PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Pharmaceutical treatments to prevent recurrence of endometriosis following surgery: A model-based economic evaluation</th>
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<tr>
<td>AUTHORS</td>
<td>Sanghera, Sabina; Barton, Pelham; Bhattacharya, Siladitya; Horne, Andrew; Roberts, Tracy</td>
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</table>

VERSION 1 - REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Kouhei Sugimoto</th>
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</thead>
<tbody>
<tr>
<td>Department of Obstetrics and Gynecology, The Jikei University School of Medicine, Tokyo Japan</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>09-Dec-2015</td>
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<tr>
<td>GENERAL COMMENTS</td>
<td>This manuscript shows unexpected result. I consider that this result depend on short duration of observation. However, this result indicates that endometriosis patients around menopause can consider to choose no treatment. This is the reason why this manuscript is worthy to be published.</td>
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<tr>
<td>Department of Clinical Sciences and Community Health, Università degli Studi, Milan, Italy</td>
<td></td>
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<tr>
<td>REVIEW RETURNED</td>
<td>30-Dec-2015</td>
</tr>
<tr>
<td>GENERAL COMMENTS</td>
<td>Sanghera and co-workers conducted an economic evaluation comparing different strategies to prevent postoperative recurrence of endometriosis. They developed a Markov model with a 36-month follow-up, and considered treatment with a levonorgestrel-releasing intrauterine device (LNG-IUD), intramuscular medroxyprogesterone acetate (DMPA), combined oral contraceptive pill (COCP), and no treatment. According to the authors, all strategies were more expensive and generated fewer QALYs compared to no treatment. Therefore, they conclude that &quot;there is currently no evidence to support any treatment being recommended to prevent the recurrence of endometriosis following conservative surgery&quot;. There is a great need of this type of study in the area of endometriosis management, especially considering that endometriosis is a chronic disease with a high risk of recurrence, and that medical treatments may be needed for prolonged periods of time. The risk of endometriosis recurrence is about 10% per year for the first five years of follow-up (Recurrence of endometriosis and its control. Hum Reprod Update. 2009;15:441-61). Overall, the methodological approach adopted is appreciable. However, based on both, experimental evidence and clinical experience, long-term suppressive therapy indeed seems to be effective and cost-effective.</td>
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in reducing the risk of symptoms’ and lesions’ recurrence after conservative surgery for endometriosis, and the authors’ conclusions might not be of benefit for women undergoing (or who underwent) surgery for this disease. A recent study reached different conclusions (Cost-effectiveness of recommended medical intervention for treatment of dysmenorrhoea and endometriosis in Japan setting. Value Health. 2015 Nov;18:A736-7).

The main problem appears to lie in the model assumptions. i) Postoperative medical treatment is generally suggested either because ectopic foci may have not been removed (endometriosis persistence), or because retrograde menstruation after radical surgery may generate recurrent lesions. In both cases, ectopic endometrium (similarly to the intrauterine mucosa) can be pharmacologically suppressed, but not eliminated. There is ample evidence supporting this concept (see, as reviews: Reducing low-value care in endometriosis between limited evidence and unresolved issues: a proposal. Hum Reprod. 2015;30:1996-2004. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 2014;10:261-75. ‘Waiting for Godot’: a commonsense approach to the medical treatment of endometriosis. Hum Reprod. 2011;26:3-13).

Therefore, the rationale on which to base treatment cycles of a few months’ duration is difficult to understand. It is expected that using suppressive hormones for short periods would lead to long-term results (36 months) similar to not treating at all, as the ectopic endometrium readily resumes its metabolic activity at resumption of ovulation and oestrogen production. Maintaining that “If a woman is asymptomatic whilst receiving treatment with either COCP or DMPA the treatment will not be stopped for at least 6 months. Following these 6 months the women can stop treatment and it is assumed women will remain asymptomatic without further treatment” (page 6) looks like an unproven and possibly wrong assumption that could have undermined the entire analysis.


iii) There is an immense amount of published data demonstrating that excision of endometriomas results in a reduction of ovarian reserve (The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. J Clin Endocrinol
This damage seems to be additive, in terms of postoperative pregnancy rates, in case of second-line surgery for recurrent endometriotic cysts (The effect of second-line surgery on reproductive performance of women with recurrent endometriosis: a systematic review. Acta Obstet Gynecol Scand. 2009;88:1074-82). Thus, in order to fully evaluate the economic impact of postoperative preventive measures, also the additional costs of assisted reproduction techniques in women with infertility associated with gonadal damage derived from repeated surgical procedures should be taken into account.

iv) It is unclear if only dysmenorrhoea has been considered or also other pain symptoms. As an example, it has been observed that prolonged progestin therapy for recurrent endometriosis after conservative surgery significantly reduces pain at intercourse and improves sexual satisfaction (Surgical versus medical treatment for endometriosis-associated severe deep dyspareunia: I. Effect on pain during intercourse and patient satisfaction. Hum Reprod. 2012;27:3450-9. Surgical versus low-dose progestin treatment for endometriosis-associated severe deep dyspareunia II: effect on sexual functioning, psychological status and health-related quality of life. Hum Reprod. 2013;28:1221-30). The LNG-IUD abolishes menstruations in the majority of women using it. Thus, it might reveal a cost-effective measure for the prevention of dysmenorrhoea recurrence when the main symptom referred is pain at menstruation, whereas the effect on other types of pain may differ. The LNG-IUD does not inhibit ovulation, whereas DMPA and COCP do. This may result in different effects on non-menstrual pelvic pain.

v) The authors assumed that “the second hormonal treatment will comprise one of the two remaining treatment strategies or GnRHa, which includes HRT to enable the treatment to be used longer term than 6 months”. GnRHa are not cytoreductive, as all the other treatments considered, but are extremely more costly. Why did not the authors consider nor-ethisterone acetate (NETA) as a cost-effective alternative treatment in case of failure of LNG-IUD, DMPA, and COCP? There is ample evidence on the effect of NETA on symptomatic and recurrent endometriosis. NETA is associated with about 70% amenorrhoea rate and a similar satisfaction rate in intention-to-treat analyses (see, as an example, Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. Fertil Steril. 2015 Dec 8. pii: S0015-0282(15)02092-0. doi: 10.1016/j.fertnstert.2015.11.016).


In conclusion, although the authors state that “a pragmatic literature
search was carried out to identify evidence on the four treatment strategies" (page 7), they seem to have missed important information on the effect of prolonged postoperative medical treatment. It is unclear how they performed their literature search, as only five small studies seem to have been considered (references 10-14). However, there is much more published information that could have led to different conclusions on cost-effectiveness of tertiary prevention of endometriosis. The authors should re-consider their conclusions in light of the now fairly robust evidence on (not short-term) postoperative medical treatment. Suggesting that "there is currently no evidence to support any treatment being recommended to prevent the recurrence of endometriosis following conservative surgery" does not appear to be based on the entire available evidence and could pose patients at iatrogenically increased risk of the detrimental consequences of recurrent endometriosis.

The authors are sometimes inconsistent in their verbiage throughout the text when discussing that this is an analysis focusing on recurrence of endometriosis after conservative surgery. The fact that this is specifically after conservative surgery is left out on several occasions. This needs to be consistent throughout the text.

Methods: It is not clear exactly how the sensitivity analysis is being performed in terms of holding the transition probabilities constant. No base-case estimate is being provided in Table 1 as is done for the utility parameters in Table 2. These values need to be provided. I would recommend adding these values to Table 1. Additionally, no details are given on the "pragmatic" literature search. If the literature was still searched in a structured way (e.g. with various subject headings, keywords and combinations) this should be described.

Results: The results of the sensitivity analysis of holding certain parameters constant while varying others are not presented with enough detail. Figures 3 and 4 should be accompanied by cost-effectiveness acceptability curves as was done in Figure 2. This will allow the reader to better see how results change based on these sensitivity analyses. Furthermore, I was quite surprised to see model results indicate that no treatment was both less costly and resulted in more QALYs. I would not expect that better outcomes in terms of QALYs would occur from no treatment. Based on Table 2, I would surmise this is stemming from a lower quality of life for treatment than no treatment which is not offset enough from a higher probability of recurrence for no treatment compared to treatment. This type of trade-off for treatment is not entirely common. Whatever
the true underlying reason for no treatment being dominant, this warrants being expanded on in the discussion.

Discussion: It is not correct to state that "no treatment is the appropriate course of action to prevent recurrence..." on the bottom of page 13. While a recurrence may not happen with no treatment, that is not the same as saying no treatment actually prevented a recurrence. This should be rephrased to state no treatment is the appropriate course of action due to it being more cost-effective, and in fact dominant.

Limitations: It should be reiterated that, given the pragmatic approach to searching the literature, it is possible that additional usable studies could be found from a comprehensive systematic review. While it is unlikely a systematic review would reveal enough additional information to have a much higher level of confidence on parameter values, it cannot be ruled out. Additionally, it should also be reiterated that the transition probabilities found in the literature were based on results using different measures, and thus were difficult to synthesize into the model. This can, and should, be tempered with the use of wide distributions in the analysis.

VERSION 1 – AUTHOR RESPONSE

• Reviewer: 1

This manuscript shows unexpected result. I consider that this result depend on short duration of observation. However, this result indicates that endometriosis patients around menopause can consider to choose no treatment. This is the reason why this manuscript is worthy to be published.

Thank you

• Reviewer: 2

The main problem appears to lie in the model assumptions.
i) Postoperative medical treatment is generally suggested either because ectopic foci may have not been removed (endometriosis persistence), or because retrograde menstruation after radical surgery may generate recurrent lesions. In both cases, ectopic endometrium (similarly to the intrauterine mucosa) can be pharmacologically suppressed, but not eliminated. There is ample evidence supporting this concept (see, as reviews: Reducing low-value care in endometriosis between limited evidence and unresolved issues: a proposal. Hum Reprod. 2015;30:1996-2004. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 2014;10:261-75. 'Waiting for Godot': a commonsense approach to the medical treatment of endometriosis. Hum Reprod. 2011;26:3-13). Therefore, the rationale on which to base treatment cycles of a few months' duration is difficult to understand. It is expected that using suppressive hormones for short periods would lead to long-term results (36 months) similar to not treating at all, as the ectopic endometrium readily resumes its metabolic activity at resumption of ovulation and oestrogen production. Maintaining that "if a woman is asymptomatic whilst receiving treatment with either COCP or DMPA the treatment will not be stopped for at least 6 months. Following these 6 months the women can stop treatment and it is assumed women will remain asymptomatic without further treatment" (page 6) looks like an unproven and possibly wrong assumption that could have undermined the entire analysis.

Thank you for these comments which we do not contest. However it is important to stress the context of the study reported here. We do not report the full randomised controlled trial which is currently in progress and will not report for four years. The study reported here is a pre-trial model based
economic evaluation based on the current available evidence, explored the key aspects of uncertainty to highlight particular areas on which to focus data collection for the main randomised controlled trial which is currently taking place. Prior to the trial, a survey of the British Gynaecological Endoscopy Society members was carried out. The survey, which was reported in the funding application and the final trial protocol, provided the following important information used to design the main trial. (i) that 24% of clinicians used no post-operative treatment. (ii) LNG-IUS, combined oral pill (COCP) and DMPA are commonly prescribed, while oral progestogens and GnRH analogues are not. (iii) LNG-IUS (88%), COCP (42%), no treatment (38%) and DMPA (27%) were felt to be most in need of evaluation. It was imperative to respond to the funding call appropriately and design a trial that was deliverable. To best inform practice, we initially opted for a four arm randomised trial to evaluate the clinical and cost effectiveness of the two commonest long acting progestogens (LNG-IUS or DMPA) alongside usual treatment (COC or no treatment). In the study reported here we explore this defined group of four alternative treatment strategies that were also taken forward in the nested pilot phase of the main randomised controlled trial. The analysis reported here is a pre-trial model based economic evaluation using the existing pre-trial evidence for these four alternative treatment strategies and provides useful insight for the final design and data collection. We have now added information on the survey and the emphasised the purpose of this paper in the Introduction.


Thank you for this overview of information of which we are aware. The information presented is correct in terms of the suggestion of effectiveness provided. These studies are not however definitive or conclusive but the evidence they provide remains inadequate and the case to support a full randomised controlled trial (in progress) was considered appropriate by the funders. Again we emphasise that this paper reports the pre-trial model based economic evaluation to inform the design of full, main randomised controlled trial currently in progress and will report in four years. This point has been clarified in the background section of the paper in response to the point above.

iii) There is an immense amount of published data demonstrating that excision of endometriomas results in a reduction of ovarian reserve (The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. J Clin Endocrinol Metab 2012;97:3146-3154). This damage seems to be additive, in terms of postoperative pregnancy rates, in case of second-line surgery for recurrent endometriotic cysts (The effect of second-line surgery on reproductive performance of women with recurrent endometriosis: a systematic review. Acta Obstet Gynecol Scand. 2009;88:1074-82). Thus, in order to fully evaluate the economic impact of postoperative preventive measures, also the additional costs of assisted reproduction techniques in women with infertility associated with gonadal damage derived from repeated surgical procedures should be taken into account.
Thank you for this. However this information is beyond the objective of the current paper. In as much as the treatments being compared are trying to prevent further surgery, if further surgery is required then the treatment has failed in its objective. Furthermore, continued use of treatments such as the combined oral contraceptive pill is unlikely to enhance short term fertility either. We have now made explicit in the assumptions on page 7 that we have not considered the impact of any treatments on long term fertility in the model.

iv) It is unclear if only dysmenorrhoea has been considered or also other pain symptoms. As an example, it has been observed that prolonged progesterin therapy for recurrent endometriosis after conservative surgery significantly reduces pain at intercourse and improves sexual satisfaction (Surgical versus medical treatment for endometriosis-associated severe deep dyspareunia: I. Effect on pain during intercourse and patient satisfaction. Hum Reprod. 2012;27:3450-9. Surgical versus low-dose progesterin treatment for endometriosis-associated severe deep dyspareunia II: effect on sexual functioning, psychological status and health-related quality of life. Hum Reprod. 2013;28:1221-30). The LNG-IUD abolishes menstruations in the majority of women using it. Thus, it might reveal a cost-effective measure for the prevention of dysmenorrhoea recurrence when the main symptom referred is pain at menstruation, whereas the effect on other types of pain may differ. The LNG-IUD does not inhibit ovulation, whereas DMPA and COCP do. This may result in different effects on non-menstrual pelvic pain.

Thank you for this information. We can confirm that pain is being measured and fully assessed in the main randomised controlled trial. Quality of life instruments are being used and data is being collected prospectively alongside the trial and its follow up period. An assessment of pain is integral to those instruments. However the model based pre-trial economic evaluation reported here did not find any data on quality of life that could be used in the current preliminary evaluation.

v) The authors assumed that "the second hormonal treatment will comprise one of the two remaining treatment strategies or GnRHa, which includes HRT to enable the treatment to be used longer term than 6 months". GnRHa are not cytoreductive, as all the other treatments considered, but are extremely more costly. Why did not the authors consider nor-ethisterone acetate (NETA) as a cost-effective alternative treatment in case of failure of LNG-IUD, DMPA, and COCP? There is ample evidence on the effect of NETA on symptomatic and recurrent endometriosis. NETA is associated with about 70% amenorrhoea rate and a similar satisfaction rate in intention-to-treat analyses (see, as an example, Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. Fertil Steril. 2015 Dec 8. pii: S0015-0282(15)02092-0. doi: 10.1016/j.fertnstert.2015.11.016). NETA at the oral dose of 2.5 mg per day costs a few pounds a year, and suppresses ovulation, menstruation, and endometriotic lesions.

Thank you for this comment. The response to this has already been presented in the response to comment (i) above. The main response is re-stated here. Prior to the trial, a survey of the British Gynaecological Endoscopy Society members was carried out. The survey, which was reported in the funding application and the final trial protocol, provided the following information used to design the main trial. (i) that 24% of clinicians used no post-operative treatment. (ii) LNG-IUS, combined oral pill (COCP) and DMPA are commonly prescribed, while oral progestogens and GnRH analogues are not. (iii) LNG-IUS (88%), COCP (42%), no treatment (38%) and DMPA (27%) were felt to be most in need of evaluation. It was imperative to respond to the funding call appropriately and design a trial that was deliverable. Hence the survey directly influenced the comparisons in the trial and therefore the comparisons in the pre-trial model based evaluation reported in the current paper.

vi) Although the authors sought the opinion of expert in the field, they should have also taken into account all the major published international guidelines on endometriosis management, which recommend postoperative medical treatment with the specific aim of reducing the symptoms' and recurrences' rates (see, in addition to the ESHRE guideline cited by the authors, The American College of Obstetricians and Gynecologists. Practice bulletin no. 114. Management of endometriosis.
In conclusion, although the authors state that “a pragmatic literature search was carried out to identify evidence on the four treatment strategies” (page 7), they seem to have missed important information on the effect of prolonged postoperative medical treatment. It is unclear how they performed their literature search, as only five small studies seem to have been considered (references 10-14). However, there is much more published information that could have lead to different conclusions on cost-effectiveness of tertiary prevention of endometriosis. The authors should re-consider their conclusions in light of the now fairly robust evidence on (not short-term) postoperative medical treatment. Suggesting that “there is currently no evidence to support any treatment being recommended to prevent the recurrence of endometriosis following conservative surgery” does not appear to be based on the entire available evidence and could pose patients at iatrogenically increased risk of the detrimental consequences of recurrent endometriosis.

The pragmatic literature review is explained further below. But here we emphasise that design of the main randomised controlled trial, was informed by the review undertaken by ESHRE Endometriosis Guideline Development Group, September 2013 (page 88) and the survey of the British Gynaecological Endoscopy Society. The main randomised controlled trial which is currently in progress will report in four years’ time. The current pre trial model based economic evaluation reported in the current paper was purposely designed to replicate the current trial design based on the best available current evidence for that design in order to inform and help to refine the design and highlight areas where uncertainty could be resolved by informed data collection. We thank the reviewer for his comments and have tried to emphasise as many of the points he has raised in the revised paper as far as possible.

Reviewer: 3
Reviewer Name: James P. Moriarty
Institution and Country: Mayo Clinic, United States of America
Please state any competing interests or state ‘None declared’: None declared

General Comments: This paper aims to provide initial insight to the cost-effectiveness of four courses of action following conservative surgery for endometriosis. Specifically, the intent is to gain a better understanding on data lacking in the literature which may drive results and then use that knowledge to better inform data collection for a trial-based economic evaluation. This type of analysis is not often paired with a trial-based economic evaluation and would be a welcomed addition to the literature.

i) The authors are sometimes inconsistent in their verbiage throughout the text when discussing that this is an analysis focusing on recurrence of endometriosis after conservative surgery. The fact that this is specifically after conservative surgery is left out on several occasions. This needs to be consistent throughout the text.

Thank you this has now been clarified throughout the manuscript.

ii) Methods: It is not clear exactly how the sensitivity analysis is being performed in terms of holding the transition probabilities constant.
We have added the following sentence to page 12 to provide further detail on how the sensitivity analysis holding transition probabilities was carried out.

“This analysis was carried out by fixing parameters (i.e. transition probabilities) to the last values that were obtained from a random draw of the distribution and allowing the parameters for the utilities to be randomly sampled from the assigned distribution and vice versa.”

No base-case estimate is being provided in Table 1 as is done for the utility parameters in Table 2. These values need to be provided. I would recommend adding these values to Table 1. As outlined in the manuscript base case estimates are not used throughout the evaluation. Due to a lack of available evidence our aim was to assess the extent to which values for parameters need to change to affect the treatment decision. Therefore only distributions were assigned to parameters. The distributions for the transition probabilities were used to ensure a suitably wide distribution to reflect the extent of uncertainty in the estimates. The estimates in the first column presented in table 2 are not base case estimates they are taken from clinicians and are used as a basis for assigning a distribution around the utility value parameters, which is used in the analysis. This has been clarified by adding the following footnote to table 2.

“*The estimate reflects the values provided by clinicians and is used only to set the range of values for the analysis”

Additionally, no details are given on the “pragmatic” literature search. If the literature was still searched in a structured way (e.g. with various subject headings, keywords and combinations) this should be described.

Additional information has been provided on the literature search strategy on page 8 and the limitations of such an approach are highlighted in the limitations.

“The evidence on current medical therapies which was included in the PRE-EMPT trial protocol was reviewed to identify evidence on effectiveness which would provide data for the transition probability parameters in the model. To identify literature for the utility values for the health states in the model we searched the web of science database using the following key words ‘endometriosis’ and ‘economic’ and ‘EQ-5D’ or ‘quality of life’ or ‘SF-6D’.”

iii) Results: The results of the sensitivity analysis of holding certain parameters constant while varying others are not presented with enough detail. Figures 3 and 4 should be accompanied by cost-effectiveness acceptability curves as was done in Figure 2. This will allow the reader to better see how results change based on these sensitivity analyses.

The purpose of a CEAC is to show the overall probability that any option will be cost-effective at a given threshold ICER. Thus a CEAC is only meaningful when all the parameter uncertainty is included in the model. The purpose of Figures 3 and 4 is to show how much of the uncertainty in Figure 2 can be attributed to different parameter sets (i.e. utilities or transition probabilities) and therefore to aid in the identification of areas that should be considered for further data collection in the trial. Drawing a CEAC from these scatterplots would be misleading. We have added the following sentence to the methods on page 13:

"Cost-effectiveness planes were produced for each set of parameters varied, but it is inappropriate to use all these planes to produce cost effectiveness acceptability curves (CEACs) as they will not show the overall uncertainty. CEACs were only produced to illustrate the overall uncertainty."

Furthermore, I was quite surprised to see model results indicate that no treatment was both less costly and resulted in more QALYs. I would not expect that better outcomes in terms of QALYs would
occur from no treatment. Based on Table 2, I would surmise this is stemming from a lower quality of life for treatment than no treatment which is not offset enough from a higher probability of recurrence for no treatment compared to treatment. This type of trade-off for treatment is not entirely common. Whatever the true underlying reason for no treatment being dominant, this warrants being expanded on in the discussion.

Thank you for this observation. We agree that the likely effect here is due to the fact that we have given a substantial reduction in quality of life for the fact of being on treatment, in line with the estimates provided by our clinicians. We have added the following sentence to the discussion, immediately following the amended sentence in response to the next comment (on page 15):

"This result appears to be driven by the assumption that being on treatment will itself lead to a substantial reduction in quality of life,"

While considering this comment, we have realised that Table 2 is not clear on the nature of the distributions used for sampling the quality of life values for the various health states. We have added the following footnote:

"These beta distributions are applied within the ranges shown in the previous column, not across the full range of possible values from 0 to 1. Thus the sampled value for any asymptomatic state will always be higher than the sampled value for the corresponding symptomatic state."

iv) Discussion: It is not correct to state that "no treatment is the appropriate course of action to prevent recurrence..." on the bottom of page 13. While a recurrence may not happen with no treatment, that is not the same as saying no treatment actually prevented a recurrence. This should be rephrased to state no treatment is the appropriate course of action due to it being more cost-effective, and in fact dominant.

Thank you. We have now amended this sentence as follows:

"The model based analysis, based on best available current data, suggests that no treatment is the appropriate course of action due to it being more cost-effective when compared to other treatment strategies (DMPA, COCP and LNG-IUS)."

Limitations: It should be reiterated that, given the pragmatic approach to searching the literature, it is possible that additional usable studies could be found from a comprehensive systematic review. While it is unlikely a systematic review would reveal enough additional information to have a much higher level of confidence on parameter values, it cannot be ruled out. Additionally, it should also be reiterated that the transition probabilities found in the literature were based on results using different measures, and thus were difficult to synthesize into the model. This can, and should, be tempered with the use of wide distributions in the analysis.

Thank you. These two statements have now been added to the limitations.

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<td>GENERAL COMMENTS</td>
<td>The authors have addressed all the concerns. The manuscript seems now more clear and balanced. I am satisfied with the modifications made.</td>
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<tr>
<td>REVIEWER</td>
<td>James Moriarty&lt;br&gt;Mayo Clinic&lt;br&gt;Rochester, MN&lt;br&gt;USA</td>
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<tr>
<td>REVIEW RETURNED</td>
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<td>All of my prior comments and concerns have been addressed to my satisfaction. I have no further comments.</td>
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Pharmaceutical treatments to prevent recurrence of endometriosis following surgery: a model-based economic evaluation
Sabina Sanghera, Pelham Barton, Siladitya Bhattacharya, Andrew W Horne and Tracy Elizabeth Roberts

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