Date: Nov 20, 2018
To: "Joseph A Dottino" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1942

RE: Manuscript Number ONG-18-1942

The cost-effectiveness of niraparib for maintenance treatment of recurrent ovarian cancer

Dear Dr. Dottino:

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 Dec 10, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

This is a cost-effectiveness study to evaluate 4 strategies for maintenance therapy in patients with platinum sensitive recurrent ovarian cancer.

Main issues:

1- The idea of any cost-effectiveness analysis is to see if the cost of utilizing a therapy would result in extending QALY with a cost that is compared to a cut off which is usually set at a level of 50K and in this study is was set on a different levels from 50-100K. The prices of medication is very variable here in the US and there is no cap on the price of medication. There is also the sticker price and the insurance negotiated prices which is considered a trade secret and not readily available. I would suggest that this study provide and emphasize more the price of niraparib and other PARPI based on a QUALY of 50K and 100K? I believe this approach might be a good approach to explore the right price of a medication in the future. Instead of looking for increasing the QUALY value, we would have a price that can be a base of negotiation that fit the current standard for QUALY. This price /month or per year and not per dose should also be highlight in the conclusion of the study.

2- Basing all the analysis on one RCT is not recommended and the authors should use all the available data and sensitivity analyses should be done to provide a range based on evidence form RCT and well-designed observational studies. If there is no enough published data, then the author should weight to do the cost-effectiveness study when the data is available. Summarizing the data for all PARPi would be also recommended as they are one group and will allow providing a "reasonable" price to guide negotiations with drug companies. Certain price limits would be also presented with different levels of use. For all patients, for those with the mutation.

Specific issues:

3- Abstract:
a. I would recommend presenting the "reasonable price" of the medication based on a 50K or 100K QUALY instead of presenting the QUALY that fit the un-reasonable price"
b. I would also suggest including all the PARPi in this cost-effectiveness study
c. Presenting the price per month or per year of prescription would fit better than per dose.

4- Introduction:
a. Well written

b. Please consider changing the objective to include all PARPi if all FDA approved medications are under the same group

5- Methods:
a. Please add any other evidence form other observational studies or other RCT not included and conduct a systematic review of the literature to make sure you include all the available literature
b. Please consider adding all the FDA approved PARPi in the same study to allow more evidence to be considered for your decision analysis.

6- Results:
a. Please present the "realistic" cost of medication for a QUALY of 50K or 100K and provide info per month of use or a year of use instead of dose.

7- Discussion:
a. Please include all the PARPi in the study

REVIEWER #2:

OVERALL: This is an original research study that examines the cost-effectiveness of use of niraparib, a PARP inhibitor, as maintenance therapy for recurrent platinum-sensitive ovarian cancer. It builds on prior literature that has found that olaparib is not cost-effective as maintenance therapy for recurrent platinum sensitive ovarian cancer (Secord et al. Int J Gynecol Cancer, 2013; Smith et al. Gynecol Oncol, 2015). Uniquely, this study uses data from the NOVA trial to estimate clinical outcomes. There are few studies in the literature examining the cost-effectiveness of PARP inhibitors in the treatment of ovarian cancer, and none that examine the cost-effectiveness of niraparib. However, given that the lack of cost-effectiveness of olaparib has been established in the literature (it seems that rucaparib has been less well-studied), the findings in this manuscript are less compelling. There are typos throughout.

INTRODUCTION:

1-The introduction clearly describes the role of PARP inhibitors in ovarian cancer therapy and the background of niraparib and the NOVA study. I think it would benefit from smoother transitions, particularly between the first and second paragraphs.

2-I was surprised that the introduction did not mention the olaparib cost-effectiveness studies. I think the introduction would benefit from a reframing, with more emphasis on prior work about the cost-effectiveness of PARP inhibitors and how/why niraparib may be different or how this study approaches the question in a different way (using actual outcomes data).

3-Line 93: Add "(HRD)"

4-Line 111: What were the differences in reported outcomes seen in biomarker-stratified subgroups?

5-Lines 113-117: The "we wished to study the cost implications of more restrictive, biomarker-driven use of PARPi as maintenance therapy" seems to differ from the following "This study sought to determine cost-effectiveness of unselective and selective use of maintenance niraparib…" Is the focus unselective and selective use or is the focus the more restrictive use?

6-Line 115: Please clarify how you are defining selective and unselective. This is the first time you are using these terms in the introduction.

METHODS:

7-I found it unclear whether the patients undergoing HRD testing were gBRCA positive or negative or both. I assume that HRD testing was done on gBRCA negative tumors, but this should be clarified.

8-With the clinical data estimated form the NOVA trial, I think that it is important to include more information about the NOVA trial in the manuscript (e.g. size, patient characteristics, study type, basic outcomes, etc.). The Methods section is currently written with an assumed baseline familiarity with the NOVA trial, which may not be a reasonable assumption.

9-Line 149: What is the 20% based on?

10-Line 154: The phrase in parentheses may be more appropriate in the introduction

11-Lines 158-159: Please include a citation for the EQ-5D

12-Lines 161-165: How dose LYG factor into the willingness-to-pay cost threshold?

13-Line 205: Include a citation for HCPCS, CPT and CMS fee schedule, etc.

RESULTS:

14-Line 237: Effective in what way?

15-Lines 268-273: I don't believe the methods for these results are included in the Methods section

16-I would consider including an appendix with more detailed results

DISCUSSION:

17-Line 289: The idea of selective treatment with niraparib resulting in significant cost savings is initially confusing. I would include "compared to treatment in all patients."

18-The discussion talks a lot about the prior literature on the cost-effectiveness of PARPi. I think that some of this should be moved to the introduction.

19-One of the most compelling ideas in the discussion is the general cost of cancer therapy. The authors suggest that a reduction in the price of niraparib by 62% would result in a cost-effective drug. Is this possible? Has this degree of price reduction been seen with other cancer drugs? Is there any precedent? Is there any way to encourage price reduction?

20-I also find the idea of the ICER compelling. While there is an established ICER, is it possible that it is not accurate? While the ICER may be accurate on a population-level, it may not be accurate for an individual patient. How should an oncologist take that into consideration when prescribing a PARPi?

REVIEWER #3:

Dottino and colleagues have submitted a cost effectiveness evaluation of the use of niraparib in women with platinum sensitive recurrent ovarian cancer. This manuscript performs an analysis on several different clinically appropriate strategies which utilize niraparib in either a portion of this patient population, none of the population (observation alone) or the entire patient population. Not surprisingly when considering the cost of this medication, none of the strategies appear to be cost effective when utilizing the standard willingness to pay thresholds, when compared to observation alone. While this is not to say the medications do not have a role in these patients, but that rather they remain much too costly to be considered a cost effective therapy for general use in the United States. Overall, the manuscript is very well written and clear although I have a fair number of comments and questions for the authors as outlined below.

1. Title - Since none of the strategies are cost effective, how about a title that notes that "Niraparib is too costly for maintenance therapy in recurrent ovarian cancer: A Cost Effectiveness Analysis" or similar declarative title about the study findings.

2. Précis - No comments

3. Abstract - No comments

4. Introduction - Line 90 - most would use the full title of the medication rather than just polymerase inhibitor prior to PARPi, otherwise a fairly nicely written introduction and summary of key issues.

5. Methods - Line 141 consider adding the reference to the NOVA trial here as well.

6. Line 145-6 since you used the term BRCA wild type earlier, should you use that in this sentence as well? Did you consider modeling on using a dose of 200mg as many would use this (not currently FDA approved label) dose to start patients? Were any analysis considered in which only a proportion of the patients had BRCA testing?

7. Results - No comments.

8. Discussion - Line 320-2 is somewhat unclear, should the price of niraparib be included in this sentence?

9. Tables - In Table 1 utility is not referenced or made clearer for the casual reader.

10. Figures - No comments.

STATISTICAL EDITOR'S COMMENTS:

1. lines 42-43: Should elaborate that "not-cost effective" applies to all subsets.

2. lines 274-275: Should elaborate on this section. That is, what were the model results if cost of germ line testing and/or

HRD testing were were reduced?

3. Table 1: Should cite references for the utility proportions.

4. Table 3: Should include a footnote stating that the threshold for cost-effectiveness was $100,000/PF-QALY.

5. Fig 1: Should indicate the region where the strategy in the cost-effective region based on $100,000/PF-QALY.

ASSOC-EDITOR GYN

1 - The topic will be of high interest to the gyn onc community, but the paper as currently written would not be so to the rest of the readership. Yet it is very important for the green journal to have broad appeal to our international audience. The way to make it more attractive would be, starting with the Intro, to briefly present the topic to the readership within the context of cost-effectiveness in OB/GYN and segue this into PARP as maintenance therapy in ovarian cancer without the level of detail (other PARP inhibitors, biomarkers, etc) and then try to maintain this tone throughout the paper.

2 - Discussion points should include this study along with similar findings for olaparib put into the context of where PARPs should fit in the queue for ovarian cancer.

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. Please note that, in addition to the "Authorship" section of the third page of the Author Agreement form, all authors must also complete the "Disclosure of Potential Conflicts of Interest" section. All updated and missing forms should be uploaded with the revision in Editorial Manager.

3. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:
a. Was this study presented at SGO? If so, please disclose the name, date, and location of the meeting in your title page.

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), 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), and quality improvement in health care (ie, SQUIRE 2.0). 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, CHEERS, or SQUIRE 2.0 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 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.

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 appendixes).

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

7. 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).

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

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

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

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

11. Our readers are clinicians and a detailed review of the literature is not necessary. Please shorten the Discussion and focus on how your results affect or change actual patient care. Do not repeat the Results in the Discussion section.

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.

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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 Dec 10, 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

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In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

[redacted]

December 17th, 2018
Nancy C. Chescheir, MD
Editorial Office, *Obstetrics & Gynecology*
409 12th Street, SW
Washington, DC 20024-2188

RE: "The cost-effectiveness of FDA-approved PARP inhibitor maintenance therapy for recurrent ovarian cancer"

Dear Dr. Chescheir,

We would like to submit our revisions to the manuscript now entitled "The cost-effectiveness of niraparib for maintenance treatment of recurrent ovarian cancer" for consideration for publication in *Obstetrics & Gynecology*. As previously stated, it is our intent to submit solely to *Obstetrics & Gynecology*, and this manuscript is not under consideration elsewhere, and we do not intend to submit this manuscript elsewhere until the editors of this journal render a final decision. We affirm that the revisions made to this manuscript reflect 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.

We are grateful to the reviewers and editors for the time taken to provide thoughtful and constructive comments and are hopeful that the changes made will strengthen our manuscript. The revisions reflect both the individual reviewer's comments as well as the broader suggestions made by the associate editor and editorial office. Listed below are our enumerated responses to the comments. We are happy to further clarify any unclear responses or further revise as needed.

Thank you for your consideration. We look forward to hearing from you.

Sincerely,

Joseph Dottino, MD, MPH
Fellow
Gynecologic Oncology & Reproductive Medicine
University of Texas MD Anderson Cancer Center

REVIEWER COMMENTS:

REVIEWER #1:

This is a cost-effectiveness study to evaluate 4 strategies for maintenance therapy in patients with platinum sensitive recurrent ovarian cancer.

Main issues:

1- The idea of any cost-effectiveness analysis is to see if the cost of utilizing a therapy would result in extending QALY with a cost that is compared to a cut off which is usually set at a level of 50K and in this study is was set on a different levels from 50-100K. The prices of medication is very variable here in the US and there is no cap on the price of medication. There is also the sticker price and the insurance negotiated prices which is considered a trade secret and not readily available. I would suggest that this study provide and emphasize more the price of niraparib and other PARPI based on a QUALY of 50K and 100K? I believe this approach might be a good approach to explore the right price of a medication in the future. Instead of looking for increasing the QUALY value, we would have a price that can be a base of negotiation that fit the current standard for QUALY. This price /month or per year and not per dose should also be highlight in the conclusion of the
study.

The cost per month based on an ICER of $100,000/PF-QALY was included in both the abstract and results section and abstract of the paper, as follows:

Lines 85-88 now read, “Using the current FDA label for maintenance PARPi regardless of biomarker status, the third party payer cost per month (28-day supply) would need to be reduced from approximately $14,700 to $3,600 to be considered cost-effective compared to observation using a willingness to pay threshold of $100,000/PF-QALY.”

2- Basing all the analysis on one RCT is not recommended and the authors should use all the available data and sensitivity analyses should be done to provide a range based on evidence form RCT and well-designed observational studies. If there is no enough published data, then the author should weight to do the cost-effectiveness study when the data is available. Summarizing the data for all PARPi would be also recommended as they are one group and will allow providing a "reasonable" price to guide negotiations with drug companies. Certain price limits would be also presented with different levels of use. For all patients, for those with the mutation.
-3b. I would also suggest including all the PARPi in this cost-effectiveness study
-4b. Please consider changing the objective to include all PARPi if all FDA approved medications are under the same group
-5b. Please consider adding all the FDA approved PARPi in the same study to allow more evidence to be considered for your decision analysis.

We acknowledge the reviewer’s suggestion that inclusion of all PARPi in this study and thought towards setting a more universal goal of pricing for this drug category and indication is a forward thinking idea that would help to move inform broader policy changes rather than addressing a single drug. In order to address the potential for dose reductions and financial consequences of adverse effects, discontinuations, and different treatment effects seen in different subgroups, using a single primary data source such as the NOVA trial is ideal. Specifically, when looking at subgroups like HRD + patients, the literature does not have uniform prospective data using the same

HRD test. However, we have extensively edited the manuscript to now reflect the similarities between the different PARPis in the maintenance setting, including their cost and observed clinical outcomes (included in discussion, lines 316-320). The manuscript now reflects that rather than directly addressing niraparib as the primary focus, we are addressing FDA-labeled PARPi maintenance use, while still using primarily the NOVA study (lines 137-140 and lines 150-152).

Price limits for meeting ICER $100,000/PF-QALY are included in abstract and results in lines 281-283.

Specific issues:

3- Abstract:
a. I would recommend presenting the "reasonable price" of the medication based on a 50K or 100K QUALY instead of presenting the QUALY that fit the un-reasonable price"

See above, this is now included in the abstract as well as in lines 247-241 in the manuscript body.

c. Presenting the price per month or per year of prescription would fit better than per dose.
See above, price per month is now included in results and abstract

4- Introduction:
a. Well written

5- Methods:
a. Please add any other evidence form other observational studies or other RCT not included and conduct a systematic review of the literature to make sure you include all the available literature

References 8, 9, and 10 cite the randomized controlled trials of other FDA-approved PARPi maintenance therapies; reference 14 is an independent economic analysis of PARPi in ovarian cancers, which, while different in scope and purpose from the current study, provides corroborating cost and outcome data.

6- Results:
a. Please present the "realistic" cost of medication for a QUALY of 50K or 100K and provide info per month of use or a year of use instead of dose.

See above, this is now included in the results section

REVIEWER #2:

OVERALL: This is an original research study that examines the cost-effectiveness of use of niraparib, a PARP inhibitor, as maintenance therapy for recurrent platinum-sensitive ovarian cancer. It builds on prior literature that has found that olaparib is not cost-effective as maintenance therapy for recurrent platinum sensitive ovarian cancer (Secord et al. Int J Gynecol Cancer, 2013; Smith et al. Gynecol Oncol, 2015). Uniquely, this study uses data from the NOVA trial to estimate clinical outcomes. There are few studies in the literature examining the cost-effectiveness of PARP inhibitors in the treatment of ovarian cancer, and none that examine the cost-effectiveness of niraparib. However, given that the lack of cost-effectiveness of olaparib has been established in the literature (it seems that rucaparib has been less well-studied), the findings in this manuscript are less compelling. There are typos throughout.

The focus of the extensively edited manuscript now addresses the broader question of FDA-labeling that has taken place since the publication of previous olaparib cost-effectiveness studies. The manuscript also now

reflects the study as using primary data from the NOVA trial (the data first used for a biomarker-independent labeling of maintenance PARPi in ovarian cancer), rather than focusing on niraparib the drug itself, which should broaden both the readership of the study as well as emphasize its novelty. The manuscript has been edited for typographic errors.

INTRODUCTION:

1-The introduction clearly describes the role of PARP inhibitors in ovarian cancer therapy and the background of niraparib and the NOVA study. I think it would benefit from smoother transitions, particularly between the first and second paragraphs.

2-I was surprised that the introduction did not mention the olaparib cost-effectiveness studies. I think the introduction would benefit from a reframing, with more emphasis on prior work about the cost-effectiveness of PARP inhibitors and how/why niraparib may be different or how this study approaches the question in a different way (using actual outcomes data).

The introduction (lines 96-115) has now been edited to reflect suggestions made by the associate editor, and reflects a refocus on cost-effectiveness in gynecologic cancer care more broadly with emphasis on the current literature to date in cost-effectiveness of PARPi, as well as a clarification of the focus of this study (FDA-labeling, and the implications of a more selective use of this targeted therapy).

3-Line 93: Add "(HRD)"

Line 103 now reflects the introduction of the acronym HRD.

4-Line 111: What were the differences in reported outcomes seen in biomarker-stratified subgroups? –

Line 101-103 introduces the idea of improved response by biomarker subgroups. Lines 144-148 now explicitly state the reported outcomes in biomarker stratified subgroups.

5-Lines 113-117: The "we wished to study the cost implications of more restrictive, biomarker-driven use of PARPi as maintenance therapy" seems to differ from the following "This study sought to determine cost-effectiveness of unselective and selective use of maintenance niraparib…" Is the focus unselective and selective use or is the focus the more restrictive use?

The focus of the study is now clarified in lines 111-115, “Given the recent FDA approval of PARPi as maintenance therapy in all patients with recurrent, platinum sensitive ovarian cancer despite differences in reported effectiveness in biomarker-identified subgroups, this study sought to determine cost-effectiveness of maintenance PARPi using a decision analysis model. Specifically, we examined the implications of the broader FDA labeling compared to biomarker-driven use of PARPi.”

6-Line 115: Please clarify how you are defining selective and unselective. This is the first time you are using these terms in the introduction.

The introduction was edited to now introduce the idea of biomarker-driven use, and the subgroups selected are initially defined in the first part of the methods in lines 120-125 “…1) treatment of all patients with maintenance PARPi (‘treat all’); 2) BRCA germline mutation testing, followed by selective treatment of only those patients with germline BRCA mutations with maintenance PARPi (‘gBRCA only’); 3) both BRCA germline mutation testing and tumor HRD testing, followed by selective treatment of only those patients with either BRCA germline mutations or those with HRD positive tumors with maintenance PARPi (‘gBRCA and HRD only’)…”

METHODS:

7-I found it unclear whether the patients undergoing HRD testing were gBRCA positive or negative or both. I assume that HRD testing was done on gBRCA negative tumors, but this should be clarified.

Line 142-144 now states "As part of an exploratory analysis, the BRCA wild type patients in this study had tumor testing for HRD to determine its use in predicting outcome."

8-With the clinical data estimated form the NOVA trial, I think that it is important to include more information about the NOVA trial in the manuscript (e.g. size, patient characteristics, study type, basic outcomes, etc.). The Methods section is currently written with an assumed baseline familiarity with the NOVA trial, which may not be a reasonable assumption.

Lines 137-148 now summarize the trial and its basic outcomes: "For our model's base case, we primarily utilized the supporting data from the first FDA maintenance approval in PARPi, the NOVA study, a randomized, double blind, phase 3 trial of 553 patients with platinum sensitive recurrent ovarian cancer randomized to niraparib or placebo[7]. The median age ranged between 57-63, and most patients had stages III or IV disease at the time of diagnosis. Both germline BRCA mutation carriers and BRCA wild type patients were included. As part of an exploratory analysis, the BRCA wild type patients in this study had tumor testing for HRD to determine its use in predicting outcome. In this trial, the greatest progression-free survival (PFS) benefit of niraparib was seen in patients with germline BRCA mutations (21 months). BRCA wild type patients but with tumor HRD also saw PFS benefit from niraparib (12.9 months). Less benefit was seen in patients who were biomarker negative: BRCA wild type patients without evidence of tumor HRD (6.9 months)."

9-Line 149: What is the 20% based on?

This 20% is based on Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: A report from the Australian ovarian cancer study group. *J Clin Oncol*. 2012;30(21):2654-2663 as well as has been utilized in other cost-effectivness studies looking at this subgroup in recurrent ovarian cancer. This citation (reference 16) has been added.

10-Line 154: The phrase in parentheses may be more appropriate in the introduction

This parenthetical description was deleted and instead this term is clarified in the introduction in lines 101-103, "In ovarian cancer, poly ADP ribose polymerase inhibitors (PARPi) are a relatively recently FDA-approved class of drug where improved response is predicted by a BRCA mutation or tumor homologous recombination deficiency (HRD)."

11-Lines 158-159: Please include a citation for the EQ-5D

The appropriate citation is now added in lines 141-143: (The EuroQol GroupEuroQol-a new facility for the measurement of health-related quality of life Health Policy, 16 (1990), pp. 199-208)

12-Lines 161-165: How dose LYG factor into the willingness-to-pay cost threshold?

In our study we used a quality adjusted progression free life year gained in the absence of overall survival data. This metric has been utilized by other authors in the literature where progression-free survival is the metric by which the drug or therapy has been approved.

13-Line 205: Include a citation for HCPCS, CPT and CMS fee schedule, etc.

The following citations were added:

Centers for Medicare and Medicaid Services. Physician fee schedule. Available at: https://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx

2017 clinical diagnostic Lab fee schedule. Available at: (https://www.cms.gov/apps/ama/license.asp?file=/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Downloads/17CLAB.zip)

RESULTS:

14-Line 237: Effective in what way?

Line 246-249 now reads, "Under our base case assumptions, all maintenance therapy strategies with niraparib for women with platinum sensitive recurrent ovarian cancer were both costlier and conferred greater PF-QALYs than observation alone"

15-Lines 268-273: I don't believe the methods for these results are included in the Methods section

Lines 234-236 added to the sensitivity analysis portion of the methods: "Finally, the cost of PARPi was tested to determine the cost at which treatment with PARPi would be cost-effective compared to observation given a willingness-to-pay threshold of $100,000/PF-QALY."

16-I would consider including an appendix with more detailed results

Due to the space limitations with our current model and results that includes space allotted for appendix, this would be challenging – however, all effort was made to include specific results or methods details as indicated by reviewers and editors.

DISCUSSION:

17-Line 289: The idea of selective treatment with niraparib resulting in significant cost savings is initially confusing. I would include "compared to treatment in all patients."

Discussion structure has been modified in accordance with editors comments. The introductory paragraph of the discussion briefly summarizes the study results as follows in lines 297-301: "This study demonstrates that use of maintenance PARPi therapy in platinum sensitive recurrent ovarian cancer is not cost-effective compared to observation. Selective maintenance treatment using either BRCA mutation status or HRD tumor status has a favorable cost-effectiveness ratio when compared to use in all recurrent, platinum sensitive ovarian cancer patients."

18-The discussion talks a lot about the prior literature on the cost-effectiveness of PARPi. I think that some of this should be moved to the introduction.

Lines 108-110 in the introduction now read, "The cost-effectiveness literature to date has been limited to olaparib, and has not included HRD testing as a means of selecting patients where the relative value of PARPi may

be higher.", with relevant citations introduced.

19-One of the most compelling ideas in the discussion is the general cost of cancer therapy. The authors suggest that a reduction in the price of niraparib by 62% would result in a cost-effective drug. Is this possible? Has this degree of price reduction been seen with other cancer drugs? Is there any precedent? Is there any way to encourage price reduction?

Paragraphs added to discussion which touch on the Society of Gynecoglogic Oncology and ASCO's recent position statement (line 333-343, lines 351-354) regarding rising costs related to cancer therapy, and introduce policy initiatives suggested by these professional organizations, including increased transparency in drug pricing, improving access to generic medications, allowing for CMS to negotiate cancer drug pricing, and value-based pricing.

20-I also find the idea of the ICER compelling. While there is an established ICER, is it possible that it is not accurate? While the ICER may be accurate on a population-level, it may not be accurate for an individual patient. How should an oncologist take that into consideration when prescribing a PARPi?

This is an interesting point that warrants further discussion. Lines 320-232 include the challenges of the current ICER thresholds, now reading, "Additionally, although used by other authors, use the $100,000/PF-QALY ICER threshold may be criticized for lack of applicability in an updated healthcare landscape. The significant burden of the cost of oncologic care may also suggest an exploration of a different willingness-to-pay threshold specific to cancer care." Relevant citations included. While this paper seeks to point out the challenges of drug cost at a policy level, being aware of potential financial toxicities at a provider level may help oncologists continue to discuss the efficacy of prescribed therapies and work with available resources to minimize financial toxicity to the patient through patient advocacy and engaging with insurers when able.

REVIEWER #3:

Dottino and colleagues have submitted a cost effectiveness evaluation of the use of niraparib in women with platinum sensitive recurrent ovarian cancer. This manuscript performs an analysis on several different clinically appropriate strategies which utilize niraparib in either a portion of this patient population, none of the population (observation alone) or the entire patient population. Not surprisingly when considering the cost of this medication, none of the strategies appear to be cost effective when utilizing the standard willingness to pay thresholds, when compared to observation alone. While this is not to say the medications do not have a role in these patients, but that rather they remain much too costly to be considered a cost effective therapy for general use in the United States. Overall, the manuscript is very well written and clear although I have a fair number of comments and questions for the authors as outlined below.

1. Title - Since none of the strategies are cost effective, how about a title that notes that "Niraparib is too costly for maintenance therapy in recurrent ovarian cancer: A Cost Effectiveness Analysis" or similar declarative title about the study findings.

Obstetrics and Gynecology's instructions for authors discourages use of a declarative in the title— "The manuscript title, which should contain no more than a total of 100 characters (counting letters and spaces) and should not be declarative or pose a question; do not use abbreviations or commercial names in the title." (https://journals.lww.com/greenjournal/Pages/instructionsforauthors.aspx#title_page); However, the title now reflects other manuscript changes suggested by reviewers and editors and now reads, "**The cost-effectiveness of FDA-approved PARP inhibitor maintenance therapy for recurrent ovarian cancer"**

2. Précis - No comments

3. Abstract - No comments

4. Introduction - Line 90 - most would use the full title of the medication rather than just polymerase inhibitor prior to PARPi, otherwise a fairly nicely written introduction and summary of key issues.

Introduction has been edited to reflect editor's comments, and line 101-103 now reads In ovarian cancer, poly ADP ribose polymerase inhibitors (PARPi) are a relatively recently FDA-approved class of drug where improved response is predicted by a BRCA mutation or tumor homologous recombination deficiency (HRD)."

5. Methods - Line 141 consider adding the reference to the NOVA trial here as well.

Lines 137-140 now include a description of the NOVA trial as well as citation of the study, "In ovarian cancer, poly ADP ribose polymerase inhibitors (PARPi) are a relatively recently FDA-approved class of drug where improved response is predicted by a BRCA mutation or tumor homologous recombination deficiency (HRD)."

6. Line 145-6 since you used the term BRCA wild type earlier, should you use that in this sentence as well?

The term BRCA wild type is now incorporated throughout manuscript to refer to BRCA negative patients.

Did you consider modeling on using a dose of 200mg as many would use this (not currently FDA approved label) dose to start patients?

We wanted to currently use the FDA-approved dosing for the purposes of addressing drug pricing and value in gynecologic cancer care. While NOVA suggests that 200mg dosing is equivalent, the study was not powered to look at this specific dose. While this would also likely reduce the number of patients suffering from adverse effects of full dose niraparib (and spare them the cost of these adverse effects), the exact rates of drug reduction would be an extrapolation. In this case we aimed to use the primary data the FDA used to approve maintenance niraparib, which would be at the full dose with the known adverse effects. This question would be an interesting one for future study, (especially given some of the now-identified risk factors for hematologic side effects in niraparib published after the NOVA study) but introduces an additional line of inquiry beyond the scope of this current model. For example, a future prospective study could evaluate stratifying patients by risk factors and adjusting starting maintenance dosing based on this and looking at efficacy and adverse effects.

Were any analysis considered in which only a proportion of the patients had BRCA testing?

We incorporated a baseline rate of BRCA positive patients and then varied that rate from 5% to 50% in sensitivity analysis. We also varied the number of patients tested prior to entering the model to vary the financial impact of such testing. In the case of an alternate scenario where no patients have had any BRCA testing, this would fall outside standard of care practices. Efficacy of PARPi in this population would the same as the "treat all" strategy – where testing does not influence use of maintenance PARPi.

7. Results - No comments.

8. Discussion - Line 320-2 is somewhat unclear, should the price of niraparib be included in this sentence?

Line 324-327 now reads, “To estimate the cost of adverse hematologic effects, we used cost estimates adapted from the breast cancer literature, which may not accurately reflect cost of hematologic adverse events in ovarian cancer patients.”

9. Tables - In Table 1 utility is not referenced or made clearer for the casual reader.

Footnote now added to Table 1 which reads, “*Utility scores adapted from the European Quality of Life scale, 5-Dimensions (EQ-5D-5L) measurements from NOVA trial, Mirza et al. 2016.”

10. Figures - No comments.

STATISTICAL EDITOR’S COMMENTS:

1. lines 42-43: Should elaborate that "not-cost effective" applies to all subsets.

Precis now reads “While maintenance PARPi is not cost-effective in recurrent ovarian cancer patients regardless of biomarker status, lowering drug prices may potentially make this therapy cost-effective.”

2. lines 274-275: Should elaborate on this section. That is, what were the model results if cost of germ line testing and/or HRD testing were were reduced?

Lines 277-278 read “Reduction of the cost of HRD testing had no effect on cost effectiveness ranking down to a cost of $0.”, and now lines 288-289 reads, “Similar to HRD testing, reduction in the cost of germline testing had no effect on cost-effectiveness rankings.” To emphasize the findings that costs of testing had little effect on the model results.

3. Table 1: Should cite references for the utility proportions.

See above, footnote now added to Table 1 which reads, “*Utility scores adapted from the European Quality of Life scale, 5-Dimensions (EQ-5D-5L) measurements from NOVA trial, Mirza et al. 2016.”

4. Table 3: Should include a footnote stating that the threshold for cost-effectiveness was $100,000/PF-QALY.

Footnote now reads, “The ICER threshold for considering a strategy cost-effective was $100,000/PF-QALY.”

5. Fig 1: Should indicate the region where the strategy in the cost-effective region based on $100,000/PF-QALY.

Figure 1 current illustrates the difference between base case strategies and the relative costs and effectiveness of strategies with decreased cost in treatments based on sensitivity analysis. The $100,000/PF-QALY threshold for individual strategies compared to observation may be illustrated better in another figure.

ASSOC-EDITOR GYN

1 - The topic will be of high interest to the gyn onc community, but the paper as currently written would not be so to the rest of the readership. Yet it is very important for the green journal to have broad appeal to our

international audience. The way to make it more attractive would be, starting with the Intro, to briefly present the topic to the readership within the context of cost-effectiveness in OB/GYN and segue this into PARP as maintenance therapy in ovarian cancer without the level of detail (other PARP inhibitors, biomarkers, etc) and then try to maintain this tone throughout the paper.

Introduction has been redone to briefly introduce and emphasize the context of cost-effectiveness studies and the importance of such scholarship in the context of rising healthcare costs, followed by a brief introduction of PARP as maintenance omitting the background on mechanism.

2 - Discussion points should include this study along with similar findings for olaparib put into the context of where PARPs should fit in the queue for ovarian cancer.

Discussion has been redone to omit a rehashing of results and instead focus more on context of use of PARPi, cost-effectiveness studies already performed (olaparib studies), and changes for cost control.

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.

OPT-IN

2. Please note that, in addition to the "Authorship" section of the third page of the Author Agreement form, all authors must also complete the "Disclosure of Potential Conflicts of Interest" section. All updated and missing forms should be uploaded with the revision in Editorial Manager.

Disclosures of potential conflicts of interest are included as additional documents uploaded as “Disclosures of Potential Conflicts of Interest”. For those authors that did not have potential conflicts of interest this was reflected on the Author Agreement Forms and additional documents were not uploaded. If needed this can be conveyed or documents presented in a more specific or different way.

3. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:

a. Was this study presented at SGO? If so, please disclose the name, date, and location of the meeting in your title page.

Line 16-17 in title page states, “Version of this abstract was presented at the Society for Gynecologic Oncology on March 24-27, 2018 in New Orleans, LA”

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), 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), and quality improvement in health care (ie, SQUIRE 2.0). 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, CHEERS, or SQUIRE 2.0 guidelines, as appropriate.

CHEERS guidelines reviewed and checklist included with revision submission.

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 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.

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 appendixes).

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

Abstract is now edited to less than 250 words, Introduction has been edited to 233 words and Discussion has been edited to now 735 words. Total manuscript length is 22 pages and totals less than 5,000 words.

7. 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).

Financial support for the authors directly related to the study are included on the title page, “This work was supported by T32 training grant for training of academic gynecologic oncologists (T32CA101642), the MD Anderson Cancer Center Support Grant (P30CA016672)”.

The following disclosures are thought to be unrelated to the study and manuscript submitted: *Dr Alvarez Secord discloses that she has received clinical trial grant funding from AbbVie, Amgen, Astellas Pharma Inc., Astex Pharmaceuticals Inc., AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb,* Eisai, *Endocyte, Exelixis, Incyte, Merck, PharmaMar,* Prima Biomed, *Roche/Genentech, TapImmune and TESARO. She has also received honoraria for Advisory Boards from Alexion, Aravive, Astex, AstraZeneca, Boehringer Ingelheim, Clovis, Janssen/Johnson & Johnson, Merck, Mersano, Myriad, Oncoquest, Precision Therapeutics, Roche/Genentech, and TESARO within the past 36 months.*
Dr. Havrilesky discloses that she has received clinical trial grant funding from AstraZeneca and TESARO.

This information can be added to the title page or body of the manuscript as needed.

No manuscript preparation assistance was used apart from work provided by authors listed, and no additional acknowledgements are indicated.

The abstract on which this manscuript is based was presented at the annual the Society for Gynecologic Oncology meeting on March 24-27, 2018 in New Orleans, LA. This information is included on the title page.

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

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

Abstract has been edited and updated according to manuscript revision. Word count is now less than 250 words.

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

PARPi and HRD are not listed in the standard list available online- however, these abbreviations are commonly used in the literature. To clarify, should I refrain and instead replace these with “poly ADP ribose polymerase inhibitors” and “homologous recombination deficiency” throughout manuscript?

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

The virgule symbol is now only used to express cost-effectiveness ratio data in text.

11. Our readers are clinicians and a detailed review of the literature is not necessary. Please shorten the Discussion and focus on how your results affect or change actual patient care. Do not repeat the Results in the Discussion section.

The discussion has now been edited to omit a detailed review of the literature and provides a more limited reference to previously performed cost-effectiveness studies related to the current study. Discussion has been also shortened to comply with word limitation guidelines.

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.

The table checklist was reviewed and tables are thought to conform with journal style.

Daniel Mosier

From: Dottino,Joseph [redacted]
Sent: Friday, January 4, 2019 2:01 PM
To: Daniel Mosier
Subject: RE: Manuscript Revisions: ONG-18-1942R1
Attachments: 1.4Dottino-revisionresponses_LH.docx; 1.4JDedit.18-1942R1 ms (1-2-19v2)_LH.docx

Thanks Daniel – see attached. For #8 – please let us know if there is more clarification needed (or edits need to be made in the manuscript body).

Joe

From: Daniel Mosier <dmosier@greenjournal.org>
Sent: Thursday, January 3, 2019 7:39 AM
To: Dottino,Joseph [redacted]
Subject: [EXTERNAL EMAIL] RE: Manuscript Revisions: ONG-18-1942R1

Dr. Dottino,

You can send your edited files and responses to me in a response email, no need to upload to Editorial Manager.

Please let me know if you have any other questions.

-Daniel Mosier

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

From: Dottino,Joseph [redacted]
Sent: Thursday, January 3, 2019 7:02 AM
To: Daniel Mosier <dmosier@greenjournal.org>
Subject: RE: Manuscript Revisions: ONG-18-1942R1

Thanks for the clarification – one more question, should these corrections/edits be uploaded to the Editorial Manager, or returned to you in email?

From: Daniel Mosier [mailto:dmosier@greenjournal.org]
Sent: Wednesday, January 02, 2019 11:49 AM
To: Dottino,Joseph [redacted]
Subject: [EXTERNAL EMAIL] RE: Manuscript Revisions: ONG-18-1942R1

Dr. Dottino,

Sorry for the line number discrepancy, the relevant line for query #8 is: “Results were not dissimilar from the current study; however, HRD status has not previously been included. ”

If there is any further confusion: When you open the Word document and click on the “Comment” icon (shaped like a word bubble), Word will highlight the portion of that manuscript pertaining to that specific comment.

Please let us know if you have any other questions.

Sincerely,
-Daniel Mosier

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

From: Dottino,Joseph [redacted]
Sent: Wednesday, January 2, 2019 12:46 PM
To: Daniel Mosier <dmosier@greenjournal.org>
Subject: RE: Manuscript Revisions: ONG-18-1942R1

Thank you – to quickly clarify, does # 8 line 279 refer to the statement, To date, published studies of the cost-effectiveness of maintenance PARP inhibitor therapy have examined maintenance olaparib.”?

From: Daniel Mosier <dmosier@greenjournal.org>
Sent: Wednesday, January 2, 2019 11:38 AM
To: Dottino,Joseph [redacted]
Subject: [EXTERNAL EMAIL] Manuscript Revisions: ONG-18-1942R1

Dear Dr. Dottino,

Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:

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 submit an Author Agreement form for Dr. Lu with both the “Disclosure of Potential Conflicts of Interest” and “Authorship” sections completed.
3. LINE 53: Please re-order these strategies to be in same sequence as reported out below in Results
4. LINE 61: Please be sure the months for each cost are stated in the body of your paper, tables, or figures. Statements and data that appear in the Abstract must also appear in the body text for consistency.
5. LINE 75: Please review page 4 of your Ref #1 to cite appropriately. Throughout the rest of the revised Intro, please re-do the citations to reflect updated content.
6. LINE 106: Please keep the same order as in the Abstract
7. LINE 121: Please add the reason for study exemption.
8. LINE 279: Would you provide details of a literature search to support this statement? Include databases searched, years searched, and search terms.

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on **Friday, January 4th.**

Sincerely,

-Daniel Mosier

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From: [redacted]
To: Stephanie Casway
Subject: RE: O&G Figure Revision: 18-1942
Date: Friday, January 4, 2019 5:32:56 PM

Stephanie – I think everything looks great. I forwarded along to my senior author for confirmation.

[redacted]

From: Stephanie Casway
Sent: Wednesday, December 19, 2018 9:11 AM
To: [redacted]
Subject: O&G Figure Revision: 18-1942

Good Morning Dr. Dottino,

Your figure has been edited, and PDFs of the figure and legend are attached for your review. Please

review the figure and legend CAREFULLY for any mistakes.

PLEASE NOTE: Any changes to the figures must be made now. Changes made 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, 12/21. Thank you for your help.

Best wishes,

Stephanie Casway, MA
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