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: Jul 13, 2020
To: "Catherine Watson" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1856

RE: Manuscript Number ONG-20-1856

An analysis of adherence to oral anticancer therapeutics in the gynecologic oncology population

Dear Dr. Watson:

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).

Due to the COVID-19 pandemic, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by Aug 12, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is an interesting area of research with limited studies in the literature.

I commend the authors for using a combination of quantitative and qualitative techniques.

Some feedback are as follows:

1.) A description of the patients included in the qualitative portion of the study will be important and provide context to the reader. I suspect that the themes derived from patients who are on progesterones for endometrial hyperplasia/low grade cancer (who are often seeking fertility preservation, young) may be different from those obtained from patients with advanced stage ovarian cancer on PARP inhibitors following debulking surgery and multiple cycles of chemotherapy. Finally women with recurrent or advanced stage endometrial cancer on progesterone therapy may also be different. Their motivations for adherence, their tolerance of side effects, may differ given their slightly different circumstances.

2.) I think a more robust analyses can be completed on the interviews of the healthcare providers to extract themes, similar to that completed for the patients.

Reviewer #2: Thank you for allowing me to review this article. Strict adherence to anticancer treatment is crucial in determining patient survival. In general, adherence to oral anticancer treatment is far from prefect in many areas all over the world. This is a real problem searching for solution. The article is a preliminary pilot study examining the rate of non-adherence to oral anticancer among gynecological malignancy patients, and searching for the possible causes for non-adherence. The article is simple, concise with few typographic errors. However, the main problems of this article are summarized in the following points:

- The article didn't add much to the well known facts about oral anticancer drugs adherence. The authors included 100 women in the quantitative analysis and they didn't find any specific factor related to non-adherence. As the authors themselves stated, these results are consistent to previous ones. In addition, they made qualitative research on only 14 cases and 14 providers. They found 5 main causes of non-adherence but they didn't do any statistical analysis. This deprived the article from adding any evidence to the practice.
- The authors didn't perform sample size calculation. This defect creates questions about statistical power.
- The authors didn't provide the details of the three-item measure for assessing adherence. What are the items of the measure and how to calculate the class of adherence?
- Missing only one dose is not fair to classify the patient as "non-adherent. I think that dichotomous classification is not very correct and inflates the non-adherence rate.

- Was there any software used for statistical analysis? What is the critical p value used to identify statistical significance? What are the statistics used to describe the data? And how did the authors determined normality assumptions? Please add these details.
- Many areas in the results are lacking quantitative values. The authors used many vague terms like "majority, almost all, many, some…etc" while these terms are acceptable in the discussion, they are not appropriate for the results section.
- Line 76: The 1st sentence wasn't proved by the study. The study didn't determine the rate of oral anticancer use. This sentence shouldn't be in the conclusion.
- Line 136: Why the authors determined 30days as a cutoff for inclusion in the study. Please explain.
- Line 136-139: It is not clear why the authors restricted the eligibility to certain oral medications not all available ones. Please explain.
- Line 145: It is not clear why the authors studied QOL. Was a poor QOL a cause or a result of non-adherence?
- Table 1:

o Why the authors reported both the mean and median age. Either of them should be presented according to normality of data.
o Please add the unit in length on medications and length after diagnosis.

- Table 2:

o Please provide the actual p values. "NS" is inappropriate.
o How the authors could compare the adherence status in the total population. What is the compared group?
o In the methods, the authors stated that they dichotomized adherence into adherent and "equivocal + non-adherent". Despite that, the results were presented in this table as 3 classes. Please explain.

- Table 3:

o It is unclear why the authors presented adherence in table 2 as 3 classes while in table 3, only 2 classes were presented.
o Please provide the actual p values.
o It is unclear why the authors presented the quantitative data in median and range despite using the t test in comparison. Please explain.
o The "N(%)" is better to be transferred to a footnote.
o Please add the range of the length of time since diagnosis in non-adherent group.
o Please add the percent in anxiety, depression, and REALM score.
o Please add "mean and SD" for FACT-G score.

Reviewer #3: This is a survey (n=100) and qualitative interview (n=14) study exploring factors affecting adherence and use of oral anticancer therapeutics in a gynecologic oncology population. I appreciate the authors' contribution to this often neglected part of the patient experience and thank the editors for the opportunity to review this paper.

Strengths

* The authors performed both qualitative interviews with patients and with providers to determine both actual patient perceptions about adherence and reasons for non-adherence as well as provider MISperceptions about barriers to therapy. This both illuminated the nuances of patient considerations and common breakdowns in communication between patient and provider about adherence. The qualitative methods are rigorous and appropriate to the subject matter.
* This study is quite novel, as the reviewer also knows of no literature that qualitatively or quantitatively examines adherence to anti-cancer therapy in this gynecologic population. This is a blank spot in our perception of patient treatment in this arena. This study is pioneering, so could aid in powering or guiding future studies on this topic in the quantitative or qualitative realm.
* The authors integrate health literacy, stress and anxiety, and quality of life measures into their analyses, which shines light on different aspects of the patient experience that are likely important in adherence to therapy.

Limitations

* This is a lower level of evidence, as in all survey studies, so there is no way to know that the sampling completely represents the population and there is no way to know if these considerations are specific to oral anticancer therapy or to other situations/medication types as well.
* The sampling size of the survey was arbitrarily chosen. There is no power analysis presented (even post-hoc) and no primary risk factor analysis chosen to which you could power the study. Although the qualitative interview sampling was based on thematic saturation, which is appropriate, why was the arbitrary number of 100 chosen for the survey? How do we know that this sampling was reasonably representative of the entire population? Was it a continuous sample or were patients enticed to volunteer in some way? This should be better described.
* Although the authors include quality of life, anxiety and stress, and health literacy measures, there is no description in the methods of how analyses of these, or analyses of these in relation to other outcome measures like adherence, were planned or executed.

Comments for authors by section

Abstract:

* Line 66-67: I believe that readers would want to know, briefly, what separates equivalent from non-adherence here. Although the authors briefly define that missing one dose is equivalent, what tips them into the "non-adherent" category.
* Line 76: The first statement in the conclusions of the abstract is not supported by the evidence of this type. A

survey study of selected patients taking anti-cancer therapy does not display or convince me that oral anti-cancer therapy is common. I would suggest saving this space for an important statement regarding the results, such as the specific misperceptions of providers.

Introduction:
* Clear and pertinent description of the ballooning use of these medications and the gap in knowledge.
* Line 128-130: Clear statement of the purpose of the study. Was there a hypothesis associated with this?

Methods:
* Line 133-134: As noted above, there should be better description of the sampling of patients, so that the reader can determine if it is representative of the entire population of patients. Was this a continuous sample, offering participation to every patient prescribed this medication? Was advertising or incentivizing done to attract patients that were already on medication? Was the population slanted somehow toward women that saw the doctor more often or had already started medication, as opposed to those just being started on it? These are important things for the reader to be able to examine.
* Line 160-163: I would consider defining here exactly what adherence versus equivalent adherence meant, not just in terms of score but in actual translation to what it means in terms of frequency of dosing. This was briefly mentioned in the abstract (that equivalent means missing one dose, etc.) and should be more detailed here.
* Line 169: This seems rather arbitrary to get more non-adherent patients than adherent, and not include anyone from the equivalent group. This is not the distribution of patients according to the survey, so why was n=10 and n=4 selected?
* Line 212: There should be more statistical explanation in here regarding both the descriptive and the association analyses. Were there analyses examining the relationship between health literacy and adherence. Between stress/anxiety and adherence? How were these performed? Table 3 indicates this was done, but methods statistically should be described in this section here. The quantitative methods should have as much description as qualitative methods.

Results:
* The authors do a good job illuminating with meaningful quotes the 5 themes that emerged from the interviews.
* Line 300-308: I would like to have seem more quotes from the physicians to exemplify the misperceptions and their beliefs as to why patients are not taking the medication. If this was a matter of length, perhaps a Table or Appendix so that the illumination about provider perceptions is given more "air-time"?
* Line 226-233: There is very little "air-time" and attention given to the survey results or analysis, even though the Tables have the information and are well constructed. I would suggest at least performing a post-hoc power analysis so that we know the power of determining a difference in patient characteristics between adherent and non-adherent groups based on the smallest group size (n=21 for the equivalent group, I am assuming). This would also make the quantitative analysis choice of 100 women for the survey seem less arbitrary, or at least more considered.

Discussion:
* Good discussion of the literature about lack of adherence or imperfect adherence in other oncological populations exploring this issue.
* Line 339-349: There is a good discussion here of the weaknesses of the study; thank you. I would only add that there is no way to know if the sample is representative of all patients who are in the gynecologic oncology population. That is one of the big limitations of survey studies where the population is "whomever happens to be in the clinic".
* Line 347-348: Thank you for acknowledging that power is an issue. But the authors missed an opportunity to perform a post-hoc power analysis, which may have been meaningful to the reader.
* Line 354: I would add you strengths that you examined other factors that might, in this exploration, have yielded some hypothesis about factors affecting adherence (quality of life, medical literacy, etc.)

ASSOCIATE EDITOR - GYN

Please read over the Abstract from a non-gyn oncology point of view to provide adequate orientation to the broad readership.

EDITOR 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. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). 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.

As of 7/13/20, the following authors haven't completed the form. We sent them a link to it by email from our Editorial Manager email account:

Laura J. Fish, Margaret Falkovic, Amelia Lorenzo, Laura J. Havrilesky, Angeles Alvarez Secord

2. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* 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." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

3. For studies that report on the topic of race, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes).

Use "Black" and "White" (capitalized) when used to refer to racial categories.

The category of "Other" is a grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

5. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. 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.

7. Manuscript Editor comment about your title: Consider deleting "An anaylsis of" and using just "adherence to oral anticancer therapeutics in the gynecologic oncology population."

8. 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).

9. 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 limit for Original Research articles is 300 words. Please provide a word count.

10. 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.

11. ACOG is moving toward discontinuing the use of "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

12. Please use only the standard headings for an Original Research in the body text: Introduction, Methods, Results, and Discussion. All other subheads should be removed.

13. Your manuscript contains a priority claim (Line 311: "This study is the first exploration of gynecologic oncology patient adherence..."). 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 it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

12. 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.

13. 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 https://wkauthorservices.editage.com/open-access/hybrid.html.

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.

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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 30 days from the date of this letter. If we have not heard from

you by Aug 12, 2020, we will assume you wish to withdraw the manuscript from further consideration.***.

Sincerely,

The Editors of Obstetrics & Gynecology

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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August 10, 2020

Re: Adherence to oral anticancer therapeutics in the gynecologic oncology population
Editorial Staff
Obstetrics and Gynecology

Dear Editors,

On behalf of my co-authors, I am pleased to submit our manuscript, "Adherence to oral anticancer therapeutics in the gynecologic oncology population" for consideration for publication as original research in *Obstetrics and Gynecology.* Each author participated actively in conducting analyses, drafting sections of the manuscript, editing, and approving the final, submitted version. No author has a financial or other conflict of interest. I affirm 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.

Our institutional review board approved this study. The manuscript has not been previously submitted to another journal for publication. It was accepted as a poster presentation at the annual meeting of the Society of Gynecologic Oncology in 2020. In this study we performed a cross-sectional quantitative analysis of self-reported adherence to oral anticancer agents among women with gynecologic malignancies. We also performed a qualitative analysis of a subsection of these women to gain a better understanding of the patient perspective of and experiences with these medications. We found that only 54% of women reported perfect adherence to their oral anticancer agent. Interestingly, although qualitative interviewees did describe the benefits of self-administered oral therapy, they also described several potential barriers– both psychological (anxiety) and physical (side effects) - to perfect adherence. This study is novel, as adherence to these medications has not yet been investigated in this patient population, and its findings could greatly benefit patient care and form the foundation for future work in this area.

If you have any questions about the manuscript, I will be serving as the corresponding author. Thank you for your consideration.

Sincerely,

Catherine H. Watson, MD
Duke University
Department of Obstetrics and Gynecology
Division of Gynecologic Oncology
[redacted]

Reviewer #1: This is an interesting area of research with limited studies in the literature.

I commend the authors for using a combination of quantitative and qualitative techniques.
Response:
Thank you for your thoughtful review of our manuscript.

Some feedback are as follows:

1.) A description of the patients included in the qualitative portion of the study will be important and provide context to the reader. I suspect that the themes derived from patients who are on progesterones for endometrial hyperplasia/low grade cancer (who are often seeking fertility preservation, young) may be different from those obtained from patients with advanced stage ovarian cancer on PARP inhibitors following debulking surgery and multiple cycles of chemotherapy. Finally women with recurrent or advanced stage endometrial cancer on progesterone therapy may also be different. Their motivations for adherence, their tolerance of side effects, may differ given their slightly different circumstances.

Response:

Thank you for this insight. We agree that it is important to delineate specific regimens for those patients who were included in the qualitative portion of the study. We have now included a table (Table 4) describing the qualitative interviewees, and representative quotations are now attributed to the individual patient. We have also included in the discussion a brief review of the potential associations that you mention. For example, both adherent and non-adherent patients include descriptions of the benefit of oral therapy. Although concern about side effects seems like a reasonable differentiating factor between adherent and non-adherent patients, many of the quotations available regarding this issue were provided by adherent patients. However, all of the salient quotations regarding anxiety and the mental burden of medication self-management were provided by non-adherent patients. Thus, while there are no clear patterns regarding medication type, indication for medication or experience with side effects, there is some evidence to suggest that the mental burden of medication self-administration, related to the patient's own assumptions and experience with the medication, could be related to her adherence. We have included these thoughts in the discussion (lines 546-556).

2.) I think a more robust analyses can be completed on the interviews of the healthcare providers to extract themes, similar to that completed for the patients.
Response:
Thank you for this suggestion. We have now expanded on this section of the results in lines 422-477and have included further representative quotations regarding provider beliefs that cost and side effects are the most common reasons for non-adherence.

Reviewer #2: Thank you for allowing me to review this article. Strict adherence to anticancer treatment is crucial in determining patient survival. In general, adherence to oral anticancer treatment is far from prefect in many areas all over the world. This is a real problem searching for solution. The article is a preliminary pilot study examining the rate of non-adherence to oral anticancer among gynecological malignancy patients, and searching for the possible causes for non-adherence. The article is simple, concise with few typographic errors. However, the main problems of this article are summarized in the following points:
1. The article didn't add much to the well known facts about oral anticancer drugs adherence. The authors included 100 women in the quantitative analysis and they didn't find any specific factor related to non-adherence. As the authors themselves stated, these results are consistent to previous ones.

Response:

While our data demonstrates similarities to medication non-adherence literature in other subspecialties, there is a paucity of data regarding this subject in the field of gynecologic oncology. Thus, rather than attempting to add to current facts regarding oral anticancer agents, we were attempting to break new ground for a specific population with no data regarding adherence. Our patient population is not identical to that of breast cancer patients or chronic myeloid leukemia patients, for example, (two populations in which similar research has been done), and we cannot assume that adherence rates to oral anticancer agents used in these populations would be similar in our own. We have now clarified the pilot status of this study in the manuscript (lines 56, 142 and 149). As we have shown in this study, not all gynecologic oncology patients take their oral anticancer therapies as prescribed. Armed with this knowledge, we hope in the future to further evaluate possible factors that predict or contribute to non-adherence.

2. In addition, they made qualitative research on only 14 cases and 14 providers. They found 5 main causes of non-adherence but they didn't do any statistical analysis. This deprived the article from adding any evidence to the practice.

Response:

The goal for accrual in qualitative research is thematic saturation, which was reached. The use of thematic saturation to determine subject population size in qualitative studies is addressed in the methods section lines 214-216. Qualitative analysis differs significantly from quantitative analysis. However, we have now added more quantitative data to our qualitative results to better capture the incidence of the described themes (lines 320-418).

3. The authors didn't perform sample size calculation. This defect creates questions about statistical power.

Response:

Because this is a pilot study, formal sample size calculations and traditional powering are not considered standard. We discuss this in lines 271-272. We therefore acknowledge that, as this was a pilot study designed to obtain adherence estimates in this population, we were not able to power the study to detect predictors of nonadherence. This point is mentioned in the limitation section in lines 566-568. One of the purposes of performing the qualitative analysis was to identify candidate predictors of non-adherence as described by patients themselves. Armed with the qualitative results, subsequent studies can be powered based on these variables.

We did perform an exploratory analysis that compared certain demographic information and patient-reported quality of life, anxiety and depression and healthcare literacy between adherent and non-adherent or equivocally adherent patients (for the purposes of this exploratory analysis, non-adherent and equivocally adherent patients were grouped together). To further respond to reviewer comments, we have now also performed a post hoc power analysis regarding the patient population size that would be required to detect a difference in quality of life between medication adherence cohorts. For quality of life as assessed by the FACT-G score, the difference between groups (adherent vs non-adherent) was 3.5 points with the standard deviation of 15. Using two-sample t-test, we would need 289 patient per group in order to have at least 80% power to declare the difference of 3.5 significant at an alpha of 0.05. We also performed a post hoc analysis to determine the sample size that would be required to detect a significant difference in adherence between maintenance and active medication indications. The proportion of adherence among the maintenance group is 44% and the proportion of adherence among the active group is 61%. To detect a difference of (0.61 - 0.44 = 0.17), we would need 134 patients per group. This information is included in lines 509-528.

4. The authors didn't provide the details of the three-item measure for assessing adherence. What are the items of the measure and how to calculate the class of adherence?

Response:

The three-item scale is now described in the methods section lines 161-183. The measure is a published, validated tool[1]. Participants answer three items using medication adherence in the last seven days, including “I took all doses of my cancer medication”, “I missed or skipped at least one dose of my cancer medication”, and “I was not able to take all of my cancer medication.” There are five response options: never, rarely, sometimes, often, and always. It should be noted (and is now included in the manuscript in lines 181-183), that the Voils et al adherence survey uses a score threshold of 2 or greater for non-adherence. However, we believe that receiving any point against adherence differentiates that person from a truly adherent person. Thus, we kept those with a score of 1 as a separate group.

1. Voils, CI et al. Initial validation of a self-report measure of the extent of and reasons for medication nonadherence. *Med Care* 2012. 50(12): 1013-9

5. Missing only one dose is not fair to classify the patient as "non-adherent." I think that dichotomous classification is not very correct and inflates the non-adherence rate.

Response:

In this measure, the questions regarding adherence refer to the patient's last week of taking her medication, not the use of the medication in its entirety. We agree that this is a reasonable suggestion, and that the inclusion of the equivocally adherent group could inflate the non-adherence rate. However, we wanted to delineate between perfect adherence and all other medication practices. Moreover, the use of a self-reported survey has been previously shown to overestimate adherence[2]. We have revised the manuscript to emphasize that the recall period was only seven days, rather than entirety of medication prescription. We have also explained our reasoning (lines 181-183) behind differentiating between 0 and 1 points, and we have consistently grouped results into the three established categories.

2. Given et al. The challenges of oral agents as antineoplastic treatments. *Semin Oncol Nurs* 2011; 27:93-103.

6. Was there any software used for statistical analysis? What is the critical p value used to identify statistical significance? What are the statistics used to describe the data? And how did the authors determined normality assumptions? Please add these details.

Response:

Yes; we used R statistical software for our analysis, and this information has now been included in the manuscript in line 260. The critical p value used to identify significance is < 0.05 (line 226-256). As described in lines 231-259, pertinent variables were compared between adherent and non-adherent and equivocal groups as an exploratory analysis using either chi-squared for discrete data or paired t-test for continuous data. The Mann Whitney U test was used for non-normal continuous data.

7. Many areas in the results are lacking quantitative values. The authors used many vague terms like "majority, almost all, many, some…etc" while these terms are acceptable in the discussion, they are not appropriate for the results section.

Response:

Thank you for this suggested revision. We have made appropriate changes to the results section in lines 321-421 to provide more concrete, quantitative data for the qualitative results. For example, rather than stating in line 321 that "A majority of subject commented…" we now state in lines 321-323 that "Twelve (85.7%) of the subjects commented that taking an oral medication at home had significant practical and psychological advantages compared to intravenous chemotherapy received in a clinical setting."

8. Line 76: The 1st sentence wasn't proved by the study. The study didn't determine the rate of oral anticancer use. This sentence shouldn't be in the conclusion.

Response:

Thank you for this suggestion; this sentence has been deleted. The first sentence of the conclusion of the abstract has been revised to state: "Almost half of the patients surveyed reported equivocal or non-adherence to their oral anticancer agent" (line 82).

9. Line 136: Why the authors determined 30days as a cutoff for inclusion in the study. Please explain.

Response:

While we wanted to be as inclusive as possible, we also wanted the patients to have developed at least a short-term pattern of medication administration. Additionally, from a logistical standpoint, many of these patients are not seen for a period of weeks after initiating their medication.

10. Line 136-139: It is not clear why the authors restricted the eligibility to certain oral medications not all available ones. Please explain.

Response:

Our study was designed to capture all any patient prescribed an oral anticancer medication in our gynecologic oncology clinic. Protocol eligibility criteria were women > 18 years old with a diagnosis of a gynecologic malignancy, who read and speak English and to whom oral anticancer agents had been prescribed for more than 30 days. The inclusion criteria listed in the manuscript have been modified as such, rather than providing a list of discrete examples of oral medications. This has been amended in the manuscript (lines 151-154).

11. Line 145: It is not clear why the authors studied QOL. Was a poor QOL a cause or a result of non-adherence?

Response:

The quality of life measure utilized (FACT-G; or the Functional Assessment of Cancer Therapy – General) is a generalized quality of life survey for cancer patients. We obtained this information from patients as part of a general description of the study population. Additionally, we wished to perform an exploratory evaluation of quality of life as a possible predictor of non-adherence, with the hypothesis that patients who had a lower baseline quality of life in relation to their cancer diagnosis would be less likely to take their medication as prescribed. The reasoning behind the inclusion of this survey is now included in the discussion section in lines 184-188. We also address the fact that the study was not specifically powered to compare the adherent and non-adherent groups in the limitations section of the manuscript in line 562-563.

12. Table 1:
12a Why the authors reported both the mean and median age. Either of them should be presented according to normality of data.

Response:

The mean is now presented (the data is normally distributed).

12b Please add the unit in length on medications and length after diagnosis.

Response:

The unit of months has now been added for both of these variables.

13 Table 2:
13a Please provide the actual p values. "NS" is inappropriate.

Response:

This has now been corrected in the tables; and actual p values have been provided.

13b How the authors could compare the adherence status in the total population. What is the compared group?

Response:

This is accurate and was a typographical error; the “NS” P value has been removed.

13c In the methods, the authors stated that they dichotomized adherence into adherent and "equivocal + non-adherent". Despite that, the results were presented in this table as 3 classes. Please explain.

Response:

We have now clarified this discrepancy in the methods section. We have kept the three groups separate for the descriptive section, as we do think it is important to distinguish between the three categories. We have grouped the non-adherent and the equivocally adherent into one category solely for the exploratory analysis of possible predictive factors, as we were hoping to identify possible predictive factors for any medication utilization that was not perfect (Lines 257-259).

14 Table 3:
14a It is unclear why the authors presented adherence in table 2 as 3 classes while in table 3, only 2 classes were presented.

Response:

Please refer to Reviewer 2 Response 13c above.

14b Please provide the actual p values.

Response:

The actual p-values have been added.

14c It is unclear why the authors presented the quantitative data in median and range despite using the t test in comparison. Please explain.

Response:

Data which is distributed normally is reported as a mean with SD and a t test was used in comparison. Data which was not normally distributed is reported as a median with range and the Mann Whitney U test was used for comparison. This information is now included in the methods section in lines 254.

14d The "N(%)" is better to be transferred to a footnote.

Response:

We have amended this so that (N%) is now in a footnote.

14e Please add the range of the length of time since diagnosis in non-adherent group.

Response:

We have corrected this; the range of length of time since diagnosis in the non-adherent group is 3.5 to 288 months.

14f Please add the percent in anxiety, depression, and REALM score.

Response:
These percentages have now been added.

14g Please add "mean and SD" for FACT-G score.

Response:

The mean and SD have now been added.

Reviewer #3: This is a survey (n=100) and qualitative interview (n=14) study exploring factors affecting adherence and use of oral anticancer therapeutics in a gynecologic oncology population. I appreciate the authors' contribution to this often neglected part of the patient experience and thank the editors for the opportunity to review this paper.

Strengths

* The authors performed both qualitative interviews with patients and with providers to determine both actual patient perceptions about adherence and reasons for non-adherence as well as provider MISperceptions about barriers to therapy. This both illuminated the nuances of patient considerations and common breakdowns in communication between patient and provider about adherence. The qualitative methods are rigorous and appropriate to the subject matter.
* This study is quite novel, as the reviewer also knows of no literature that qualitatively or quantitatively examines adherence to anti-cancer therapy in this gynecologic population. This is a blank spot in our perception of patient treatment in this arena. This study is pioneering, so could aid in powering or guiding future studies on this topic in the quantitative or qualitative realm.
* The authors integrate health literacy, stress and anxiety, and quality of life measures into their analyses, which shines light on different aspects of the patient experience that are likely important in adherence to therapy.

Limitations

1. This is a lower level of evidence, as in all survey studies, so there is no way to know that the sampling completely represents the population and there is no way to know if these considerations are specific to oral anticancer therapy or to other situations/medication types as well.

Response:

We agree that a survey study is a lower level of evidence; this is mentioned in our limitations section. We have also addressed the potential limitation of random sampling (line 561). It may be true that these considerations are not specific to oral anticancer therapy; there is a vast amount of literature regarding medication adherence in general and in specific subspecialties. Please refer to Reviewer 2 Comment 1 for the remainder of this response.

2. The sampling size of the survey was arbitrarily chosen. There is no power analysis presented (even post-hoc) and no primary risk factor analysis chosen to which you could power the study. Although the qualitative interview sampling was based on thematic saturation, which is appropriate, why was the arbitrary number of 100 chosen for the survey? How do we know that this sampling was reasonably representative of the entire population? Was it a continuous sample or were patients enticed to volunteer in some way? This should be better described.

Response:

Like most survey studies, this was a continuously recruited sample of patients who are willing to participate (lines 150-151). Please refer to Reviewer 1 Comment 3 for the remainder of this response.

3. Although the authors include quality of life, anxiety and stress, and health literacy measures, there is no description in the methods of how analyses of these, or analyses of these in relation to other outcome measures like adherence, were planned or executed.

Response:

Thank you for this comment. We have now included the descriptive data regarding the results of these measures for the total population. We have also included a description of the exploratory analyses of these outcomes in relation to adherence category in the methods section. As described in lines 231-259, pertinent variables were compared between adherent and non-adherent and equivocal groups as an exploratory analysis using either chi-squared for discrete data or paired t-test for continuous data. The Mann Whitney U test was used for non-normal continuous data.

Comments for authors by section

Abstract:
4. Line 66-67: I believe that readers would want to know, briefly, what separates equivalent from non-adherence here. Although the authors briefly define that missing one dose is equivalent, what tips them into the "non-adherent" category.

Response:

We agree with this revision; we have included a more in-depth description of this in the abstract results.

5. Line 76: The first statement in the conclusions of the abstract is not supported by the evidence of this type. A survey study of selected patients taking anti-cancer therapy does not display or convince me that oral anti-cancer therapy is common. I would suggest saving this space for an important statement regarding the results, such as the specific misperceptions of providers.
Response:

Please refer to Reviewer 2 Comment 8 for our response.

Introduction:
6. Clear and pertinent description of the ballooning use of these medications and the gap in knowledge.
7. Line 128-130: Clear statement of the purpose of the study. Was there a hypothesis associated with this?
Response:

Yes; we hypothesized that providers would assume a higher level of adherence than patients would report. We have now included a hypothesis statement in lines 144-147.

Methods:
8. Line 133-134: As noted above, there should be better description of the sampling of patients, so that the reader can determine if it is representative of the entire population of patients. Was this a continuous sample, offering participation to every patient prescribed this medication? Was advertising or incentivizing done to attract patients that were already on medication? Was the population slanted somehow toward women that saw the doctor more often or had already started medication, as opposed to those just being started on it? These are important things for the reader to be able to examine.

Response:

Patients were continuously identified in the gynecologic oncology outpatient clinic. Study enrollment was offered to any patient who was prescribed an oral anticancer therapy for their gynecologic cancer. No advertising or incentivizing was done for the study. We have now included this information in the manuscript in lines 154-156. As it was a random and continuously accrued sampling, there should not be an obvious predisposition toward the enrollment of women who recently started the medication versus those who had been taking it for a longer period of time. There should also not be a bias for women who see

their doctor less frequently, as the study was open for twelve months and all patients on an oral anticancer therapy in our gynecologic oncology clinics are seen at least annually.

9. Line 160-163: I would consider defining here exactly what adherence versus equivalent adherence meant, not just in terms of score but in actual translation to what it means in terms of frequency of dosing. This was briefly mentioned in the abstract (that equivalent means missing one dose, etc.) and should be more detailed here.

Response:

We agree with this assessment (assuming that the reviewer here means equivocal, rather than equivalent). Please refer to our response for Reviewer 2 Comment 4.

10. Line 161: This seems rather arbitrary to get more non-adherent patients than adherent, and not include anyone from the equivalent group. This is not the distribution of patients according to the survey, so why was n=10 and n=4 selected?

Response:

We attempted to evenly enroll adherent (n=4), non-adherent (n=4) and equivocally adherent (n=6) patients in the qualitative portion of the study. Subjects were purposively sampled to obtain interviews from different races, ages, medication types and adherences scores. We have now delineated the number of qualitative subjects in each adherence group. This point has been clarified in lines 211-212 and lines 305-306.

11. Line 212: There should be more statistical explanation in here regarding both the descriptive and the association analyses. Were there analyses examining the relationship between health literacy and adherence. Between stress/anxiety and adherence? How were these performed? Table 3 indicates this was done, but methods statistically should be described in this section here. The quantitative methods should have as much description as qualitative methods.

Response:

We have now expanded the methods section to describe the analysis performed regarding the relationship between health literacy, distress and anxiety, and quality of life to adherence (lines 231-259).

Results:
12. The authors do a good job illuminating with meaningful quotes the 5 themes that emerged from the interviews.

Response:

Thank you again for the thoughtful review our manuscript.

13. Line 300-308: I would like to have seem more quotes from the physicians to exemplify the misperceptions and their beliefs as to why patients are not taking the medication. If this was a matter of length, perhaps a Table or Appendix so that the illumination about provider perceptions is given more "air-time"?

Response:

Thank you for this recommendation; please refer to Reviewer 1 Comment 2 for our response and revisions.

14. There is very little "air-time" and attention given to the survey results or analysis, even though the Tables have the information and are well constructed. I would suggest at least performing a post-hoc power analysis so that we know the power of determining a difference in patient characteristics between adherent and non-adherent groups based on the smallest group size (n=21 for the equivalent group, I am assuming). This would also make the quantitative analysis choice of 100 women for the survey seem less arbitrary, or at least more considered.

Thank you for this suggestion. Please refer to Reviewer 2 Comment 3 regarding the post hoc analysis as you suggested. In terms of the quantitative analysis enrollment of 100 women, please also refer to Reviewer 2 Comment 3. We agree that the prior draft had an insufficient description of the survey results and analysis. The survey results for the total population are now described in lines 297-300 and are included in Table 1.

Discussion:

* Good discussion of the literature about lack of adherence or imperfect adherence in other oncological populations exploring this issue.

15. Line 339-349: There is a good discussion here of the weaknesses of the study; thank you. I would only add that there is no way to know if the sample is representative of all patients who are in the gynecologic oncology population. That is one of the big limitations of survey studies where the population is "whomever happens to be in the clinic".

Response:

Thank you for this suggestion; we agree that this a limitation of any survey study. This limitation is now addressed in lines 561-562.

16. Line 347-348: Thank you for acknowledging that power is an issue. But the authors

missed an opportunity to perform a post-hoc power analysis, which may have been meaningful to the reader.

Thank you for this consideration. Please refer to Reviewer 2 Comment 3 for the remainder of our response and post hoc analysis.

17. Line 354: I would add you strengths that you examined other factors that might, in this exploration, have yielded some hypothesis about factors affecting adherence (quality of life, medical literacy, etc.)

Response:

We appreciate this suggestion; we have added these strengths to the discussion section in lines 570-572.

ASSOCIATE EDITOR - GYN

Please read over the Abstract from a non-gyn oncology point of view to provide adequate orientation to the broad readership.

EDITOR 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:

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As of 7/13/20, the following authors haven't completed the form. We sent them a link to it by email from our Editorial Manager email account:

Laura J. Fish, Margaret Falkovic, Amelia Lorenzo, Laura J. Havrilesky, Angeles Alvarez Secord

2. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* 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." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

Response:

This has now been included in the cover letter.

3. For studies that report on the topic of race, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes).

Use "Black" and "White" (capitalized) when used to refer to racial categories.

The category of "Other" is a grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

Response:

In Table 1 (total population demographics), we use appropriate race designations. Black and White are capitalized.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys
(CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at https://urldefense.com/v3/__http://ong.editorialmanager.com__;!!OToaGQ!5-f2W4XDijK1vZHEwszs8GrJVnARue5ob1dFI2aoiazo5uw5rVL_UD9bc-XNbe-Km3rzV_o$. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

5. 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 data definitions at https://urldefense.com/v3/__https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions__;!!OToaGQ!5-f2W4XDijK1vZHEwszs8GrJVnARue5ob1dFI2aoiazo5uw5rVL_UD9bc-XNbe-K0P4om1E$ and the gynecology data definitions at https://urldefense.com/v3/__https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions__;!!OToaGQ!5-f2W4XDijK1vZHEwszs8GrJVnARue5ob1dFI2aoiazo5uw5rVL_UD9bc-XNbe-KWBuTHps$. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. 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.
Response:

Our manuscript is within this range, excluding references.

7. Manuscript Editor comment about your title: Consider deleting "An anaylsis of" and using just "adherence to oral anticancer therapeutics in the gynecologic oncology population."

Thank you for this suggestion, we have deleted “an analysis” from the title of our manuscript.

8. 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).
Response:
All of these guidelines have been followed.

9. 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 limit for Original Research articles is 300 words. Please provide a word count.
Response:
Our abstract word count is 266 words.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online
at https://urldefense.com/v3/__http://edmgr.ovid.com/ong/accounts/abbreviations.pdf__;

!!OToaGQ!5-f2W4XDijK1vZHEwszs8GrJVnARue5ob1dFI2aoiazo5uw5rVL_UD9bc-XNbe-KzZud2Lw$. 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.

11. ACOG is moving toward discontinuing the use of "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.
Response:
We have replaced the term provider as appropriate throughout the manuscript.

12. Please use only the standard headings for an Original Research in the body text: Introduction, Methods, Results, and Discussion. All other subheads should be removed.
Response:

All other subheads have been removed.

13. Your manuscript contains a priority claim (Line 311: "This study is the first exploration of gynecologic oncology patient adherence..."). 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 it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.
Response:

Thank you for bringing this to our attention; we have now taken this line out of the manuscript.

12. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: https://urldefense.com/v3/__http://edmgr.ovid.com/ong/accounts/table_checklist.pdf__;!!OToaGQ!5-f2W4XDijK1vZHEwszs8GrJVnARue5ob1dFI2aoiazo5uw5rVL_UD9bc-XNbe-KBrL0QxY$.

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* 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.

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