OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: Jan 23, 2020
To: "Alison Edelman" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-2360

RE: Manuscript Number ONG-19-2360

Cannabinoids for Pain Control during Medical Abortion: A Randomized Controlled Trial

Dear Dr. Edelman:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Feb 13, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: In this manuscript, the authors present an RCT comparing the effect of cannabinoids on pain control in women undergoing a medical abortion. Overall, the study is very well done but the survey response rate among study participants is less than 60% and over 40% of the survey responses were 2hrs late meaning women were having to recall their pain. The mixture of recalled pain at time "x" and on-time reported pain at time "x" presents some concern. The study finds no effect of cannabinoids on reported pain and I suspect this is correct. The discussion is excellent and features informative considerations on this topic that is of general interest relative to the question of non-opiate pain control w/ surgery. I have the following specific questions/comments:

1) The authors are reminded that a comma is necessary before "which" when this word is used as a conjunction. Alternatively, and to some preferably, use the word, "that" instead.

2) How did the characteristics of women not "willing and able" to receive text messages differ from those that could? Also, how did the excluded current MJ users compare to the study population? Obviously, a limitation is any RCT is the generalizability of the study. Arguably, excluding current MJ users and those not "willing and able" to receive text message may have selected a more well-adjusted population that was more stoic about pain. What were the characteristics of the decline/not-responding enrolled subjects relative to the included subjects? Related to these questions is the statement in the discussion, "if one were present." Can you clarify?
Overall, very well done study but some troubling missingness in the subject responses (and I really feel your pain).

Reviewer #2: Thank you for this interesting and novel study on a common and important topic. While the findings were negative, this represents a unique contribution of the literature that can be built upon for future research. Please see some minor considerations below.

* Line 25: Define or don't use the acronym THC in the precis

* Per author guidelines, remove acronyms from the abstract

* Citations 1 and 2: there is a newer CDC abortion surveillance report that should be cited, either on it's own or in place of the older report.

* Throughout, please write out numbers less than 10

* Within the methods, please clarify instructions that patients received for how to manage pain (e.g. was ibuprofen not recommended after the initial dose?). This can help contextualize the results for table 3 and can help readers understand your usual care.

* Line 186: should be "approximately"

* Line 192: do you mean "moderate to severe"?

* Line 193: Do you mean median maximum pain score (for the second use in this line)?

* Line 198-200: this seems like a fair amount of missing or delayed data. Consider an additional analysis looking at the timepoint with the least amount of missing data, or may be worth mentioning this is in the discussion.

* Make sure to define all acronyms (line 226 FDA, line 242 NIH, etc.) and no need to re-define acronym as well (THC line 227)

* Lines 257-259: is this true? Wouldn't combining CBD with a synthetic THC be able to be patented like your study drug?

* Line 261: Use of participant instead of patient is more consistent

* Line 266: 24x7 isn't a conventional abbreviation- consider changing to "around the clock" or spelling it out

* Line 275-276: Be more specific with your concluding line! Maybe something like "continued research into the role of cannabinoids/complementary and alternative medications for pain control…"

* I'm not too familiar with the literature around this so might be wrong, but my understanding is there may be different effects experienced by regular users of marijuana/THC compared to non-regular users, where regular users may experience decreased side effects like anxiety compared to new users, but also may experience increased tolerance. I'm not sure if there's a differential effect on pain perception. Could your exclusion of those who've used marijuana recently possibly explain why there wasn't an effect (compared to the literature you cite in the intro)? Consider adding to discussion.

* Please define acronyms in the tables and figures, as these should stand alone. In the tables, make sure you also label what is in the parentheses/+/-. SD, SE, IQR, etc.

* Figure 1: "Other" in the exclusion is pretty high. Please explain or give examples of some of these- either here or in text.

Reviewer #3: Well designed and executed RCT looking at the potential benefits of a synthetic form of THC. The trial demonstrated a lack of benefit, however this may be due to the 5 mg dose and the lack of an anti nausea effect may be due to the administration of 4 mg oral ondansetron to all research patents. In my experience ondansetron is not a routine medication give for medication abortion. The dose issue should be specifically addressed in conjunction with consideration for a combined THC-CBD product if and when available. I anticipate that there will be additional studies of acute pain in other situations which may help guide future studies with regard to specific THC formulation and dose. The study assessed pain during the first 24 hours as well as at 21 days. A shorter interval such as 3-7 days might have yielded additional information as the ability to recall pain after 21 days may be limited.
I would include the above points in the limitations and recommendations for future studies.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Abstract: Would need to conform to our RCT abstract template.

lines 162-163, 189-190, Table 2 and fig 2: Need to clearly separate the primary from the secondary endpoints in Table 2. Also, need to clarify how many women in each cohort had reported the max pain score (in both the ITT and the PP

groups). Specifically, need to report how many in each cohort had data for ITT analysis of the primary and how many had data for the PP analysis of the primary. It appears that there was such a high proportion of women in each cohort that did not adhere to the protocol and/or did not report pain scores, that the study was actually under powered to discern a difference in primary outcome. Certainly Table 2 analysis was under powered, since there were only 22 vs 20 individuals analyzed.

Tables: Given the column totals, the %s should all be rounded to nearest integer % for those in the n(%) format. The counts are insufficient to cite precision to nearest 0.01%. Also, age, BMI and GA should all be rounded to nearest 0.1 unit

General: There was a wide range of baseline pain scores (Fig 2). It appears that a better study design would have been to compare the change from baseline to max pain as the primary outcome using each woman as her own control, rather than comparing mean differences baseline vs max pain.

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

Line 25: spell out all abbreviations on first use, considering the abstract, precis and manuscript as 3 different places to do this (ie, spell out on first use in each portion of your submission). If you don't need to use the abbreviation because you don't reference it again, don't include it.

Please use the abstract for RCTs—template here: https://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf

Line 61: This should read From November 2018 to May 2019. Same as on line 119., line 183

Line 95: Perhaps "continue to increase" rather than rise would be clearer.

Line 122: Give unit for age.

Line 134: what were the various block sizes?

Line 162: could you describe how the NRS appeared on the text messaging platform? Did the participant place a point on a linear scale, or pick a integer value?

Line 167: How did you decide 2 points was clinically significant?

Line 194: You should mention the per protocol analysis in the methods section.

Lines 196-200: what type of scales were used for nausea, anxiety

Line 208: Not sure I understand about maintaining blinding. Did you ask people what drug they thought they were on. Given it was a binary choice, it sort of makes sense that about ½ the people would guess correctly.

Line 223: This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the databases you have searched (PubMED, Google Scholar, EMBASE for example), the dates searched, and the search terms used. If not done, please edit it out of the paper.

Line 227: spell out CB

Please note that the significant concerns raised by the statistical editor need to be satisfactorily addressed in order to move this paper past the first revision stage.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with

efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

6. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

7. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

8. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

9. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

10. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using

"and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

11. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

12. Line 223: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

14. Figures 1 and 2 may be resubmitted with the revision as-is.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

16. If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Feb 13, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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Cover letter

[redacted]

February 1, 2020

Dear Editor,

Please find attached our **re-submission** to Obstetrics & Gynecology, titled "Cannabinoids for pain control during medical abortion." We have responded to the reviewer and editors comments below as well as in the manuscript.

This manuscript has not been submitted to any other publication, and I do not intend to submit this manuscript to any other publication while It is under review at Obstetrics & Gynecology.

All those named in the acknowledgements have given written permission. All individuals meet criteria for authorship.

The trial was registered to clinicaltrials.gov. NCT03604341 and received IRB approval by the Oregon Health & Science University IRB. Informed written consent was obtained from all participants and these are filed with other study materials.

The lead author* (below) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Please contact me with any outstanding questions or concerns.

Alison Edelman, MD, MPH
Professor, OB/GYN
Director, Family Planning Fellowship
Oregon Health & Science University
[redacted]

Author Responses to REVIEWER COMMENTS **(BOLD)**: **All lines correspond to simple markup view.**

Reviewer #1: In this manuscript, the authors present an RCT comparing the effect of cannabinoids on pain control in women undergoing a medical abortion. Overall, the study is very well done but the survey response rate among study participants is less than 60% and over 40% of the survey responses were 2hrs late meaning women were having to recall their pain. The mixture of recalled pain at time "x" and on-time reported pain at time "x" presents some concern. The study finds no effect of cannabinoids on reported pain and I suspect this is correct. The discussion is excellent and features informative considerations on this topic that is of general interest relative to the question of non-opiate pain control w/ surgery. I have the following specific questions/comments:
In light of your comment, we realized that we did not represent the 'completeness' of our data for our primary outcome of maximum pain well which was 94.3% (66/70). We have clarified this in the results, lines 201-202.

1) The authors are reminded that a comma is necessary before "which" when this word is used as a conjunction. Alternatively, and to some preferably, use the word, "that" instead. **We have inserted a comma before 'which' and have changed one which to 'that' (lines 101, 109, 224, 286).**

2) How did the characteristics of women not "willing and able" to receive text messages differ from those that could? **As noted in Figure 1 CONSORT, we only had n=2 exclusions for not willing and able to agree to study terms – which could include unwilling or unable to use text messages or unwilling to receive study drug or be randomized, etc. Eligibility criteria is stated on in lines 121-126. "Our major eligibility criteria were English speaking women aged 21 years and older who had a confirmed pregnancy of 70 days gestation or less or pregnancies of unknown locations (PUL) at ≤ 35 days gestational age at low risk for ectopic pregnancy, willing and able to receive text messages, no recent history of methadone, buprenorphine, or heroin use, and no recent routine use of marijuana (five or more days in the last week) or opioids (within the last 30 days)."**
Also, how did the excluded current MJ users compare to the study population? **Unfortunately, we do not collected demographic data on excluded women other than their reason for exclusion. We have included the limitation of excluding current MJ users in the discussion section in lines 272-276. "We chose a group of subjects that were likely to see a response, if one were present, from the study drug and excluded those that use marijuana regularly. Marijuana is legal both recreationally and medically in the state of Oregon, however in order to have a population that better represents the entire country and the variable availability of marijuana, frequent users were excluded."**

What were the characteristics of the decline/not-responding enrolled subjects relative to the included subjects? Related to these questions is the statement in the discussion, "if one were present." Can you clarify? **We only had 3 women, who were subjects that early terminated, who we did not receive data for our primary outcome; we have included some additional information for them on lines 270-271 but they were no different demographically then responders. We have added additional information in the discussion section on our limitations to address generalizability (lines 272-276).**

Overall, very well done study but some troubling missingness in the subject responses (and I really feel your pain). **As mentioned earlier, we did not well represent our response rate in regard to our primary outcome. We have significantly revised this to better reflect our high response rate for our primary outcome (66/70 = 92.3%). Our text messaging data collection process actually helps to ensure higher rates of complete data rather than the return of a paper diary where we would have no idea how 'late' a response might be. We have revised lines 201-202 to include our response rate of 92.3% (66/70) for our primary outcome of maximum pain. Additionally, lines 268-270 also includes 'Excluding the 3 participants that prematurely discontinued, we had a response rate of 99% for our primary outcome of maximum pain (66/67)." Lines 278-280 clarifies late data: Additionally, just over half of respondents completed the surveys eliciting a pain score within a two hour window and 41% had at least a two hour delay in responding to at least one survey. Therefore, some pain scores may reflect recall bias.**

Reviewer #2: Thank you for this interesting and novel study on a common and important topic. While the findings were negative, this represents a unique contribution of the literature that can be built upon for future research. Please see some minor considerations below.

* Line 25: Define or don't use the acronym THC in the precis. **We have removed the acronym (Line 25) and replaced with Tetrahydrocannabinol.**

* Per author guidelines, remove acronyms from the abstract. **We have removed the acronyms from the abstract.**

* Citations 1 and 2: there is a newer CDC abortion surveillance report that should be cited, either on it's own or in place of the older report. **The Jatlaoui study has been updated to the 2019 publication in our manuscript and our references.**

* Throughout, please write out numbers less than 10. **We have changed this throughout the manuscript unless it was related to specific time points, results, drug dosage or the description of the numerical rating scale etc.**

* Within the methods, please clarify instructions that patients received for how to manage pain (e.g. was ibuprofen not recommended after the initial dose?). This can help contextualize the results for table 3 and can help readers understand your usual care. **We have included this information on line 139-141: "Participants were provided with two additional ibuprofen 800mg tablets and could take it as needed for pain as instructed by their provider." Additionally we have included an asterix below table 3 to further explain the 'standard' administration of prophylactic ibuprofen and ondansetron which was not included in this table. This reads "*All participants were instructed to take Ibuprofen 800mg and ondansetron 30 minutes prior to buccal misoprostol. These prophylactic medications are not included in this table."**

* Line 186: should be "approximately". **We have changed approximate to approximately (line 189).**

* Line 192: do you mean "moderate to severe"? **Yes, thank you. We have corrected to moderate to severe (line 195).**

* Line 193: Do you mean median maximum pain score (for the second use in this line)? **Yes, we have added 'median' on lines 192 and 193.**

* Line 198-200: this seems like a fair amount of missing or delayed data. Consider an additional analysis looking at the timepoint with the least amount of missing data, or may be worth mentioning this is in the discussion. We recognized this was a major misrepresentation on our part regarding the completeness of our response rate for our primary outcome. **We have two women who did not complete baseline pain scores and one woman who did not complete the survey for maximum pain at 6 and 24 hours. We have further clarified our response rate for our primary outcome in lines 201-202 "The response rate for our primary outcome of maximum pain was 92.3% (66/70)." Additionally, we have clarified our late response rates in lines 278-280: "Additionally, just over half of respondents completed the surveys eliciting a pain score within a two hour window and 41% had at least a two hour delay in responding to at least one survey. Therefore, some pain scores may reflect recall bias."**

* Make sure to define all acronyms (line 226 FDA, line 242 NIH, etc.) and no need to re-define acronym as well (THC line 227) **FDA acronym is first defined on line 130, the acronym is then used throughout the manuscript. In line 247, NIH acronym was removed and replaced with National Institutes of Health. Line 232 was changed to remove the redefinition of THC.**

* Lines 257-259: is this true? Wouldn't combining CBD with a synthetic THC be able to be patented like your study drug? **While possible, there is no**

current drug that is FDA approved and therefore able to be used in a study. We have discussed the issues regarding studying cannabinoids in lines 251-264 in the discussion section. "Although considerable media attention and public interest in the use of CBD products for pain has led to their widespread availability, no randomized trials have evaluated potential benefit for gynecologic pain. Federal law does not prohibit the possession or distribution of CBD. However, as of June 2018 no CBD product had received FDA approval, so we could not obtain regulatory approval to test any CBD in our study. Combining CBD with THC has been shown in other research to reduce the psychotropic effects while maintaining the analgesic and anxiolytic effects of THC.[26] This combination deserves further attention to manage the physical and emotional symptoms experienced during medical abortion. In states where cannabis is legal for recreational or medical use, a variety of combined THC-CBD products are readily available to the public through cannabis dispensaries.[27] Unfortunately, clinical trials of non-FDA approved forms of cannabinoids are not permitted by the FDA. Given the absence of patent protection, the high costs of obtaining an investigational new drug application and conducting a clinical trial of a CBD or combined CBD-THC product will likely prevent further scientific studies to answer this question."

* Line 261: Use of participant instead of patient is more consistent.
Participant was substituted for patient throughout the manuscript in lines 52, 95, 120, 141, 151, 158, 160, 161, 165, 210, 211, and 266.

* Line 266: 24x7 isn't a conventional abbreviation- consider changing to "around the clock" or spelling it out. **Thank you for pointing this out. 24x7 has been changed in line 277 to "24 hour".**

* Line 275-276: Be more specific with your concluding line! Maybe something like "continued research into the role of cannabinoids/complementary and alternative medications for pain control…"
We have revised lines to state in lines 290-294 to state: "We did not find decreases in pain, anxiety and nausea during medical abortion with a synthetic THC oral medication. Other formulations of cannabinoids, including a combined THC-CBD may or may not be better suited to treat the constellation of symptoms many patients report during the procedure but this has yet to be studied."

* I'm not too familiar with the literature around this so might be wrong, but my understanding is there may be different effects experienced by regular users of marijuana/THC compared to non-regular users, where regular users may experience decreased side effects like anxiety compared to new users, but also may experience increased tolerance. I'm not sure if there's a differential effect on pain perception. Could your exclusion of those who've used marijuana

recently possibly explain why there wasn't an effect (compared to the literature you cite in the intro)? Consider adding to discussion.

As addressed above in reviewer #1's questions, excluding current MJ users may have selected a more well-adjusted population that was more stoic about pain. Marijuana is legal both recreationally and medically in the state of Oregon where this study was conducted. There is evidence that marijuana reduces perceived pain (O'Connell M et al., Medical Cannabis: Effects on Opioid and Benzodiazepine Requirements for Pain Control. Ann Pharmacother. 2019 May 25). Women do use marijuana for medical abortion-related pain (Louie, K., et al., A survey study of marijuana use for pain management during first-trimester medical abortion. Contraception. 94(4): p. 394). We wanted a population that was representative for the entire country for generalizability, of which most states do not have this broader access to and more accepted use of marijuana. We have included information on what is known about pain and marijuana in our discussion section lines 242-244, "Evidence supports that inhaled marijuana is more effective for pain treatment due to the quick onset that allows better titration of dose for symptom control compared to oral dronabinol." Lines 250-253, "Cannabidiol (CBD) is a CB_1 and CB_2 receptor antagonist that produces a non-euphoriant, anti-inflammatory analgesic effect.[19, 25] Although considerable media attention and public interest in the use of CBD products for pain has led to their widespread availability, no randomized trials have evaluated potential benefit for gynecologic pain." and 256-257 "Combining CBD with THC has been shown in other research to reduce the psychotropic effects while maintaining the analgesic and anxiolytic effects of THC". Lines 272-276 discuss our rationale for excluding frequent MJ users to broaden our generalizability. "We chose a group of subjects that were likely to see a response, if one were present, from the study drug and excluded those that use marijuana regularly. Marijuana is legal both recreationally and medically in the state of Oregon, however in order to have a population that better represents the entire country and the variable availability of marijuana, frequent users were excluded."

* Please define acronyms in the tables and figures, as these should stand alone. In the tables, make sure you also label what is in the parentheses/+/-. SD, SE, IQR, etc.

All acronyms in the tables and figures have now been defined as well as labeling what is in parentheses.

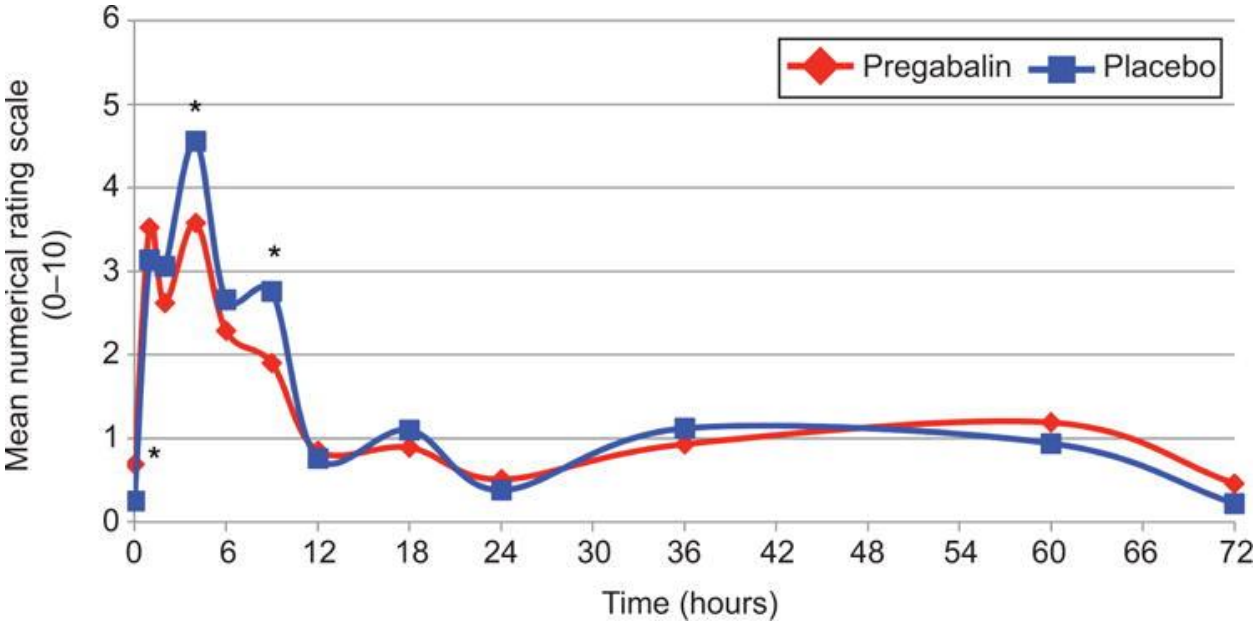
* Figure 1: "Other" in the exclusion is pretty high. Please explain or give examples of some of these- either here or in text.

Descriptions of the 18 "Other" women are now described in Figure 1 Consort diagram. After enrollment in the study began, women had the additional option to take vaginal misoprostol. In order to reduce additional protocol variables, women who took vaginal misoprostol were excluded. Our initial protocol excluded women with a pregnancy of unknown location. Our protocol changed to include these women partway through the study. Two

additional women were not approached due to lack of study staff availability.

Reviewer #3: Well designed and executed RCT looking at the potential benefits of a synthetic form of THC. The trial demonstrated a lack of benefit, however this may be due to the 5 mg dose and the lack of an anti nausea effect may be due to the administration of 4 mg oral ondansetron to all research patents. In my experience ondansetron is not a routine medication give for medication abortion. The dose issue should be specifically addressed in conjunction with consideration for a combined THC-CBD product if and when available. I anticipate that there will be additional studies of acute pain in other situations which may help guide future studies with regard to specific THC formulation and dose. The study assessed pain during the first 24 hours as well as at 21 days. A shorter interval such as 3-7 days might have yielded additional information as the ability to recall pain after 21 days may be limited.
I would include the above points in the limitations and recommendations for future studies.

We agree that the prophylactic use of ondansetron may have contributed to the lack of difference in an anti-nausea effect. Prophylactic ondansetron is a standard practice at this clinical site. We have made changes in the manuscript to reflect Lines 285-287 now include: "the lack of a demonstrated anti-nausea effect may be due to prophylactic ondansetron administration, which is standard at this clinical site to offset potential gastrointestinal symptoms induced by misoprostol use." The time frame of 24 hours was chosen based on prior literature, which did not demonstrate significant pain beyond 24 hours (Friedlander EB et al 2018) – see graph below. This was included in the discussion section in lines 225-227 "It is unlikely that we missed capturing maximum pain within a 24 hour window, as previous literature did not demonstrate significant pain beyond a 24 hour window of misoprostol use." Additionally, the 21 day follow up interval text did not ask about recalling pain scores. Pain score data was limited to the first 24 hours, in the baseline, 6 and 24 hour surveys. This is clarified in lines 152-155: "Participants received a follow up survey 21 days after enrollment to collect information on satisfaction with the pain medications, adverse side effects, any additional medication or therapies used during the process and whether the participant believed they received the study drug or placebo". Also, routine follow-up for the clinical site we partnered with was 14-21 days, which is why we chose this timeframe for follow-up for our study.



Friedlander EB et al. Prophylactic Pregabalin to Decrease Pain During Medical Abortion: A Randomized Controlled Trial. Obstet Gynecol. 2018 Sep; 132(3): 612–618.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Abstract: Would need to conform to our RCT abstract template.
Thanks for pointing this out. We have re-edited our abstract to conform to the journal's template.

lines 162-163, 189-190, Table 2 and fig 2: Need to clearly separate the primary from the secondary endpoints in Table 2. Also, need to clarify how many women in each cohort had reported the max pain score (in both the ITT and the PP groups). Specifically, need to report how many in each cohort had data for ITT analysis of the primary and how many had data for the PP analysis of the primary. It appears that there was such a high proportion of women in each cohort that did not adhere to the protocol and/or did not report pain scores, that the study was actually under powered to discern a difference in primary outcome. Certainly Table 2 analysis was under powered, since there were only 22 vs 20 individuals analyzed.

Tables: Given the column totals, the %s should all be rounded to nearest integer % for those in the n(%) format. The counts are insufficient to cite precision to nearest 0.01%. Also, age, BMI and GA should all be rounded to nearest 0.1 unit

General: There was a wide range of baseline pain scores (Fig 2). It appears that a better study design would have been to compare the change from baseline to

max pain as the primary outcome using each woman as her own control, rather than comparing mean differences baseline vs max pain.

Our primary outcome was maximum pain reported within 24 hours, this is not included in table 2. Our primary outcome results are stated in lines 192-194: "The treatment groups were no different in their median maximum pain score reported [dronabinol 7 (IQR6-8), placebo 7 (IQR5-8), p=.82]." Max pain scores are now clarified in lines 201-202: "The response rate for our primary outcome of maximum pain was 92.3% (66/70)." Therefore, we did have enough power to determine our primary outcome since 31 subjects per group were needed stated in lines 171-173: "A sample size of 31 participants per arm provided 80% probability (0.05 significance) of detecting a clinically significant ≥2 point difference in pain." Table 2 is a secondary outcome. This has been included in the table footer for clarification.
Tables: The tables are have been revised to match the editor's recommendations.
General: We did look at the wide range of baseline pain scores. Of the three participants that have baseline scores >7, two of them responded to the baseline survey >2 hours from initial contact. From prior data, we know that onset of peak pain typically begins 2-3 hours after misoprostol, therefore their baseline pain may be during peak pain if response time is greater than 2 hours (Colwill et al. Opioid Analgesia for Medical Abortion: A Randomized Controlled Trial. Obstetrics & Gynecology 134(6):1163-1170, December 2019). This is now clarified in lines 280-285: "As with many pain studies, the reported baseline pain scores had a wide range. Two of the three participants that reported a baseline pain score >7 responded greater than two hours after the initial baseline survey went out. From prior data, we know that onset of peak pain typically begins 2-3 hours after misoprostol, therefore their baseline pain may be during peak pain if response time is greater than 2 hours". Per your suggestion, we did an additional analysis to compare mean differences between baseline and maximum pain within each woman, and found no difference (p=.82).

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will

avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

Line 25: spell out all abbreviations on first use, considering the abstract, precis and manuscript as 3 different places to do this (ie, spell out on first use in each portion of your submission). If you don't need to use the abbreviation because you don't reference it again, don't include it.
Our resubmission has corrected the use of abbreviations throughout the manuscript.

Please use the abstract for RCTs—template here:
https://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf
Thank you for providing this reference. We have used this as a guide to edit our abstract for this resubmission.

Line 61: This should read From November 2018 to May 2019. Same as on line 119., line 183
We have corrected this on lines 60, 118-119, 186.

Line 95: Perhaps "continue to increase" rather than rise would be clearer.
This has been changed to 'continue to increase' on line 94.

Line 122: Give unit for age.
Years has been added to line 121.

Line 134: what were the various block sizes?
72 subjects were randomized into 4 blocks of 8 and 4 blocks of 10. This has been clarified in the manuscript on line 134.

Line 162: could you describe how the NRS appeared on the text messaging platform? Did the participant place a point on a linear scale, or pick a integer value?
The participant picked an integer value 0-10. We have clarified this in lines 164-65 "Participants defined their maximum pain as an integer between zero and 10".

Line 167: How did you decide 2 points was clinically significant?
Prior literature was used to help us determine that a 2 point difference was clinically significant as cited in the methods section on line 173.

Line 194: You should mention the per protocol analysis in the methods section.
We have added to the methods section line 183-84: "Additionally, we performed a per-protocol analysis."

Lines 196-200: what type of scales were used for nausea, anxiety
The participant picked an integer value 0-10. We have clarified this in line 166.

Line 208: Not sure I understand about maintaining blinding. Did you ask people what drug they thought they were on. Given it was a binary choice, it sort of makes sense that about ½ the people would guess correctly.
This is now clarified in lines 210-212: "Blinding was maintained as 54% of participants in the dronabinol group and 56% of participants in the placebo group accurately identified if they had received study drug or placebo, as this is similar odds to the random nature of a coin toss."

Line 223: This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the databases you have searched (PubMED, Google Scholar, EMBASE for example), the dates searched, and the search terms used. If not done, please edit it out of the paper.
Line 228-229 has been edited to the following: "Our study is novel in that we performed a randomized trial to determine the effect of cannabinoids for the treatment of gynecologic pain."

Line 227: spell out CB
This has been changed to cannabinoid (line 233).

Please note that the significant concerns raised by the statistical editor need to be satisfactorily addressed in order to move this paper past the first revision stage.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.
A – we opt-in.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your

coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.
We will confirm with our coauthors that their disclosures match our title page.

3. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).
We have included an Authors' Data Sharing statement in our revised manuscript (lines 387-402).

Authors' Data Sharing Statement

- **Will individual participant data be available (including data dictionaries)?** ***Yes.***
- **What data in particular will be shared?** ***All de-identified individual participant data collected during the trial.***
- **What other documents will be available?** ***Study protocol.***
- **When will data be available (start and end dates)?** ***Immediately following publication and ending 3 years after article publication.***
- **By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)?** ***Researchers who provide a methodologically sound proposal and rationale for use of the data set, their proposed analyses and results through academically established means. Oregon Health & Science University maintains a high community standard for the free release of data and materials. Transfer of resources is subject to the acceptance of a Materials Transfer Agreement as required by policy at Oregon Health & Science University. Oregon Health & Science University understands and agrees to comply with the NIH policy on Sharing Research Data and on Sharing Model Organisms.***

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.
We will abide by the revitalize definitions.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.
Our revised manuscript adheres to the length restrictions.

6. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).
Our acknowledgements follow the rules as governed by the journal.

7. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

The abstract has been reviewed and reflects revisions made in the body of the manuscript.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.
Abstract word count: 275

8. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.
We reviewed these guidelines, our abstract and manuscript now meets the journal's standard format.

9. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.
Our revised manuscript complies with the journals guidelines on abbreviations and acronyms.

10. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.
The manuscript was reviewed and the virgule symbol in the revised manuscript is used only to express data or a measurement.

11. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

Thank you for the feedback. Where appropriate, OR and RR with 95% CI were replaced to make the results more clinically relevant. P values reporting meets the journal's requirements.

12. Line 223: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.
Line 228-229 has been changed to state "Our study is novel in that we performed a randomized trial to determine the effect of cannabinoids for the treatment of gynecologic pain."

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.
We have reviewed the tables and they comply to the journal's style.

14. Figures 1 and 2 may be resubmitted with the revision as-is.
Figure 1 had undergone some edits and will be resubmitted.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.
We will respond to the email promptly.

16. If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:
* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

This format has been followed for our resubmission.

Date: Feb 18, 2020
To: "Alison Edelman" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-2360R1

RE: Manuscript Number ONG-19-2360R1

Cannabinoids for Pain Control during Medical Abortion: A Randomized Controlled Trial

Dear Dr. Edelman:

Your revised manuscript has been reviewed by the Statistical Editor. We would like to to address their comments before we consider the manuscript. Please upload your edited version of your manuscript in Editorial Manager.

If we have not heard from you by Feb 25, 2020, we will assume you wish to withdraw the manuscript from further consideration.

STATISTICAL EDITOR:

I appreciate the changes and work that the Authors have done in response to my queries, but would like to see the following clarifications/changes for the reader:

(1) As stated on lines 56-57, the primary outcome and the only one that the power/sample size calculation was based on was maximum pain during 24 hrs after misoprostol administration. That primary outcome (as ITT) needs to be separately cited in Tables and the conclusion should reflect that outcome, the others are secondary.

(2) To that end, the conclusion, lines 69-70 should only describe the primary outcome, not other time points nor other outcomes.

(3) Should include a separate Table, similar to Table 2, that includes the primary outcome with the N for each group.

(4) Also, please clarify lines 181-183 and Fig 1: Where are the 15% who "had not answered surveys within the allocated time frame or declined participation after randomization". Need to state how many within the N = 33 and N = 34 of fig 1 had data to state their max pain scores during the 24 hrs after misoprostol administration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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February 24th, 2020

Dear Editor,

Please find attached our **re-submission** to Obstetrics & Gynecology, titled "Cannabinoids for pain control during medical abortion." We have responded to the reviewer and editors comments below as well as in the manuscript.

This manuscript has not been submitted to any other publication, and I do not intend to submit this manuscript to any other publication while It is under review at Obstetrics & Gynecology.

All those named in the acknowledgements have given written permission. All individuals meet criteria for authorship.

The trial was registered to clinicaltrials.gov. NCT03604341 and received IRB approval by the Oregon Health & Science University IRB. Informed written consent was obtained from all participants and these are filed with other study materials.

The lead author* (below) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Please contact me with any outstanding questions or concerns.

Alison Edelman, MD, MPH
Professor, OB/GYN
Director, Family Planning Fellowship
Oregon Health & Science University
[redacted]

Author Responses to REVIEWER COMMENTS **(BOLD)**: **All lines correspond to simple markup view.**

(1) As stated on lines 56-57, the primary outcome and the only one that the power/sample size calculation was based on was maximum pain during 24 hrs after misoprostol administration. That primary outcome (as ITT) needs to be separately cited in Tables and the conclusion should reflect that outcome, the others are secondary.

Line 221 now clarifies our results do not significantly decrease median maximum pain scores:
"does not significantly decrease median maximum pain, anxiety or nausea scores over 24 hours compared to placebo"

Lines 290 was changed to specifically state our primary outcome: "We did not find decreases in median maximum pain, anxiety and nausea during medical abortion with a synthetic THC oral medication."

Additionally, we added a new table (entitled Table 2) which reflects our primary outcome of median maximum pain score between placebo and dronabinol.

Table 2: Maximum Pain Scores

	Placebo (*n*=33)	Dronabinol (*n*=33)	
	Median (IQR)	Median (IQR)	*p*
Maximum pain*	7 (5-8)	7 (6-8)	.82
Baseline pain	0 (0-2)	0.5 (0-3)	.36
Pain at 6 hours	7 (5-8)	7 (4-8)	.72
Pain at 24 hours	6 (4-8)	7 (4-8)	.45

*Primary outcome

IQR, interquartile range

(2) To that end, the conclusion, lines 69-70 should only describe the primary outcome, not other time points nor other outcomes.

Our conclusion in the abstract removes our secondary outcomes. Lines 67-68: Dronabinol does not reduce the maximum level of pain experienced by women undergoing medical abortion.

(3) Should include a separate Table, similar to Table 2, that includes the primary outcome with the N for each group.

A new Table 2 was created that describes the primary outcome with the number in each arm.

Table 2: Maximum Pain Scores

	Placebo (*n*=33)	Dronabinol (*n*=33)	
	Median (IQR)	Median (IQR)	*p*
Maximum pain*	7 (5-8)	7 (6-8)	.82
Baseline pain	0 (0-2)	0.5 (0-3)	.36
Pain at 6 hours	7 (5-8)	7 (4-8)	.72
Pain at 24 hours	6 (4-8)	7 (4-8)	.45

*Primary outcome

IQR, interquartile range

(4) Also, please clarify lines 181-183 and Fig 1: Where are the 15% who "had not answered surveys within the allocated time frame or declined participation after randomization". Need to state how many within the N = 33 and N = 34 of fig 1 had data to state their max pain scores during the 24 hrs after misoprostol administration.

Table 2 better clarifies this question by stating the *n* for placebo and dronabinol groups (see table above). We had *n*=33 in both groups to analyze our primary outcome of median maximum pain score.

Additionally, lines 193 now include *n*=33 in reporting the results of median maximum pain scores "The treatment groups were no different in their median maximum pain score reported [dronabinol 7 (IQR6-8; *n*=33), placebo 7 (IQR5-8; *n*=33), p=.82] (Table 2)."