PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Boersen, Zoë; Oosterman, Joukje; Hameleers, Esther; Delcliseur, Heidi; Lutters, Cobie; IJssel de Schepper, Alicia; Braat, Didi; Verhaak, Christianne; Nap, Annemiek

VERSION 1 – REVIEW

REVIEWER	Mikocka-Walus, Antonina Deakin University Faculty of Health, Psychology
REVIEW RETURNED	22-Aug-2021

GENERAL COMMENTS	This is a novel and much needed study, since trials of psychological and mind-body therapies in endometriosis are largely non-existent. An objective marker for stress measured on multiple occasions is the study's strength as are the broad consultations with consumers and the intervention being co-designed. The limitation is lack of blinding but that's quite typical in psychotherapy trials. Article summary – it's unclear what this means 'Treatment blinding is not possible due to used intervention which could lead to bias.' Please clarify/reword. 'CBT focuses on supporting positive cognitions' – I am not sure this is 100% true. CBT is about being realistic and noticing good and bad aspects of the current situation. I would say it is about a more balanced view of the world. CBT is different to Positive Psychology. I would also mention cognitive restructuring which is the key element of CBT. I was thinking that since BMJ is not read by psychologists but rather by doctors and other health professionals perhaps it would be useful to explain how CBT might work on pain/QoL and why it seems more promising than other psychotherapies? 'Chronic pain that could be allocated…' I think the authors mean 'attributed' Exclusions – how will the authors ensure that psychopharmacologic medication is given for mood and not for pain? In this population, there is a significant group of patients taking antidepressants for pain. Is excluding people with any mood and anxiety disorders practical? This can make the sample very hard to recruit and not really representative as psychological issues are hugely prevalent. Wouldn't it be more useful to set the levels such as severe anxiety for example?

	‘Participants will be allocated to the control or intervention group by an authorized investigator’. Isn’t it in conflict with randomisation being done by the computer? Or do the authors mean the list of random numbers will be computer generated and then a researcher will assign them? Allocation concealment may need to be better described. Also, I would emphasise this researcher will have no patient contact or won’t be involved in the analysis. Will the control group be offered the intervention after the follow-up? ‘registered psychotherapists’ or do the authors mean registered psychologists? Just checking, as in some countries ‘psychotherapists’ need several years of additional training to be able to use this title. ‘an online module CBT is available containing general information about chronic pain’ – could you please provide further details – how much material? Of what type? Is it just psychoeducation? Discussion – could a paragraph be added on implementation into practice and sustainability. If proven effective, how will it be delivered via the healthcare system? Via hospital psychology clinics? How financed? This is just out of interest as some countries have it organised better than others and it could be useful to the researchers from other countries to learn on how to ensure sustainability.

REVIEWER	Capezzuoli, Tommaso University of Florence, Department of Biomedical, Experimental and Clinical Sciences
REVIEW RETURNED	11-Sep-2021

GENERAL COMMENTS	Zoë et al aim to publish a protocol for a study with the goal of determining the effectiveness of cognitive behavioural therapy in improving quality of life in patients undergoing surgery for endometriosis. The topic is very interesting and the future paper may add new interesting information about the improvement of quality of life of women suffering from endometriosis. The English text is appropriate and the syntax is correct. The study design is good, the research question clearly defined and the statistical analysis hypothesis for the evaluation of primary and secondary endpoints is correct. Research ethics are appropriately addressed. Author correctly list strengths and limitations of the study. No results or conclusion are present in the study protocol. In conclusion, the present study protocol may be accepted for publication in the present form.

VERSION 1 – AUTHOR RESPONSE

Response to comments from review number 1:
We want to thank reviewer 1 for taking the time to review this manuscript.

Comment 1:

Article summary – it's unclear what this means 'Treatment blinding is not possible due to used intervention which could lead to bias.' Please clarify/reword.
Response: We clarified what we mean by this: "Participants are not blinded for group allocation which could lead to bias."

Comment 2:
'CBT focuses on supporting positive cognitions' – I am not sure this is 100% true. CBT is about being realistic and noticing good and bad aspects of the current situation. I would say it is about a more balanced view of the world. CBT is different to Positive Psychology. I would also mention cognitive restructuring which is the key element of CBT. I was thinking that since BMJ is not read by psychologists but rather by doctors and other health professionals perhaps it would be useful to explain how CBT might work on pain/QoL and why it seems more promising than other psychotherapies?
Response: Thank you for your comment. We agree with your first recommendation and made changes accordingly. We also added a short paragraph explaining the basic working mechanism of CBT: "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]."

Comment 3:
'Chronic pain that could be allocated…' I think the authors mean 'attributed'
Response: we did mean that and changed it accordingly.

Comment 4:
Exclusions – how will the authors ensure that psychopharmacologic medication is given for mood and not for pain? In this population, there is a significant group of patients taking antidepressants for pain. Is excluding people with any mood and anxiety disorders practical? This can make the sample very hard to recruit and not really representative as psychological issues are hugely prevalent. Wouldn't it be more useful to set the levels such as severe anxiety for example?
Response: Thank you for your comment. Patients are asked about their medication use and why they are using these medication. They know whether they use this medication to mitigate pain or to fight a depression. If they don't know it can be checked with their physician/gynaecologist. We added this to the manuscript: "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 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(18)), are undergoing psychological therapy or use psychopharmacologic medication aimed at altering mood (according to either patient or their physician) at the moment of inclusion."
We did have a discussion between members of the research group concerning your second point. We agree that excluding patients with anxiety or depression disorders can make recruitment more difficult. It also might be harder to translate results from this study to the general endometriosis population. However, because we are investigating a psychological therapy that tries to improve QoL by improving pain cognitions we decided to exclude patients that have other current problems that probably would interfere with our therapy as described in the manuscript. These patients might benefit

from a psychological intervention but probably not from a prefix protocol focussing mainly on other problems. These patients also already frequently seek help from psychologists asking them to treat their depression or anxiety issues and there are existing and proven effective psychological treatments for both of these.

Comment 5:
'Participants will be allocated to the control or intervention group by an authorized investigator'. Isn't it in conflict with randomisation being done by the computer? Or do the authors mean the list of random numbers will be computer generated and then a researcher will assign them? Allocation concealment may need to be better described. Also, I would emphasise this researcher will have no patient contact or won't be involved in the analysis.
Response: Indeed we mean that randomization will be computerized and that a researcher will assign them using computerized randomization. To prevent confusion we made changes in the manuscript. We also elaborated on the allocation concealment: "Only an authorized researcher will be able to perform randomization and have insight in randomization results."

Comment 6:
Will the control group be offered the intervention after the follow-up?
Response: Patients in the control group will not actively be offered the intervention after follow-up. It is possible to ask their gynaecologist or general practitioner to refer them to a psychologist. We made changes to the manuscript to clarify this: "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. "

Comment 7:
'registered psychotherapists' or do the authors mean registered psychologists? Just checking, as in some countries 'psychotherapists' need several years of additional training to be able to use this title.
Response: Thank you. Indeed we mean psychologist. We changed this in the manuscript: "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."

Comment 8:
'an online module CBT is available containing general information about chronic pain' – could you please provide further details – how much material? Of what type? Is it just psychoeducation?
Response: it is a module providing psychoeducation but also assignments patients can do. There is one module per session. We explained this further in the manuscript: "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."

Comment 9:
Discussion – could a paragraph be added on implementation into practice and sustainability. If proven effective, how will it be delivered via the healthcare system? Via hospital psychology clinics? How financed? This is just out of interest as some countries have it organised better than others and it could be useful to the researchers from other countries to learn on how to ensure sustainability.
Response: Thank you for your comment. This is a very important topic that will be discussed after the results of this study have been analysed. We will pay attention to implementation options then. We did add a sentence in the manuscript noting the need for implementation studies: "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."

Responds to commends from review number 2:
Thank you for taking the time to review this manuscript.