secured file. Personal data will be handled in accordance with the Dutch General Data Protection Regulation. The research data will be stored for 15 years after finalization of the project. The data required for the trial will be entered by the investigation sites into electronic Case Report Forms. Detailed edit checks will ensure high quality standard of the data entered in the database. The principal investigator of each participating study site will assure that queries are resolved by the site on an ongoing basis. In the case of missing data, a comparison with the original source data will be performed in order to locate missing data. If we are unable to retrieve missing data, this will be represented by a symbol.

Statistical analysis

Statistical analysis will be performed, using SPSS software (version 27), after all data of each participant has been collected. The significance level has been established at 0.05. Descriptive statistics will be calculated for both groups. An interim analysis will not be performed.

To answer the primary question, whether adding CBT to usual post-surgery care significantly improves QoL, multivariate repeated measures MANOVA will be conducted with time (baseline versus T1 and T2) as within-subjects variable, group (CBT versus usual care) as between-subjects variable and the QoL measures as dependent variables. If variability between subjects is larger than expected (for example due to missing data, non-normal residuals or a temporarily study halt because of the COVID-19 pandemic), a linear mixed model will be used instead of repeated measures MANOVA. An intention-to-treat analysis will be followed in the case of follow-up losses. Participants that have withdrawn from treatment will receive the same follow up as described above: they will be asked to fill in questionnaires and a hair sample will be collected at T1 and at T2.

Secondary endpoints will be analysed with computed mediation models using validated methods (using Hayes macro[26]). Briefly, regression models are calculated with the change in QoL as dependent variables (difference in QoL at baseline and T2), group (CBT versus usual care) as independent predictor, and pain cognition, pain intensity, fatigue and stress measurements as mediators. Here, we can answer the question to what extent improvements in pain cognitions, pain intensity, fatigue and stress levels underlie the anticipated positive effect of CBT on improvement in QoL in patients undergoing endometriosis surgery.

Data monitoring

A certified on-site monitor will conduct periodic monitoring visits with adequate frequency to ensure that obligations of participating sites are being fulfilled and that the facilities continue to be acceptable. All Serious Adverse Events (SAEs) will be reported to the METC after obtaining knowledge of the events. All Adverse Events (AEs) will be followed until they have abated, or until a stable situation has been reached. A summary of the progress of the trial will be submitted to the accredited METC once a year.

Premature termination of the study

The study can be terminated prematurely if there is evidence of an unacceptable risk for trial subjects, if there is reason to conclude that it is not feasible to collect the data necessary to reach the study objectives and it is therefore not ethical to continue, and in case of failure of the investigator and/or staff to follow either good clinical practice standards or to adhere to protocol requirements. The decision to end the trial prematurely will be made by de coordinating investigators in close collaboration with the principal investigator.

Ethics and dissemination

Ethics approval

The study protocol has been approved by the METC of the region Arnhem-Nijmegen from the Radboud University Medical Centre on September 2nd 2020. It has been registered on ClinicalTrails.gov with number NCT04448366 on June 3th 2020. Amendments, changes made to the research protocol after a primary favourable opinion by the accredited METC has been given, will be notified to the METC that gave the primary favourable opinion. After an amendment is approved, informed consent will be obtained from participants after receiving sufficient verbal and written information about the protocol amendments, when this is required by the METC. Participants will be asked consent to use collected data in ancillary studies.

Disclosure of interest

The authors have no conflict of interest to disclose.

Data access

Project Principal Investigators will have direct access to their own site's data sets, and will have access to other sites data by request. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

Ancillary and post-trial care

Patients that are enrolled in the study are covered by indemnity for negligent harm through the standard health insurance. Due to the used intervention the METC did not require the sponsor to take out additional insurance to cover non-negligent harm associated with the protocol. If patients in either the control or intervention group wish to respectively start or continue psychological treatment after the study has finished, they are instructed to contact their gynaecologist or general practitioner for referral for psychological treatment.

Public disclosure and publication policy

The findings of this study will be published in scientific journals and will be presented at scientific conferences. Authors that substantially contributed to the results of this study will be granted authorship. The research protocol, original dataset and statistical code will be available on request in accordance with the conditions of ethics approval. If participants wish, they will be notified of the findings when they are available.

DISCUSSION

Patients suffering from endometriosis often have impaired QoL and severe chronic pain. Non-medical therapies including cognitive behavioural interventions have been widely used and proven effective in suppressing pain and pain-related problems in several chronic pain syndromes[8-10, 13, 27, 28]. In this

study we aim to determine the efficacy of CBT to improve QoL in patients undergoing endometriosis surgery due to endometriosis-associated chronic pain. To our knowledge, this is the first research project investigating this.

To determine whether CBT is effective in improving QoL, participants will be randomized into two groups. The control group will receive surgery and care as usual, and the intervention group will additionally receive seven sessions of CBT.

Strengths and limitations

For this study a CBT protocol was developed by members of the research team consisting of gynaecologists experienced in treating women with endometriosis and of psychologists with experience in CBT, chronic pain and/or treating patients diagnosed with endometriosis. Importantly, patients' opinions on CBT were taken into account during development of the CBT protocol. By involving patients in the development of the CBT protocol we believe that the CBT protocol better meets the needs of this specific patient group. Using a fixed CBT protocol ensures that the intervention can be carried out congruently across all participating sites and by all executing psychologists. This minimizes differences in therapy. Moreover, frequent sessions of intervision between all executing psychologists will take place in order to address possible issues and queries in the execution of the CBT protocol. This will ensure in-between centre consistency and reduce variability even further. At the same time, room for individual adjustments is facilitated in the design of the CBT protocol in order to meet specific needs of individual patients.

It is important to note that CBT will be given to patients who will undergo another treatment for endometriosis: reduction surgery. One session of CBT will be scheduled before the surgical procedure, the other six will take place after surgery. Prior to surgery, patients with endometriosis-associated chronic pain have a physical explanation for the pain they experience since the endometriosis is still present at that time. After surgery, the endometriosis as cause for their pain will be removed but they may still suffer from chronic pain symptoms. At that moment, CBT may be effective in treating the psychological aspects of their chronic pain symptoms. Parrish et al.[29] showed in a recent systematic review and meta-analysis that CBT combined with lumbar-spine surgery improves QoL compared to usual care or an alternative therapy. Combining CBT with surgical treatment will stress the importance of a combined intervention targeting both physical and psychological determinants of pain as well as its interaction and will support the idea that gynaecologists, psychologists and researchers take patients' symptoms seriously. In our opinion, this is an important strength of our study. Another strength is that we measure two indicators for stress: an assessment of self-reported stress measured by a questionnaire as well as an indicator for stress measured via cortisol extracted from hair. The scalpel hair cortisol measurement enables us to objectively quantify if CBT contributes to chronic stress present in participants.

The most important limitation of this study protocol is the difference in attention given by health care professionals to patients in the intervention and the control group. Because women in the intervention group will undergo seven sessions of CBT, they will get more attention from a health care professional as compared to women in the control group. More attention because of more contact time might lead to better QoL on itself. To compensate for this, we ideally would have added a third group of patients who would receive endometriosis-reduction surgery and seven non-therapeutic appointments with for example a nurse. However, this would have greatly increased the required number of participants,

thereby increasing the costs of the study as well as the required time period for the inclusions. Because we aimed to compare usual care with the CBT intervention, we chose to investigate the two groups described in this protocol. It is important to stress that women in both the intervention as well as in the control group may contact their endometriosis nurse as often as they need for support or for answering questions.

Another limitation is that due to the used intervention, we are only able to blind accessors and gynaecologists performing the operation for treatment allocation. Psychologists performing the intervention and, more importantly, participants cannot be blinded which can introduce bias.

Finally, presence or absence of motivation to undergo CBT may bias the results of this study. From motivational interviewing[30] it is known that motivation to undergo psychological therapy can influence treatment results. In our study, prior to randomization we will measure patients' motivation to undergo psychological treatment. After finishing the treatment, we will analyse whether there were in-between group differences with respect to group allocation preference and disappointment as well as motivation to undergo cognitive behavioural treatment.

Clinical implications

Depending on the outcome of our study, advice will be provided whether CBT should be added to the treatment of patients undergoing endometriosis reduction surgery. If this study shows a positive result, patients may have an additional treatment options to improve the quality of their daily lives. Results of this study could moreover pave the road to fund more clinical trials, cost-effectiveness and implementation studies on the use of CBT in patients diagnosed with endometriosis specifically and chronic pain conditions in general.

ADMINISTRATIVE INFORMATION

Trial acronym

COGENS

Trial registration

ClinicalTrials.gov NCT04448366. Registered on June 3th, 2020.

Current protocol version

8 (1-6-2021)

Trial sponsor

Rijnstate Hospital
Address: Wagnerlaan 55, 6815 AD, Arnhem, The Netherlands
Telephone: +31 088 005 8888
Website: www.rijnstate.nl

Funding

This work was supported by the Radboudumc-Rijnstate PhD funding, grant number W.000003.1. This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Author contributions

AN conceived the study. CV, DB, JO and AN initiated the study design and ZB helped with implementation. CV and AN are grant holders. JO provided statistical expertise in the clinical trial design. AI, EH, HD, CL and AS helped develop the CBT protocol. All authors contributed to refinement of the study protocol, revised different versions of the manuscript and approved the final manuscript.

Roles and responsibilities

Principal investigator and research physician:

- Design and conduct of COGENS
- Preparation of protocols and revisions
- Preparation of CRFs
- Reviewing progress of study and if necessary agreeing changes to the protocol to facilitate the smooth running of the study
- (S)AEs reporting to Medical Ethical Committee
- Responsible for trial master file
- Budget administration and contractual issues with individual centres
- Data verification

Lead investigators:

In each participating centre a lead investigator will be identified, to be responsible for identification, recruitment, randomisation, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol.

Acknowledgements

Not applicable.

Availability of data and materials

Not applicable.

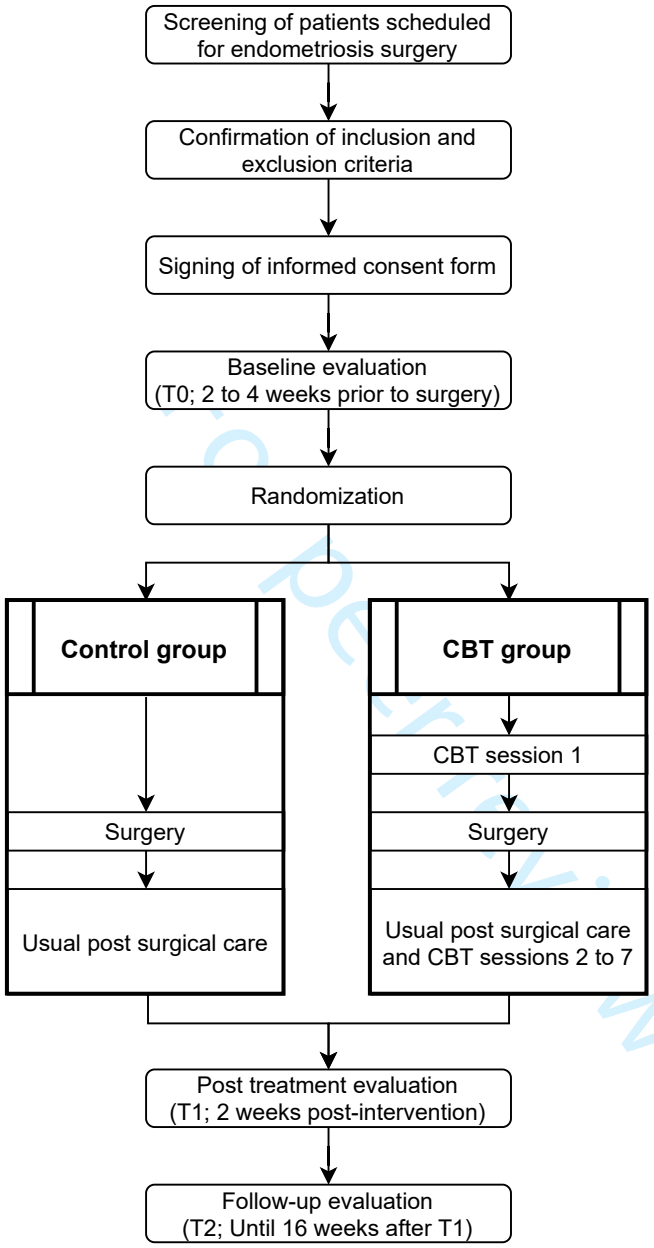
REFERENCES

1. Giudice LC, Kao LC. Endometriosis. Lancet. 2004;364:1789-99.
2. Vercellini P, Crosignani PG, Abbiati A, et al. The effect of surgery for symptomatic endometriosis: the other side of the story. Hum Reprod Update. 2009;15:177-88.
3. van Aken M, Oosterman J, van Rijn T, et al. The effect of endometriosis surgery on biopsychosocial correlates of pain. Submitted. 2019.
4. van Aken MAW, Oosterman JM, van Rijn CM, et al. Pain cognition versus pain intensity in patients with endometriosis: toward personalized treatment. Fertil Steril. 2017;108:679-86.
5. Olatunji B, Hollon S. Preface: The Current Status of Cognitive Behavioral Therapy for Psychiatric Disorders. The Psychiatric clinics of North America. 2010;33:xiii-xix.
6. Clark DA, Beck, A.T. Cognitive Behavior Therapy. In: Foreyt JP, Rathjen DP, editors. Cognitive Behavior Therapy: Research and Application. Boston, MA: Springer US; 1978. p. 109-34.
7. Clark DA. Cognitive Restructuring. The Wiley Handbook of Cognitive Behavioral Therapy2013. p. 1-22.
8. Richmond H, Hall AM, Copsey B, et al. The Effectiveness of Cognitive Behavioural Treatment for Non-Specific Low Back Pain: A Systematic Review and Meta-Analysis. PLoS One. 2015;10:e0134192.
9. Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. Am Psychol. 2014;69:153-66.

10. Wang L, Chang Y, Kennedy SA, et al. Perioperative psychotherapy for persistent post-surgical pain and physical impairment: a meta-analysis of randomised trials. Br J Anaesth. 2018;120:1304-14.
11. Boersen Z, de Kok L, van der Zanden M, et al. Patients' perspective on cognitive behavioural therapy after surgical treatment of endometriosis: a qualitative study. Reprod Biomed Online. 2021;42:819-25.
12. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. 2013;346:e7586.
13. Archer KR, Devin CJ, Vanston SW, et al. Cognitive-Behavioral-Based Physical Therapy for Patients With Chronic Pain Undergoing Lumbar Spine Surgery: A Randomized Controlled Trial. J Pain. 2016;17:76-89.
14. Karekla M, Konstantinou P, Ioannou M, et al. The Phenomenon of Treatment Dropout, Reasons and Moderators in Acceptance and Commitment Therapy and Other Active Treatments: A Meta-Analytic Review. Clinical Psychology in Europe. 2019;1:1-36.
15. Fernandez E, Salem D, Swift J, et al. Meta-Analysis of Dropout From Cognitive Behavioral Therapy: Magnitude, Timing, and Moderators. J Consult Clin Psychol. 2015;83.
16. Organization WH. International Statistical Classification of Diseases and Related Health Problems (ICD) World Health Organization2020 [Available from: https://www.who.int/classifications/classification-of-diseases.
17. Hart VA. Infertility and the role of psychotherapy. Issues Ment Health Nurs. 2002;23:31-41.
18. Chachamovich JR, Chachamovich E, Ezer H, et al. Investigating quality of life and health-related quality of life in infertility: a systematic review. Journal of Psychosomatic Obstetrics & Gynecology. 2010;31:101-10.
19. Rapaport MH, Clary C, Fayyad R, et al. Quality-of-Life Impairment in Depressive and Anxiety Disorders. 2005;162:1171-8.
20. Association AP. Diagnostic and Statistical Manual of Mental Disorders: Dsm-5: Amer Psychiatric Pub Incorporated; 2013.
21. van de Burgt TJ, Hendriks JC, Kluivers KB. Quality of life in endometriosis: evaluation of the Dutch-version Endometriosis Health Profile-30 (EHP-30). Fertil Steril. 2011;95:1863-5.
22. Jones G, Jenkinson C, Kennedy S. Evaluating the responsiveness of the Endometriosis Health Profile Questionnaire: the EHP-30. Qual Life Res. 2004;13:705-13.
23. van der Zee K, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36. Noordelijk Centrum voor Gezondheidsvraagstukken, reeks meetinstrumenten. 1993;3:1-28.
24. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull. 2004;130:601-30.
25. van Aken M, Oosterman J, van Rijn T, et al. Hair cortisol and the relationship with chronic pain and quality of life in endometriosis patients. Psychoneuroendocrinology. 2018;89:216-22.
26. Hayes AF. Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. New York, NY, US: Guilford Press; 2013. xvii, 507-xvii, p.
27. Evans S, Fernandez S, Olive L, et al. Psychological and mind-body interventions for endometriosis: A systematic review. J Psychosom Res. 2019;124:109756.
28. Till SR, Wahl HN, As-Sanie S. The role of nonpharmacologic therapies in management of chronic pelvic pain: what to do when surgery fails. Current opinion in obstetrics & gynecology. 2017;29:231-9.
29. Parrish JM, Jenkins NW, Parrish MS, et al. The influence of cognitive behavioral therapy on lumbar spine surgery outcomes: a systematic review and meta-analysis. Eur Spine J. 2021.
30. Miller WR, Rollnick S. Motivational interviewing: Helping people change: Guilford press; 2012.

Figure legend

Figure 1: Patient flow throughout the study. CBT: Cognitive Behavioural Therapy



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	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,	9

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	9
Protocol version	#3	Date and version identifier	9
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	9
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	9
Roles and responsibilities: sponsor and funder	#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	9
Roles and responsibilities: committees	#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)	9 and 10

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	3, 4 and 7

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5 and 6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5 and 6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4 and 5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	3

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	3
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	3, 4
Methods: Assignment of interventions (for controlled trials)			
Allocation: 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	4
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	4
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4
Methods: Data collection, management, and analysis			
Data collection plan	#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	7 and 9
Data collection plan: retention	#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	6
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	6

		(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	
Statistics: outcomes	#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	6 and 7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6 and 7
Statistics: analysis population and missing data	#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)	6 and 7
Methods: Monitoring			
Data monitoring: formal committee	#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	7
Data monitoring: interim analysis	#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	6
Harms	#22	Plans for collecting, assessing, reporting, and managing	7

		solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
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)	7
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	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	6

		trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
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	7
Dissemination policy: trial results	#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	8
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a

	biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable