Date: Jul 06, 2018
To: "Lauren Thaxton" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1099

RE: Manuscript Number ONG-18-1099

Nitrous oxide versus intravenous sedation for second trimester abortion: A randomized clinical trial

Dear Dr. Thaxton:

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 Jul 27, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Thank you for your work on this subject. Specific comments:

1. Abstract: do not need to put full details of your non inferiority model and sample size into the abstract.

2. Intro: Lines 84-5: please add more detail about this study, the simple phrase is too declarative. Were there any secondary outcomes measured (or planned to be measured?)

3. Methods: Overall these are well-described.

4. Results: line 171, what do the percentages represent? You had just noted all of the procedures were performed by attending or fellow, so it is confusing. Again line 173, the percentages are a bit confusing, is this the percent who had procedure same day or the percent who had dilation? You have presented this data in table 2, you should reference it rather than repeat. Also table two indicates 3 types of provider, you should be clear about this in the text as well.

5. Discussion: line 209-11 this sentence is unclear, addressing two ideas.

6. Additionally you do not address if any other data could be learned from this study. Ie: were other outcomes collected? Was there a role for N2O in patients who understood it's decreased efficacy but had need of a non-IV sedation option (you hint at this in discussion of the refusals). What are future plans for study based on what you learned here?

Reviewer #2: The authors compared pain scores between 70% inhaled nitrous oxide and IV sedation with Fentanyl 100mcg and Midazolam 2mg for outpatient second trimester abortion procedures. The goal appears to be a method of satisfactory analgesia for an outpatient procedure such that the patient can be discharged rapidly and preferably without need of a companion.

There are a few problems with the study as designed. The amnesic effect of midazolam is far superior to that of nitrous oxide (unless the subject is on chronic BZ treatment or EtOH abuse). Thus asking questions requiring recall of pain may not be appropriate. Instead, assessment at several intervals during the procedure, or at times when stimulation peaks, would be more appropriate.

The half life of IV midazolam is 1.5-2.5h. Procedure duration was reported as <15min, so thirty min post-procedure for the final recall analysis is well within the 2h range. Patients were assessed while still under the effects of midazolam while N2O would be long out of the subject's system. Regardless, even days later, the recall would be different, even if the actual pain at the time were the same.

Additionally, dosing midazolam and fentanyl should be weight-based. On occasion patients can suffer significant respiratory depression from the combination of medications.

Ideally, some assessment of the PCB quality would have been included.

Comments on manuscript itself:

1. line 76 Nitrous Oxide is N2O, not N2O/O2. And it does not offer amnesia unless the patient is asleep, which they will not be if given only nitrous.

2. Nitrous is contraindicated in people with disorders of B12.

3. Why were fetal demise patients excluded?

4. Were all the paracervical blocks placed by providers with equivalent experience and skill? Ideally, the quality of the block should have been assessed, though theoretically the failure rate should be unaffected by the analgesic method.

5. Results: Were all 7 analgesic failures by the same physician/site? Might they have had suboptimal PCB?

6. The phrase at line 170 in results is confusing "All procedures were performed by an attending physician or family planning fellow (95% nitrous group, 95% IV sedation group). Does this mean ALMOST all were performed...? Or is the 95% referring to something else?

7. Figure 3 there's a problem with the figure legend "=="?

8. Table 3, explain the "Expected" Row

9. There is a problem with Reference 3, it is incomplete.

Reviewer #3: Thank you to the authors for identifying an important area of inquiry, namely pain management for mid-trimester abortion, specifically the use of nitrous oxide vs. fentanyl and versed. This is an important question however, the manuscript cannot be published without addressing several methodological points and consultation with a statistician to explain to readers if there is enough statistical power to make the interpretation the authors make given they present a power calculation to detect differences, but report findings from an RCT that was stopped prior to the end of enrollment due to the parameters set by the data safety monitoring board. The readers need to know the data that are reported are not from the full power analysis earlier in the manuscript. Additional points are: which VAS was used (10 point converted to 100 or some other iteration?) the mm are reported in some places on a 100 scale, others 10. The authors should also state if any participant received pain medication with their cervical preparation or at any point prior to their procedure. Other minor comments:

1. Define IV prior to using in the manuscript.

2. Line 72-73 need references

3. Line 98: Authors need to define, "best obstetrical dating" - assuming LMP and ULS, but should state this for the readers.

4. Given cervical preparation was left to physician discretion, pain management (or lack thereof should be note from time of prep to procedure).

5. The authors need to address lines 137-140 in light of the DSMB...

6. A short description of the VAS needs to be explained in lines 128-136.

7. Line 189: How did authors determine over sedation? anesthesia assessment? Aldrete score?

8. In the strengths/limitation section, the authors should address the power issue (based on statistician consult) and why are the authors focused on women terminating for fetal indications? Is there an inherent assumption about pain management? Presence during procedure (Ashulter et al., 2017)? There are other places where I think these findings are not generalizable as well.

9. Table 1: Given how small the numbers are, the percentages are misleading, I would suggest using the N

10. Were the people who needed cervical preparation longer than one day included in the data?

11. Figure 2 shows pain as bad as it could be 10mm (should this be 100?) did you translate the 100 scale to 10? Typo?

12. Figure 3, I would label the "conversion" bar to be clearer that you went from Nitrous to IV sedation or include in the figure legend.

STATISTICAL EDITOR'S COMMENTS:

1. lines 160-162: What exactly were the criteria for conversion to IV sedation? How was it possible to blind the providers to the anesthesic used? If in fact it was not blinded, how do the Authors know that bias was not introduced into the choice to convert? Especially important since this was a stopping rule. Doesn't seem like a symmetrical process, that is, how could a woman sedated with fentanyl and versed decide she wanted to convert to N_2O?

2. Table 1: Since this was a randomized trial, there is no need to compare baseline characteristics, any differences are thought to be due to random chance. Furthermore, even if there were a basis for comparing them, the sample sizes are likely too

small to allow sufficient power to generalize any NS findings (which they all were). Should format each column as n(%) and enumerate any missing values, if any.

3. Table 2: Again,should format as n(%). There is insufficient power to generalize the NS findings.

4. Table 3: The most striking finding is the wide range of VAS pain scores for each cohort. Raises the question of whether comparison of max VAS score was the most logical metric, rather than change from baseline, since some women in each cohort apparently had very high initial scores.

5. Table 3, fig 2: The 95% CIs appear symmetric, were they estimated based on normal distribution? If so, the median and ranges cited appear not to conform to normality and the stat test used was a non-parametric test, implying non-normality. This is especially important, given the relatively small sizes of the cohorts.

6. In other words, although the Authors did find a significant difference by ITT in the median max VAS pain scores, that is not the same as the original study design re: non-inferiority. Estimation of 95% CIs, based on only n = 19 or n = 20 would be very imprecise, more so with skewed data. Did the Authors in fact show non-inferiority? It appears from fig 2 that the 25th%-tile for the N_2O cohort was very close to the median value for the IV sedation group?

ASSOCIATE EDITOR-GYN

1. Please revise Discussion to address Rev #2 point about the heightened amnesiac effect of midazolam compared to nitrous - that should be recognized as a limitation in assessing secondary outcome endpoints.

2. Also, speaking to the primary outcome: how many of the 7 pts needing to be switched from nitrous to IV sedation were pt request versus provider?

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, as well as subsequent author queries. 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:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. Each author on this manuscript must submit a completed copy of our revised author agreement form (updated in the August 2014 issue). Please note:

a) Any material included in your submission that is not original or that you are not able to transfer copyright for must be listed under I.B on the first page of the author agreement form.

b) All authors must disclose any financial involvement that could represent potential conflicts of interest in an attachment to the author agreement form.

c) All authors must indicate their contributions to the submission by checking the applicable boxes on the author agreement form.

d) The role of authorship in Obstetrics & Gynecology is reserved for those individuals who meet the criteria recommended by the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org):

* Substantial contributions to the conception or design of the work;
OR
the acquisition, analysis, or interpretation of data for the work;
AND
* Drafting the work or revising it critically for important intellectual content;
AND
* Final approval of the version to be published;
AND
* Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The author agreement form is available online at http://edmgr.ovid.com/ong/accounts/agreementform.pdf. Signed forms should be scanned and uploaded into Editorial Manager with your other manuscript files. Any forms collected after your revision is submitted may be e-mailed to obgyn@greenjournal.org.

3. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

4. 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 appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

5. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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).

6. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

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; Reviews, 300 words. Please provide a word count.

8. 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.

9. 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.

10. 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.

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If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

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 Jul 27, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

If you would like your personal information to be removed from the database, please contact the publication office.

RE: Manuscript Numbaer ONG-18-1099

Dear editors,

Thank you so much for your thoughtful review of this manuscript. We are happy to have the opportunity to share this important study with the readership of the journal. Below I have listed the proposed revision with line by line descriptions of how they have been addressed in the manuscript. We believe the manuscript is stronger with the revisions suggested by the reviewers and appreciate the careful review. I am also submitting a clean and track changes version of the manuscript for your review. We very much hope that these revisions will address all the thoughtful comments posed. If there are any questions or concerns, please do not hesitate to contact me.

Sincerely,

Lauren Thaxton

Reviewer #1:

1. "Abstract: do not need to put full details of your non inferiority model and sample size into the abstract." Lines 46-49 have been removed.
2. "Intro: Lines 84-5: please add more detail about this study, the simple phrase is too declarative. Were there any secondary outcomes measured (or planned to be measured?)" Yes, the authors also measured satisfaction as a secondary outcome and found similar scores between groups. This information has been added to the manuscript (lines 85-86).
3. "Results: line 171, what do the percentages represent? You had just noted all of the procedures were performed by attending or fellow, so it is confusing… Also table two indicates 3 types of provider, you should be clear about this in the text as well. (Moved from later in the question as this seems to address the same issue.)" We apologize for this typographical error and percentages have been removed. 95% of procedures were performed by Ob/Gyn fellows or attendings (5% performed by Family Medicine attendings). The text has been edited to more clearly reflect this (lines 218-219).
   "Again line 173, the percentages are a bit confusing, is this the percent who had procedure same day or the percent who had dilation? You have presented this data in table 2, you should reference it rather than repeat." Percentages have been removed to more clearly reflect the characteristics of the majority of participants with reference to Table 2 (lines 219-221).
4. "Discussion: line 209-11 this sentence is unclear, addressing two ideas." The sentence has been amended (now lines 269-271) to reflect that the participant study characteristics do not match population characteristics. This is particularly true for indication for termination: women undergoing termination for maternal indications were more likely to

enroll than those with fetal indications. We hope the added language has clarified this point.

5. "Additionally you do not address if any other data could be learned from this study. Ie: were other outcomes collected? Was there a role for N2O in patients who understood it's decreased efficacy but had need of a non-IV sedation option (you hint at this in discussion of the refusals). What are future plans for study based on what you learned here?" We appreciate and agree with the reviewer's point about benefit of nitrous sedation when there are no other options. The discussion has been expanded to incorporate these concepts of future research and benefits of nitrous sedation over no sedation (lines 284-286).

Reviewer #2:

1. To summarize, this reviewer made the important comment that the half-life of IV midazolam and fentanyl is much longer than that of nitrous sedation and therefore, even at clinic discharge, recall of maximum procedural pain may not be an even comparison between groups. We agree that differences between the half-life and amnestic effect of IV sedation and nitrous oxide may have an impact on perception of pain. We have added language in the discussion (lines 277-281).
2. "Additionally, dosing midazolam and fentanyl should be weight-based. On occasion patients can suffer significant respiratory depression from the combination of medications." Although we agree that respiratory depression is a complication of IV sedation, we chose the uniform dosing regimen as it is the most commonly used regimen among abortion clinics nationwide according to a National Abortion Federation Survey referenced in the manuscript.
3. "Line 76 Nitrous Oxide is N2O, not N2O/O2. And it does not offer amnesia unless the patient is asleep, which they will not be if given only nitrous." The manuscript utilized the abbreviation N_2O/O_2 in this setting to distinguish that nitrous oxide sedation is always provided in conjunction with oxygen. In order to more clearly elaborate that point, the text has been modified to read "nitrous oxide sedation" (line 77).
4. "Nitrous is contraindicated in people with disorders of B12." This was an exclusion criteria of the study and has been added to the manuscript now (line 128).
5. "Why were fetal demise patients excluded?" Women with a fetal demise may experience pain during the procedure differently from women with other indications and were therefore excluded. We have added language to clarify this point in the methods section (lines 130-131).
6. "Were all the paracervical blocks placed by providers with equivalent experience and skill? Ideally, the quality of the block should have been assessed, though theoretically the failure rate should be unaffected by the analgesic method. Ideally, some assessment of the PCB quality would have been included." Authors did not perform any scored assessment of the paracervical block. However, the type of block performed, as per standard practice in our clinic, was the same across multiple providers and is described in the manuscript. We appreciate this concern and have added language about the lack of measurement of PCB quality in our limitations section (lines 274-277).
7. "Results: Were all 7 analgesic failures by the same physician/site? Might they have had suboptimal PCB?" We reviewed the data: while we did not collect information on the individual providers performing procedures, we noted diversity in sites (NM and Colorado)

and provider types (fellows, attendings) among the physicians for patients converted from IV sedation to nitrous sedation. We do not believe that the conversions were due to a single provider administering suboptimal paracervical block; additionally, as mentioned, the PCB is performed similarly across physicians at our clinics (lines 206-208).

8. "The phrase at line 170 in results is confusing "All procedures were performed by an attending physician or family planning fellow (95% nitrous group, 95% IV sedation group). Does this mean ALMOST all were performed...? Or is the 95% referring to something else?" This question was addressed above in the comments by Reviewer #1.
9. "Figure 3 there's a problem with the figure legend "=="?" We apologize for this typographical error – it has now been removed.
10. "Table 3, explain the "Expected" Row" We have added language to the methods section to explain the expected and baseline pain score information (lines 139-140).
11. "There is a problem with Reference 3, it is incomplete." We apologize for this typographical error which is now corrected.

Reviewer #3:

1. "To explain to readers if there is enough statistical power to make the interpretation the authors make given they present a power calculation to detect differences, but report findings from an RCT that was stopped prior to the end of enrollment due to the parameters set by the data safety monitoring board. The readers need to know the data that are reported are not from the full power analysis earlier in the manuscript… The authors need to address lines 137-140 in light of the DSMB..." The analysis of the VAS pain scores of the 39 women enrolled in the study do show a statistically significant difference in maximum pain scores. While our original hypothesis and sample size calculation was built upon non-inferiority and despite the small sample size, we were able to demonstrate inferiority of nitrous sedation based on the 20.1mm difference in maximum pain scores between groups. In order to more clearly reflect this, language within the methods section has been added about our a priori plan to analyze the data regardless of whether or not our stopping rule was met based on the assumption that pain scores would be significantly different (lines 188-191). Additionally, clarifying language was added to the results section of the manuscript (lines 224-226).
2. "Additional points are: which VAS was used (10 point converted to 100 or some other iteration?) the mm are reported in some places on a 100 scale, others 10." Figure 2 and 3 referenced a 10mm scale. We apologize for this typographical error- the 100mm VAS was used for this study and manuscript and tables/figures have been edited to reflect this.
3. "The authors should also state if any participant received pain medication with their cervical preparation or at any point prior to their procedure." The participants may or may not have received pain medication for cervical preparation at the discretion of the physician performing the cervical preparation. We have added this information in the manuscript (lines 142-144).
4. "Define IV prior to using in the manuscript." IV is defined in the abstract first on line 40 and in the manuscript on line 70.

5. “Line 72-73 need references” This sentence has been reworked to reflect abortion client surveys which reveal that many women who have abortions in the second trimester are mothers already (lines 73-74).
6. “Line 98: Authors need to define, "best obstetrical dating" - assuming LMP and ULS, but should state this for the readers.” This was defined in our study protocol as ultrasound dating either by CRL or biometry. We have added language to clarify this point (line 124).
7. “Given cervical preparation was left to physician discretion, pain management (or lack thereof should be note from time of prep to procedure).” Addressed above with point #3 from this same Reviewer. Participants may have received pain medication with their cervical preparation and the manuscript has been edited to incorporate this information. Documentation of pain management with cervical preparation was not recorded for the purpose of this study.
8. “A short description of the VAS needs to be explained in lines 128-136.” A description of the VAS has been added to the methods section of the paper at lines 166-167.
9. “Line 189: How did authors determine over sedation? anesthesia assessment? Aldrete score?” Thank you for the opportunity to clarify: Over sedation was defined by a participant who met criteria for a level of depth of sedation greater than moderate or conscious sedation as described by the American Society of Anesthesiologists. We have added language to the methods section (lines 159-163)
10. “…why are the authors focused on women terminating for fetal indications? Is there an inherent assumption about pain management?” This comment has also been addressed above with Reviewer #2’s comments. Women with a fetal demise may experience pain during the procedure differently from women with other indications and were therefore excluded. We have added language to clarify this point in the methods section (lines 130-131).
11. “Table 1: Given how small the numbers are, the percentages are misleading, I would suggest using the N.” The table has been amended to reflect this change also described below by the statistical editor.
12. “Were the people who needed cervical preparation longer than one day included in the data?” Yes, all participants were included in the data analysis.
13. “Figure 3, I would label the "conversion" bar to be clearer that you went from Nitrous to IV sedation or include in the figure legend.” Thank you - this clarification has been added to the Figure.

STATISTICAL EDITOR'S COMMENTS:

1. “lines 160-162: What exactly were the criteria for conversion to IV sedation? How was it possible to blind the providers to the anesthesic used? If in fact it was not blinded, how do the Authors know that bias was not introduced into the choice to convert? Especially important since this was a stopping rule. Doesn't seem like a symmetrical process, that is, how could a woman sedated with fentanyl and versed decide she wanted to convert to N_2O?” In order to maximize the external validity, inadequate pain control was determined by the patient describing a need for more pain medications in conjunction with assessment and judgement of the physician. This clarification was added to the manuscript (lines 155, 181-183).

Blinding was maintained as all participants received a gas via facemask (nitrous sedation versus oxygen) and IV solution (IV sedation versus saline). Only the sedation provider was aware of what medication was being used, not the physician performing the procedure or the patient. Nitrous delivery system knobs and settings where obscured from provider view in all cases. This is described in lines 148-154 of the methods section. There is no conversion from IV sedation to nitrous in this study because the current standard of care for pain management in both clinics was IV sedation. IV sedation was the effective method that another option was being compared against so it would not be appropriate to convert patients to another agent that we did not yet know was at least similarly effective to IV.

2. "Table 1: Since this was a randomized trial, there is no need to compare baseline characteristics, any differences are thought to be due to random chance. Furthermore, even if there were a basis for comparing them, the sample sizes are likely too small to allow sufficient power to generalize any NS findings (which they all were). Should format each column as n(%) and enumerate any missing values, if any." This change in Table 1 has been made as also mentioned above by Reviewer #3.
3. "Table 2: Again,should format as n(%). There is insufficient power to generalize the NS findings." This change has been made in Table 2.
4. "Table 3: The most striking finding is the wide range of VAS pain scores for each cohort. Raises the question of whether comparison of max VAS score was the most logical metric, rather than change from baseline, since some women in each cohort apparently had very high initial scores." We elected the primary outcome of maximal pain as we felt it to be the most clinically relevant metric. In usual clinical practice, if patients describe high levels of pain during the procedure, this is what is used to determine the need for more or alternative forms of pain control. The comment about elevated baseline pain scores is important as women marked their baseline pain scores prior to their procedure, however they may or may not have received cervical preparation at the time of noting baseline pain scores. These elevated baseline scores could be explained by elevated pain secondary to cervical preparation.
5. "Table 3, fig 2: The 95% CIs appear symmetric, were they estimated based on normal distribution? If so, the median and ranges cited appear not to conform to normality and the stat test used was a non-parametric test, implying non-normality. This is especially important, given the relatively small sizes of the cohorts." As suggested above, the 95% CI have been removed from Tables 1 and 2. Table 3 describes median and ranges, and figure 2 shows box plots with median, IQR and range and the corresponding text has also been edited. The pain data described in Figure 2 and Table 3 are not normally distributed, and therefore non-parametric test were used.
6. "In other words, although the Authors did find a significant difference by ITT in the median max VAS pain scores, that is not the same as the original study design re: non-inferiority. Estimation of 95% CIs, based on only n = 19 or n = 20 would be very imprecise, more so with skewed data. Did the Authors in fact show non-inferiority? It appears from fig 2 that the 25th%-tile for the N_2O cohort was very close to the median value for the IV sedation group?" This point was also raised by Reviewer #3, point 1 with a lengthier discussion of how this was addressed above. Briefly, the Methods section was expanded in reference the a priori plan to analyze all participants even if our stopping

rule was met. Additionally, the Results section has been expanded to more clearly state that inferiority of nitrous was shown despite the small sample size.

ASSOCIATE EDITOR-GYN

1. "Please revise Discussion to address Rev #2 point about the heightened amnesiac effect of midazolam compared to nitrous - that should be recognized as a limitation in assessing secondary outcome endpoints." The Discussion section has been expanded to review the differences in properties such as amnestic effect and half-life of nitrous oxide and IV sedation (line 278-282).
2. "Also, speaking to the primary outcome: how many of the 7 pts needing to be switched from nitrous to IV sedation were pt request versus provider?" Need for additional pain medications was determined by the patient primarily, in conjunction with her provider. No participant received additional pain medication without the participant herself requesting this.

Daniel Mosier

From: Lauren Thaxton [redacted]
Sent: Thursday, August 2, 2018 1:36 PM
To: Daniel Mosier
Subject: Author credentials
Attachments: 18-1099R1 ms (7-30-18v1)_LT.docx

Daniel,

I so apologize for the multiple emails. I wanted to draw to your attention the degrees for author Jeanelle Sheeder: MSPH, PhD, highlighted below and manuscript included here with revision.

Lauren Thaxton

[redacted]

[redacted]

From: Daniel Mosier <dmosier@greenjournal.org>
Date: Tuesday, July 31, 2018 at 1:38 PM

To: Lauren Thaxton [redacted]
Subject: Manuscript Revisions: ONG-18-1099R1

Dear Dr. Thaxton,

Thank you for revising your manuscript. However, there are remaining issues that must be addressed before we can consider your manuscript further for publication. Each of these points are marked in the track changes in the attached manuscript. When revising, please leave the track changes on, and do not use the "Accept all Changes" function in Microsoft Word. You may respond to the comments in the track changes, or address each of the queries in a follow-up email. For your reference, I have copied these author queries below:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. LINE 4: Please provide completed author agreement forms for all authors except Dr. Thaxton using the latest version of our author agreement form, which can be found at http://edmgr.ovid.com/ong/accounts/agreementform.pdf. Note that both the "Authorship" and "Disclosure of Potential Conflicts of Interest" sections need to be completed, along with providing a signature. Please read the form carefully.
3. LINE 51: Please note this edit, which was made to match line 187.
4. LINE 166: Please revise "and/or" to mean either "and" or "or." Be sure this is done throughout your paper.
5. LINE 182: Abstract edited to include this information.

Please send a response to this message no later than COB on **August 2nd.**

Please let us know if you have any questions or concerns.

Sincerely,
-Daniel Mosier

Daniel Mosier
Editorial Assistant
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Web: http://www.greenjournal.org

Daniel Mosier

From: Lauren Thaxton [redacted]
Sent: Thursday, August 2, 2018 12:59 PM
To: Daniel Mosier
Cc: Singh, Rameet
Subject: Re: Manuscript Revisions: ONG-18-1099R1
Attachments: singh.pdf

Daniel

So sorry for this oversight. I am attaching a new copy inclusive of the COI section. Please let me know if there are any other issues.

Lauren Thaxton

From: Daniel Mosier <dmosier@greenjournal.org>
Date: Thursday, August 2, 2018 at 10:39 AM
To: Lauren Thaxton [redacted]
Subject: RE: Manuscript Revisions: ONG-18-1099R1

Dr. Thaxton,

Thank you for sending the forms in a timely manner. However, Dr. Singh did not complete the required "Disclosure of Potential Conflicts of Interest" section of the form. Could they revise and re-submit their agreement form?

Sincerely,
-Daniel Mosier

Daniel Mosier
Editorial Assistant
Obstetrics & Gynecology
Tel: 202-314-2342

From: Lauren Thaxton [redacted]
Sent: Thursday, August 2, 2018 11:15 AM
To: Daniel Mosier <dmosier@greenjournal.org>
Subject: Re: Manuscript Revisions: ONG-18-1099R1

Daniel,

I am attaching new signed copies of the author agreement form from all authors. Please let me know if there are any issues accessing these documents!

Appreciate it,

Lauren Thaxton

From: Daniel Mosier <dmosier@greenjournal.org>
Date: Tuesday, July 31, 2018 at 1:38 PM
To: Lauren Thaxton [redacted]
Subject: Manuscript Revisions: ONG-18-1099R1

Dear Dr. Thaxton,

Thank you for revising your manuscript. However, there are remaining issues that must be addressed before we can consider your manuscript further for publication. Each of these points are marked in the track changes in the attached manuscript. When revising, please leave the track changes on, and do not use the "Accept all Changes" function in Microsoft Word. You may respond to the comments in the track changes, or address each of the queries in a follow-up email. For your reference, I have copied these author queries below:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. LINE 4: Please provide completed author agreement forms for all authors except Dr. Thaxton using the latest version of our author agreement form, which can be found at http://edmgr.ovid.com/ong/accounts/agreementform.pdf. Note that both the "Authorship" and "Disclosure of Potential Conflicts of Interest" sections need to be completed, along with providing a signature. Please read the form carefully.
3. LINE 51: Please note this edit, which was made to match line 187.
4. LINE 166: Please revise "and/or" to mean either "and" or "or." Be sure this is done throughout your paper.
5. LINE 182: Abstract edited to include this information.

Please send a response to this message no later than COB on **August 2nd.**

Please let us know if you have any questions or concerns.

Sincerely,
-Daniel Mosier

Daniel Mosier
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Daniel Mosier

From: Lauren Thaxton [redacted]
Sent: Wednesday, August 1, 2018 10:14 AM
To: Daniel Mosier
Cc: EVE ESPEY; Pitotti, Jennifer; Teal, Stephanie; Sheeder, Jeanelle; Singh, Rameet
Subject: Re: Manuscript Revisions: ONG-18-1099R1
Attachments: 18-1099R1 ms (7-30-18v1)_LT.docx

Daniel,

Thank you so much for the journal's thoughtful consideration of our manuscript. I apologize for our oversights on these mentioned issues. We agree to all the proposed edits that were tracked here and I have reviewed the manuscript for all "and/or" verbiage and edited to reflect the process. The edited manuscript is included here. We are working towards all authors completing the author agreement form and I will send that to you as soon as it is compiled.

I opt-in to the inclusion of my revisions and all email correspondence to the supplemental digital content to the published article.

Thank you so very much!

Lauren Thaxton

From: Daniel Mosier <dmosier@greenjournal.org>
Date: Tuesday, July 31, 2018 at 3:19 PM
To: Lauren Thaxton [redacted]
Subject: RE: Manuscript Revisions: ONG-18-1099R1

Dr. Thaxton,

Apologies for the double emails, but the Journal's Mansucript Editor was reviewing your revision cover letter and noticed that you did not include answers to the Editorial Office Comments. It is very important that we receive a response to one of these questions in particular. Please include your answer to the following when you send us your latest revision:

"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, as well as subsequent author queries. 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:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries."

Please let me know if you have any questions or concerns.

Sincerely,

-Daniel Mosier

Daniel Mosier
Editorial Assistant
Obstetrics & Gynecology
Tel: 202-314-2342

From: Daniel Mosier
Sent: Tuesday, July 31, 2018 2:39 PM
To: [redacted]
Subject: Manuscript Revisions: ONG-18-1099R1

Dear Dr. Thaxton,

Thank you for revising your manuscript. However, there are remaining issues that must be addressed before we can consider your manuscript further for publication. Each of these points are marked in the track changes in the attached manuscript. When revising, please leave the track changes on, and do not use the "Accept all Changes" function in Microsoft Word. You may respond to the comments in the track changes, or address each of the queries in a follow-up email. For your reference, I have copied these author queries below:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. LINE 4: Please provide completed author agreement forms for all authors except Dr. Thaxton using the latest version of our author agreement form, which can be found at http://edmgr.ovid.com/ong/accounts/agreementform.pdf. Note that both the "Authorship" and "Disclosure of Potential Conflicts of Interest" sections need to be completed, along with providing a signature. Please read the form carefully.
3. LINE 51: Please note this edit, which was made to match line 187.
4. LINE 166: Please revise "and/or" to mean either "and" or "or." Be sure this is done throughout your paper.
5. LINE 182: Abstract edited to include this information.

Please send a response to this message no later than COB on **August 2nd.**

Please let us know if you have any questions or concerns.

Sincerely,
-Daniel Mosier

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Editorial Assistant
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[redacted] [redacted]
To: Stephanie Casway
Subject: FW: O&G Figure Revision: 18-1099
Date: Thursday, August 2, 2018 10:17:29 AM
Attachments: Fig1.pdf
Fig1.pptx

Stephanie,

Thank you so much for your email. I looked over all the figures and legend and they look great. The one thing I noticed was that there were some lines that didn't quite match up in the consort diagram (figure 1) which have been edited here (attached in pdf and ppt format). This may simply be how they display on my computer and if so, please ignore.

Thank you again!

Lauren

From: Stephanie Casway <SCasway@greenjournal.org>
Date: Wednesday, August 1, 2018 at 12:52 PM
To: Lauren Thaxton [redacted]
Subject: O&G Figure Revision: 18-1099

Good Afternoon Dr. Thaxton,

Your figures and legend have been edited, and PDFs of the figures and legend are attached for your review. Please review the figures CAREFULLY for any mistakes.

PLEASE NOTE: Any changes to the figures must be made now. Changes at later stages are expensive and time-consuming and may result in the delay of your article's publication.

To avoid a delay, I would be grateful to receive a reply no later than Friday, 8/3. Thank you for your help.

Best wishes,

Stephanie Casway, MA
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