PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Yoga, cognitive behaviour therapy versus education to improve quality of life and reduce health care costs in people with endometriosis: A randomised controlled trial
AUTHORS	Mikocka-Walus, Antonina; Druitt, Marilla; O'Shea, Melissa; Skvarc, David; Watts, Jennifer; Esterman, Adrian; Tsaltas, Jim; Knowles, Simon; Harris, Jill; Dowding, Charlotte; Parigi, Elesha; Evans, Subhadra

VERSION 1 – REVIEW

REVIEWER	Leonardi, Mathew Nepean Hospital
REVIEW RETURNED	03-Jan-2021

GENERAL COMMENTS	Dear authors, Congratulations on a relevant and well-designed study protocol. This is very well written and organized. I have taken a careful look at the protocol and hope to assist in optimising this before the start of the study, if possible. Please see the below comments: Abstract • Well written Limitations • Decision to recruit those with “suspected endometriosis”. • Are weekly educational handouts really considered “standard educational care”? I have never heard of this being standard. • It is becoming almost standard of care to integrate exercise and psychotherapy into the care of those with chronic pelvic pain/endometriosis. Education is also essential. I find it interesting that these will be compared against each other and not combined to compare against routine care that doesn’t include these care aspects. Introduction • How is popularity of mind-body interventions defined? As an endometriosis specialist, I integrate pelvic floor physiotherapy much more rigorously than yoga. Similarly, I integrate psychotherapy, but not always specifically CBT. ACT is also utilized. I think yoga and CBT are very valuable, but I caution against claiming popularity. • I am a bit confused about how cost-effectiveness analysis will incorporate medical and surgical management Methods

	• The diagnosis section of the Inclusion Criteria is concerning. There are multiple entry points, which will lead to significant variation in disease presence/absence (obviously there are many other conditions that mimic endometriosis) and disease severity. It also sounds like those who have been previously undergone surgery will be recruited. Is it really fair to compare someone who has undergone surgery with recurrent/residual symptoms (i.e. red flag for central sensitization) with someone who has no surgical history and no imaging features of endometriosis? There are many other scenarios that bring about poor comparison groups… • If all patients are continuing with routine medical care during the study period, what if someone undergoes surgery halfway through their randomised intervention? • If participants are recruited from various gynaecologists, there is surely going to be huge variations in routine care. Consider there are those who regularly prescribe GnRH agonists and those that don't. Consider that there are surgeons who perform endometriosis ablation while others perform excision. Consider the very large variation in surgical skill that exists amongst gynaecologists. o Many of these issues can be resolved by being VERY specific with inclusion/exclusion criteria • Please define o Severe mental illness o "course of yoga/CBT" – if someone did some home yoga videos, does that constitute a course of yoga? • Is it really appropriate to consider face-to-face equivalent with online? In a yoga practice, online may not allow instructors to refine participant movements and positions. Similarly, might online CBT permit the same intimateness of in-person therapy? • Authors state the educational handouts are "consistent with endometriosis education patients receive from their treating physician". I have serious concerns that this is not going to be reflective of usual care because, in reality, physicians don't spend hours doing educational sessions with their patients. • Moreover, a cursory review of these educational links on the Jean Hailes website raises concern. It is inappropriate to continue to propagate the message that, "At present, laparoscopy is the only way to diagnose endometriosis correctly." In addition, one of the links is related to fertility, which may not be relevant to patients at all, and providing them this link could be triggering from a mental health standpoint (think of the 40 something-year-old who has had infertility and failed fertility therapies). This particular fertility link is also out-of-date and not aligned with the latest evidence on surgery for fertility in endometriosis (see Leonardi M, Gibbons T, Armour M, Wang R, Glanville E, Hodgson R, et al. When to Do Surgery and When Not to Do Surgery for Endometriosis: A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 2020 Feb 29;27(2):390-407.e3., and Bafort C, Beebeejaun Y, Tomassetti C, Bosteels J, Duffy JM. Laparoscopic surgery for endometriosis. Cochrane database Syst Rev. 2020;10:CD011031.) • I have noticed there is no inclusion of adverse events in the outcome measures. The lack of rigorous evaluation of adverse events in interventional studies on endometriosis makes formulating clinical guidelines very difficult. I realize the authors identified that they would monitor adverse events (in the Ethics and dissemination section). Those with deteriorating mental health will be referred to mental health care providers. Will they remain in

	the study? What about those who experience adverse events from yoga (e.g. injury)? Discussion • This statement, “Because over half of patients experience anxiety and depression, treatments that address psychological wellbeing are urgently needed”, worries me that we are thinking CBT and yoga will treat the co-morbidities, depression and anxiety, rather than endometriosis itself. I realize all entities associated with endometriosis impact on QoL, but we should be careful to identify treatments for endo and avoid confounders. • There is increasing literature on the placebo and nocebo effects (see Petrie KJ, Rief W. Psychobiological Mechanisms of Placebo and Nocebo Effects: Pathways to Improve Treatments and Reduce Side Effects. Annu Rev Psychol. 2019;70(1):599–625., and Colloca L, Barsky AJ. Placebo and Nocebo Effects. New Engl J Med. 2020;382(6):554–61.), so I would like to see an updated citation that supports this claim: “Nevertheless, treatment effects for CBT and yoga would persist longer than placebo effects and thus a 12-month follow-up proposed in this trial may increase confidence in the efficacy of yoga and CBT.”

REVIEWER	O’Hara, Rebecca Monash University
REVIEW RETURNED	29-Jan-2021

GENERAL COMMENTS	Dear Authors, This protocol addresses a substantial gap in the literature and features a robust sample size and is well considered and I support its publication in BMJ Open. Just a few points for consideration/clarification: 1) Inclusion criteria: Given that the symptoms of endometriosis can overlap with a number of diseases - how will patients that have suspected diagnosis of endometriosis upon study entry, who then go on to have laparoscopy to investigate endometriosis and are found to not have the disease be managed in this study? 2) Will participants with co-morbid conditions be admitted to the study or will they be excluded? (e.g. endometriosis/adenomyosis or endometriosis/diabetes). 3) Recruitment - will recruitment be limited to Victoria or is it a national study? 4) Intervention - will participants choose whether they complete the intervention in-person/via zoom or will this be allocated? I look forward to reading the findings from this study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Dr. Mathew Leonardi, Nepean Hospital	
Limitations	Thank you for this comment. Our intention was to be as inclusive as possible, but the reviewer is right and the inclusion of these with

• Decision to recruit those with “suspected endometriosis”.	suspected endometriosis makes our sample less homogenous. We have now removed reference to 'suspected' endometriosis and have reworded our Inclusion Criteria.
• Are weekly educational handouts really considered “standard educational care”? I have never heard of this being standard. • It is becoming almost standard of care to integrate exercise and psychotherapy into the care of those with chronic pelvic pain/endometriosis. Education is also essential. I find it interesting that these will be compared against each other and not combined to compare against routine care that doesn’t include these care aspects.	We do agree that the educational handouts are not standard care everywhere, although some clinics do utilise educational materials. We have now renamed this group: 'education', and reworded the section on: Intervention and control condition The reviewer has accurately referred to ‘almost standard care’. While this is the case in many pain conditions, psychotherapy (or physiotherapy) is not presently available through Australian clinics supporting people with endometriosis. In fact, we believe that education is more commonly part of standard care of chronic pain-related conditions than psychotherapy. While data for endometriosis specifically are not available, a recent study from our group on availability of psychotherapy via gastroenterology clinics for an inflammatory pain condition showed only 12% of patients had access to psychologists (see https://pubmed.ncbi.nlm.nih.gov/32280760/).
Introduction • How is popularity of mind-body interventions defined? As an endometriosis specialist, I integrate pelvic floor physiotherapy much more rigorously than yoga. Similarly, I integrate psychotherapy, but not always specifically CBT. ACT is also utilized. I think yoga and CBT are very valuable, but I caution against claiming popularity. • I am a bit confused about how cost-effectiveness analysis will incorporate medical and surgical management	Thank you for this observation. We have now replaced ‘popular’ with ‘common’. The reviewer is right that other options may be considered more ‘popular’. A resource use questionnaire will be developed specifically for the study that will include questions on whether an endometriosis-related procedure had occurred and the type of procedure (surgery or dilatation and curettage). Based on these responses there are likely to be 3 possible ARDRGs (one for non-procedural management; D&C, and laparoscopic surgery) which will be costed according to the Independent Hospital Pricing Authority DRG costing information. The text has been modified to reflect this: “A DRG for each endometriosis-related hospital visit will be assumed based on whether a procedure occurred, and the type of procedure. A DRG cost will be determined from costing information from the Activity Based Funding guidelines of the Independent Hospital Pricing Authority, an independent government agency of the Commonwealth of Australia (44). The cost of primary care health

	service and pharmaceuticals will be derived from participant level Medicare data."
Methods • The diagnosis section of the Inclusion Criteria is concerning. There are multiple entry points, which will lead to significant variation in disease presence/absence (obviously there are many other conditions that mimic endometriosis) and disease severity. It also sounds like those who have been previously undergone surgery will be recruited. Is it really fair to compare someone who has undergone surgery with recurrent/residual symptoms (i.e. red flag for central sensitization) with someone who has no surgical history and no imaging features of endometriosis? There are many other scenarios that bring about poor comparison groups…	To strengthen the homogeneity of our sample, as advised by this reviewer, we have revised this section as specified above and have now removed 'suspected endometriosis'. Further, while we acknowledge the reviewer's concern re surgery, ours is a pragmatic study designed to include the group of women who commonly present to gynaecological services with pain and a past diagnosis of endometriosis. Given we will recruit a relatively large sample, events such as surgery can be controlled for in the analysis. Please note that our study needs to be feasible within the period stipulated by the funding we received from the NHMRC and this means that applying very narrow inclusion criteria would substantially extend the recruitment period, making the study impractical (while also relevant to a small proportion of women we typically see with endometriosis through our clinics). Thank you for this question. We will allow for surgery to occur since surgery may make the pain worse, better, or no different. We will record surgical findings and will control for it in our analysis.
• If all patients are continuing with routine medical care during the study period, what if someone undergoes surgery halfway through their randomised intervention?	This is true however we need to weigh this against the feasibility of the trial and ensuring its pragmatic real-life approach. Further, 2020 Cochrane review shows no convincing evidence that one approach is better than another https://www.cochrane.org/CD011031/MENSTR_laparoscopic-surgery-pain-and-infertility-associated-endometriosis We do agree that surgical skills may vary but if we only included one or two surgeons in our study, its results would only be generalisable to those two individuals. This is an appropriately powered randomised controlled trial, and we would expect variability in routine care to be evenly spread between treatment and control arms.
• If participants are recruited from various gynaecologists, there is surely going to be huge variations in routine care. Consider there are those who regularly prescribe GnRH agonists and those that don't. Consider that there are surgeons who perform endometriosis ablation while others	We have now narrowed the criteria by removing 'suspected endometriosis'. However, as per our comments above, we believe that further narrowing the criteria and moving away from our pragmatic (real life) approach would mean the study might not be generalisable on the large scale while also problematic recruitment-wise within the period of our approved funding.

perform excision. Consider the very large variation in surgical skill that exists amongst gynaecologists. o Many of these issues can be resolved by being VERY specific with inclusion/exclusion criteria	
• Please define • Severe mental illness o “course of yoga/CBT” – if someone did some home yoga videos, does that constitute a course of yoga?	We have now clarified this under our Exclusion Criteria. The study has no capacity to treat people with serious psychopathology (e.g., schizophrenia). Such participants might benefit from individual therapy. We thank the reviewer for this excellent point. We have now clarified that we mean a ‘therapist-led’ course.
• Is it really appropriate to consider face-to-face equivalent with online? In a yoga practice, online may not allow instructors to refine participant movements and positions. Similarly, might online CBT permit the same intimateness of in-person therapy?	We completely agree and our intention is to run the course face-to-face. However, given the unpredictability of the COVID-19 pandemic we need to allow for the possibility of further lockdowns when face-to-face group contact is not possible. We have now clarified under Intervention and control conditions that our preference is for face-to-face delivery.
• Authors state the educational handouts are “consistent with endometriosis education patients receive from their treating physician”. I have serious concerns that this is not going to be reflective of usual care because, in reality, physicians don’t spend hours doing educational sessions with their patients.	We agree and have reworded it as per this reviewer’s previous comment. This group is now called ‘education’.
• Moreover, a cursory review of these educational links on the Jean Hailes website raises concern. It is inappropriate to continue to	We do believe that histology is the current gold standard. However, to avoid any controversy, we will remove such debatable references from our handouts. Thank you for bringing this and the outdated link to our attention. We have now mentioned that these materials will be ‘adapted from’ the website.

propagate the message that, “At present, laparoscopy is the only way to diagnose endometriosis correctly.” In addition, one of the links is related to fertility, which may not be relevant to patients at all, and providing them this link could be triggering from a mental health standpoint (think of the 40 something-year-old who has had infertility and failed fertility therapies). This particular fertility link is also out-of-date and not aligned with the latest evidence on surgery for fertility in endometriosis (see Leonardi M, Gibbons T, Armour M, Wang R, Glanville E, Hodgson R, et al. When to Do Surgery and When Not to Do Surgery for Endometriosis: A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 2020 Feb 29;27(2):390-407.e3., and Bafort C, Beebeejaun Y, Tomassetti C, Bosteels J, Duffy JM. Laparoscopic surgery for endometriosis. Cochrane database Syst Rev. 2020;10:CD011031.)	
• I have noticed there is no inclusion of adverse events in the outcome measures. The lack of rigorous evaluation of adverse events in interventional studies on endometriosis makes formulating clinical guidelines very difficult. I realize the authors identified that they would monitor adverse events (in the Ethics and dissemination section). Those with deteriorating mental health will be	We strongly agree about the importance of monitoring adverse events. Please have a look at our ethics protocol for details. We have a large section on adverse events which could not be given justice in the manuscript due to the word count limit. We have now clarified it under outcome measures. Regarding staying in the study / withdrawing due to adverse events, this will depend on severity. Minor problems (e.g., muscle strain) will be discussed with the therapist and the adjustment in posture will be proposed. Please note ours is a therapeutic yoga program designed specifically for this group and as such injury is very unlikely. In case a major adverse event happens, participants will be referred back to their treating physician and the physician’s advice will be used regarding remaining in / withdrawing from the study.

referred to mental health care providers. Will they remain in the study? What about those who experience adverse events from yoga (e.g. injury)?	
Discussion • This statement, “Because over half of patients experience anxiety and depression, treatments that address psychological wellbeing are urgently needed”, worries me that we are thinking CBT and yoga will treat the co-morbidities, depression and anxiety, rather than endometriosis itself. I realize all entities associated with endometriosis impact on QoL, but we should be careful to identify treatments for endo and avoid confounders.	This is a fair point and we have now slightly reworded this section to indicate we are interested in treating endometriosis.
• There is increasing literature on the placebo and nocebo effects (see Petrie KJ, Rief W. Psychobiological Mechanisms of Placebo and Nocebo Effects: Pathways to Improve Treatments and Reduce Side Effects. Annu Rev Psychol. 2019;70(1):599–625., and Colloca L, Barsky AJ. Placebo and Nocebo Effects. New Engl J Med. 2020;382(6):554–61.), so I would like to see an updated citation that supports this claim: “Nevertheless, treatment effects for CBT and yoga would persist longer than placebo effects and thus a 12-month follow-up proposed in this trial may increase confidence in the efficacy of yoga and CBT.”	Thank you for this great suggestion. The references have now been added to the discussion.

Reviewer: 2 Dr. Rebecca O'Hara, Monash University	
1) Inclusion criteria: Given that the symptoms of endometriosis can overlap with a number of diseases - how will patients that have suspected diagnosis of endometriosis upon study entry, who then go on to have laparoscopy to investigate endometriosis and are found to not have the disease be managed in this study?	This is a great point. As per our response to reviewer 1, we have now removed the reference to 'suspected endometriosis' and will only be recruiting those with confirmed diagnosis.
2) Will participants with co-morbid conditions be admitted to the study or will they be excluded? (e.g. endometriosis/adenomyosis or endometriosis/diabetes).	We plan to include people with comorbidities in our pragmatic trial. If we exclude comorbidities, which affect many people with pain associated with endometriosis, we will have a non-representative sample that is different to who we typically see in clinics.
3) Recruitment - will recruitment be limited to Victoria or is it a national study?	We have now clarified that we will target Victorian hospitals/support groups.
4) Intervention - will participants choose whether they complete the intervention in-person/via zoom or will this be allocated?	Our preference is to offer interventions face-to-face, however, given the uncertainty of the COVID-19 pandemic situation and possibility of further lockdowns, we want to have the opportunity to continue recruitment. In that case, CBT and yoga will be offered online.

VERSION 2 – REVIEW

REVIEWER	Leonardi, Mathew Nepean Hospital
REVIEW RETURNED	04-Apr-2021

GENERAL COMMENTS	Comments on Response to Reviewer Comments - Thank you for your reply to reviewer comments - What does a D&C have to do with endometriosis? Why is this one of the ARDRGs? - I appreciate the extreme challenges that exist with running RCTs for endometriosis interventions. The pragmatic approach will have to do based on time, funding, and practical clinical limitations. I would encourage the authors to record some of the factors I discussed in my review (surgeon level using RANZOG/AGES scale, surgical technique used, complete vs incomplete treatment at the discretion of surgeon). These will also have to be listed as study limitations.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1	
- What does a D&C have to do with endometriosis? Why is this one of the ARDRGs?	Our apologies, while D&C is often done at the same time, it is not part of the specific endometriosis management. Therefore, our ARDRGs will include non-procedural management, laparoscopy and laparotomy. We have clarified it under Analysis.
I appreciate the extreme challenges that exist with running RCTs for endometriosis interventions. The pragmatic approach will have to do based on time, funding, and practical clinical limitations. I would encourage the authors to record some of the factors I discussed in my review (surgeon level using RANZOG/AGES scale, surgical technique used, complete vs incomplete treatment at the discretion of surgeon). These will also have to be listed as study limitations.	We have amended this as requested. See Methods under Exclusion criteria.