OBSTETRICS & GYNECOLOGY

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

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

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

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

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

Date: Jan 18, 2022
To: "Bruce S. Kahn" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-2303

RE: Manuscript Number ONG-21-2303

36-Month Prospective Study of Transvaginal Mesh versus Native Tissue Repair for Pelvic Organ Prolapse

Dear Dr. Kahn:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Feb 08, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

I have enjoyed reading this interesting article. It summarized as the experience of a significant number of operations performed at a variety of clinical sites. The authors are to be congratulated for conducting a surgical trial of the scope. The authors acknowledge the limitations of this study design which, although not as strong as a randomized trial, is a pragmatic demonstration of diffuse effectiveness. They have attempted to minimize differences in characteristics between the two cohorts with propensity matching.

1. Moving the brief description of the composite endpoint to the methods section would make it easier for the reader.
2. Adding the actual data for the secondary composite endpoint in the abstract would strengthen the abstract. The level of statistical significance is provided but not the actual data is it is for the other factors.
3. Line 10: This number isn't credible and is not based on current outcome definitions. Providing data from 1 of the pelvic floor disorders network randomized trials that had a native tissue arm would provide a more accurate and contemporary estimate. Honest failure rates are plenty high enough to justify this type of research.
4. Line 11: Not all studies of mesh augmented repairs have shown better subjective outcomes. The language should be revised.
5. Line 33: Simply saying that the sponsor's role as disclosed does not say what Boston Scientific Employees did. Who analyzed the data, what role industry employees played in writing, etc.. Please provide full details.
6. This study evaluates the outcome of Uphold Lite mesh. Because the term "transvaginal mesh" could mean so many different operations, I would favor stating the product name in the title. The phrase "transvaginal mesh" is nonspecific.
7. It would be helpful to explicitly state who did the assessment at each of the postoperative time points. Was it the surgeon?
8. Line 88: There needs to be an evidence-based justification for the authors deciding to use this secondary endpoint provided in the methods section. It is mentioned later, but leaves the reader wondering. I realize this is commentary to add in the methods section but I believe it would improve ease of understanding for the reader. It is not consistent with the current consensus about outcome variables that been well established by data from the pelvic floor disorders at work and this needs to be acknowledged in the discussion.
9. The authors as are to be congratulated on using propensity scoring. This greatly strengthens the paper.
10. Analysis that includes both intent to treat and per protocol analyses is another strength of the study.
11. Line 200: Since the authors have provided specific percentage is on all the other evaluations in this paragraph, they should be added for subjective success and the "no treatment" rates as well.
12. Line 222: The subjective outcome should also be listed here as this is clearly the primary factor that patients are interested in.

13. Line 265: The statement that begins at the end of this line conflicts with the 1st sentence of the abstract conclusion. Being careful about language here is appropriate.
14. Overall, the authors give greater emphasis on the anatomical endpoints and less to the subjective endpoints that did not differ. For example, these subjective outcomes are not provided in the abstract. Greater weight should be given in the manuscript to the subjective reports of the women who had surgery. This is what the patients experience and is the most important thing for them. This critical information needs to be provided along with its percentages in the abstract, the conclusion of the abstract, and receive a more prominent place in the discussion.
15. The discussion needs to acknowledge the higher rate of uterine preservation (24%) in the mesh group and discuss the potential occurrence of endometrial or cervical pathology in the future and possible cancer from the fallopian tubes or ovaries that might have been removed during hysterectomy. In addition, complications from placement of mesh between the cervix and bladder that might arise at future hysterectomy that require removal of the cervix is not known and could potentially be surgically challenging and deserve mention. If the mesh becomes adherent to the bladder there might be a higher rate of bladder injury. Of course, these factors are not yet proven, but logic suggests they be considered.

Reviewer #2: Comments to the authors

The authors present an FDA 522 postmarket surveillance study comparing the efficacy and safety of transvaginal mesh to native tissue repair for pelvic organ prolapse at 36 months. The study design is a prospective multi center cohort study with the primary composite end point of success and retreatment. Secondary composite outcomes include quality of life, mesh exposure and complications. Some of this data has been reported back the FDA with the following response. "The two Boston Scientific 522 studies were completed, and the final reports (36-month follow-up data) were reviewed by the FDA. The study results showed that Boston Scientific transvaginal POP mesh had similar effectiveness and safety outcomes to native tissue repair at 36 months. The FDA continues to believe that devices of this type for transvaginal POP mesh repair presents potential additional risks compared to native tissue repair, including mesh exposure and erosion. Therefore, the FDA maintains that these devices do not have a favorable benefit-risk profile". FDA.org

Abstract:
Without reading the FDA 522 the abstract is confusing as to the prospective nature of the study. I would suggest clearly stating the FDA 522 order of the primary out come was a superiority trial vs non inferiority for secondary outcomes.

Introduction:
Line 10-11 Expand on recurrence by compartments. Ie anterior, posterior and apical. The references listed are all the anterior compartment.
Line 14-16 Discuss the evolution of materials and porous size related to infection and mesh exposure.
Line 25-35 The disclosure is very important and I assume with blinding the editors will be able to see this and vet any concerns.

Methods:
Line 38-42 Reading the FDA 522 it is not clear if these patients were enrolled prior to post marketing or before. Giving a time line and dates would be helpful.
Line 43 How did the sponsor, I assume Boston Scientific, choose sites? If they only chose high volume sites and or academic centers it may not reflect the real world experience and outcomes and underestimate risk.
Line 48-66 Explain more about the collaborative efforts with FDA, industry and professional organizations in determining the outcomes and inclusion/exclusion criteria. What materials and or sutures were used in the NTR? I could not find details in table 1.
Line 77-78 Was the post procedure assessment for POP blinded or was it determined by the primary surgeon?

Sample size
Line 104 Reviewing the references for historic success 16-20 The follow up for outcomes varied quite a bit. . Am J Obstet Gynecol. 1998;179(1):13-20 was a 4-9 year follow up for NTR vs 6 and 12 mths for mesh Obstetrics and gynecology. 2011;117(2 Pt 1):242-250. Since the primary outcome here is 36 mths the assumptions and references should be short term success and as similar as possible.

Results:
Line 145-148 The loss to follow up was slightly different 76% in the mesh 83% in the NTR. This may have biased some of the outcomes. If there was dissatisfaction and or unreported complications in the mesh arm they may have been less likely to follow up.
Line 159 Was there an explanation for higher hysterectomy concurrent procedures in the NTR due to concerns for apical erosion?
Line 177-178 This is helpful knowing the driver of the composite outcome was for anterior repair.

Line 181 Although 36 mths was the predetermined follow up, POP and repairs along with erosion continues to occur. Is there plan for longer term follow up?
Table 2 There is overlap with the primary and secondary POP definitions. From reading the manuscript the primary outcome was at or above the hymen chosen by the FDA. Why was the secondary outcome chosen of above the hymen? It does not seem as though this is clinically relevant unless it is a proxy for long term success. Please explain in more detail the clinical relevance.

Discussion:
Line 224 This explains the 2nd end point proposed by investigators.
Line 230 Where were the mesh exposures? When did they show up?
Line 262-267 This addresses some of the comments in the beginning. I would recommend stating this position in the Introduction to help the reader understand the rationale for superiority vs non inferiority.

Reviewer #3:

This is a prospective study of the Uphold LITE mesh (Boston Scientific) vs. native tissue repair with 36 months outcomes. Patients included were recruited in the Uphold LITE 522 study, or from the American Urogynecologic Society Pelvic Floor Disorders Registry (shared control pool for other 522 studies). Results show similar composite outcomes in both groups when using the hymen as a cut off for prolapse recurrence. When using recurrence past the hymen as an endpoint, transvaginal mesh appeared superior to native tissue repair. Adverse events were similar in both groups. Mesh complications were uncommon (4.9% mesh exposure, with only 1 individual requiring outpatient excision, others resolved conservatively). This study was conducted and reported rigorously to satisfy the FDA's 522 study requirements. Some clarifications are recommended.

Abstract:
- methods: recommend to specify that the primary composite outcome includes both subjective and objective measures
- results: first sentence: specify this is primary composite treatment success?
Methods:
- line 43: Why did this study use separate centers for the study arms? This could introduce further bias as surgeon factors/center factors could impact results. Please clarify.
Results:
- There is no mention of what the native tissue repairs were. Were they all vaginal repairs, or all approaches? Please add information on type of native tissue repairs (uterosacral vs. sacrospinous ligament suspensions). Did the type of native tissue repair influence recurrence rate in that group, and could this affect the comparison?
- In the native tissue repair group, there were more hysterectomies and less hysteropexies. Was there an association between hysteropexy and recurrence rate in either group?
- lines 146-148: include a lost to follow-up %
- line 208: add % of mesh exposure rate here as well (already included in the discussion)
- Tables 6 and 9: include posterior compartment as well
- would recommend adding other important postoperative outcomes in the tables including: de novo SUI (as well as persistent SUI, and reoperation for SUI), de novo OAB (and persistent OAB), voiding dysfunction, sexual function scores (mean +/- SD), de novo dyspareunia, non-sexual pelvic pain.
Discussion:
- line 258: what is meant by "lower volume type" mesh. The Uphold has both a lower overall surface area of mesh and a lighter weight density than the Prolift used in many previous studies. Both these factors should be specified.
- line 266: would be more conservative in this sentence and rephrase to " suggests that TVM MAY BE superior…"
- Would emphasize that there was no difference in patient symptomatology or quality of life demonstrated in either study.

Reviewer #4: Abstract Results section, line 3: The (6.5%, CI -0.2%,13.2%) needs clarification, since it represents the propensity adjusted treatment vs that available to the reader from the crude rates. Should cite all the primary outcomes first, then any relevant secondary ones.

lines 102-112 and Table 2: There were actually 4 primary endpoints, so the inference threshold would need to be stricter than 0.05, to account for multiple hypothesis testing. That makes the study underpowered for the various primary outcomes cited. It would have been preferable to stipulate one primary (e.g., non-inferiority of treatment success rates at 36 months) and made the remainder as secondary outcomes.

Table 4: Should format LOS as median(range or IQR), unless the LOS were normally distributed. Need to include IQR or range wiht the median times and volumes.

Tables 5, 6: It appears from the multiple imputation vs available case analysis that there were ~56 with some missing dat in TVM and ~ 85 with missing data among the NTR group. Need to enumerate which of the characteristics were missing for each group (could in supplemental information, with relevant summary in main text. Also, did those with complete data differ in any baseline characteristics
from those who had incomplete data?

Table 7: The differences were NS, but the rates of adverse outcomes was low and the power to discern any difference was also low, so one cannot generalize the NS treatment differences from these data.

Table 8,9: Same issues as with Tables 5,6 re: missing data and any differences between the groups with complete data vs those who required imputation.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

4. 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.

5. For studies that report on the topic of race or include it as a variable, 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). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience 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.

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

7. 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.

8. 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.

9. 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 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

10. 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).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

11. 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; Reviews is 300 words; Case Reports is 125 words; Current Commentary articles is 250 words; Executive Summaries, Consensus Statements, and Guidelines are 250 words; Clinical Practice and Quality is 300 words; Procedures and Instruments is 200 words. Please provide a word count.

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

13. 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.

14. 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.

15. ACOG avoids using "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.

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

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

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

17. 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.

18. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and replaced by a newer version, please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

19. When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

20. 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.

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.

If you choose open access, you will receive an Open Access Publication Charge letter from the Journal's Publisher, Wolters Kluwer, and instructions on how to submit any open access charges. The email will be from publicationservices@copyright.com with the subject line, "Please Submit Your Open Access Article Publication Charge(s)." Please complete payment of the Open Access charges within 48 hours of receipt.

***

If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. 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. Do not omit your responses to the Editorial Office or Editors' comments.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Feb 08, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD
Deputy Editor, Gynecology

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

_____

February 2, 2022

RE: Manuscript Number ONG-21-2303

36-Month Prospective Study of Transvaginal Mesh versus Native Tissue Repair for Pelvic Organ Prolapse

Dear Editors:

We appreciate this opportunity to submit a revised version of our original manuscript, "36-Month Prospective Study of Transvaginal Mesh versus Native Tissue Repair for Treatment Prolapse Overview" to *Obstetrics & Gynecology*. The reviews were thorough and thought-provoking and have, we believe, shaped this into a clearer and more effective manuscript.

As requested in the revision guidelines, we have responded point by point to the reviewer and editor comments, below. Review comments are in black font, followed by our responses in blue. Page and line numbers referenced in our responses are those of the revised, tracked changes version of the manuscript.

We note that after addressing reviewer comments, the word count of the manuscript text (including tables) is 5,645, putting it 145 words over the limit specified in the author guidelines. We are open to making additional edits to bring the word count back down but thought it appropriate to provide comprehensive revisions based on the review before making any additional changes.

As lead author, 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. Finally, we opt in to this revision letter being posted as supplemental digital content to the published article online.

Please contact me with any questions or concerns.

Best regards,

Bruce Kahn

REVIEWER COMMENTS AND AUTHOR RESPONSES:

Reviewer #1:

I have enjoyed reading this interesting article. It summarized as the experience of a significant number of operations performed at a variety of clinical sites. The authors are to be congratulated for conducting a surgical trial of the scope. The authors acknowledge the limitations of this study design which, although not as strong as a randomized trial, is a pragmatic demonstration of diffuse effectiveness.

They have attempted to minimize differences in characteristics between the two cohorts with propensity matching.

1. Moving the brief description of the composite endpoint to the methods section would make it easier for the reader.

R1 Response 1: This suggested change has been made to the abstract.

2. Adding the actual data for the secondary composite endpoint in the abstract would strengthen the abstract. The level of statistical significance is provided but not the actual data is it is for the other factors.

R1 Response 2: We have added this data to the abstract results as suggested.

3. Line 10: This number isn't credible and is not based on current outcome definitions. Providing data from 1 of the pelvic floor disorders network randomized trials that had a native tissue arm would provide a more accurate and contemporary estimate. Honest failure rates are plenty high enough to justify this type of research.

R1 Response 3: Agreed. This statement and better references were revised the manuscript based on data from the PFDN as suggested. Thank you.

4. Line 11: Not all studies of mesh augmented repairs have shown better subjective outcomes. The language should be revised.

R1 Response 4: Page 7, lines 11-13 have been revised to qualify that some studies have shown better outcomes, while others have found complications.

5. Line 33: Simply saying that the sponsor's role as disclosed does not say what Boston Scientific Employees did. Who analyzed the data, what role industry employees played in writing, etc.. Please provide full details.

R1 Response 5: Thank you for this clarification, as we initially followed the recommended text for this section from the author guidelines. We have updated page 8, line 32-38 accordingly.

6. This study evaluates the outcome of Uphold Lite mesh. Because the term "transvaginal mesh" could mean so many different operations, I would favor stating the product name in the title. The phrase "transvaginal mesh" is nonspecific.

R1 Response 6: In preparing the manuscript, we followed the author guidelines that advise against using brand names in the title. If the editors desire, we would be happy to revise to include the brand name.

7. It would be helpful to explicitly state who did the assessment at each of the postoperative time points. Was it the surgeon?

R1 Response 7: Baseline and subsequent objective assessments were completed by the surgeon performing the procedure. We felt that any bias introduced in this non-blinded fashion would be equal in the comparison groups. We did not include this in the original manuscript to conserve word use. Per this comment and a comment by Reviewer 2, we have added this information as a footnote to Table 1 (Data Collection at Study Time Points).

8. Line 88: There needs to be an evidence-based justification for the authors deciding to use this secondary endpoint provided in the methods section. It is mentioned later, but leaves the reader wondering. I realize this is commentary to add in the methods section but I believe it would improve ease of understanding for the reader. It is not consistent with the current consensus about outcome variables that been well established by data from the pelvic floor disorders at work and this needs to be acknowledged in the discussion.

R1 Response 8: During design of the trial, investigators disagreed with the FDA that the primary objective outcome measure include points that were the same as objective inclusion criteria. This was the reason for the inclusion of the secondary composite measure. We think we have stated this efficiently in the methods section and described this better later, but we are happy to revise if desired. Regarding outcomes variables defined by the PFDN, the most relevant publication we could find (Defining success after surgery for pelvic organ prolapse - PubMed (nih.gov), simply seems to indicate

that there are many ways to report outcomes. We believe the composite outcome measures reported here represent the “best of both worlds” in regards to reporting subjective and objective measures.

9. The authors as are to be congratulated on using propensity scoring. This greatly strengthens the paper.

R1 Response 9: We appreciate this positive comment and agree that propensity scoring adds great value in a non-randomized trial. We have added this as a strength of the study.

10. Analysis that includes both intent to treat and per protocol analyses is another strength of the study.

R1 Response 10: Thank you. We have added this to the list of study strengths in the discussion, page 19, line 292.

11. Line 200: Since the authors have provided specific percentage is on all the other evaluations in this paragraph, they should be added for subjective success and the "no treatment" rates as well.

R1 Response 11: These rates from Table 9 have been added to the text on page 16, line 217. Additionally, we added the NS differences to the page 15, line 189 where the primary subjective and retreatment rates are addressed. We also have added a sentence to the methods on page 11, line 102, stating that the subjective success and retreatment components of the composite outcome measures were the same as one another, as this may provide more explicit clarity on why the results for those components were identical.

12. Line 222: The subjective outcome should also be listed here as this is clearly the primary factor that patients are interested in.

R1 Response 12: For the sake of readability and flow, we have added this suggestion a bit further down in the same paragraph, beginning on line 248, “Subjective success was the same…”

13. Line 265: The statement that begins at the end of this line conflicts with the 1st sentence of the abstract conclusion. Being careful about language here is appropriate.

R1 Response 13: Lines 290-291 have been revised to address this conflict.

14. Overall, the authors give greater emphasis on the anatomical endpoints and less to the subjective endpoints that did not differ. For example, these subjective outcomes are not provided in the abstract. Greater weight should be given in the manuscript to the subjective reports of the women who had surgery. This is what the patients experience and is the most important thing for them. This critical information needs to be provided along with its percentages in the abstract, the conclusion of the abstract, and receive a more prominent place in the discussion.

R1 Response 14: We have added more comment on/reporting of the subjective outcomes as noted in responses 11 and 12 above, and we have also added more description of subjective outcomes to the abstract as suggested in this comment.

15. The discussion needs to acknowledge the higher rate of uterine preservation (24%) in the mesh group and discuss the potential occurrence of endometrial or cervical pathology in the future and possible cancer from the fallopian tubes or ovaries that might have been removed during hysterectomy. In addition, complications from placement of mesh between the cervix and bladder that might arise at future hysterectomy that require removal of the cervix is not known and could potentially be surgically challenging and deserve mention. If the mesh becomes adherent to the bladder there might be a higher rate of bladder injury. Of course, these factors are not yet proven, but logic suggests they be considered.

R1 Response 15: Regarding the risks of uterine preservation, this topic was addressed fairly comprehensively in the 2019 SUPeR trial report, which compared sacrospinous hysteropexy with graft vs vaginal hysterectomy with uterosacral ligament suspension (Supp data, pg 5):

“- In the past, justifications for removal of the uterus include concerns regarding cervical hypertrophy, future cervical or uterine pathology, or even a non-evidenced belief that the uterus organ itself is involved in the prolapse process. Uterine pathology is rare (<1%) in women undergoing prolapse surgery.27 Thus, the common practice of hysterectomy at the time of vaginal prolapse repair is to

facilitate apical suspension. While hysterectomy is the norm, it is not clear whether removing the uterus is necessary or leads to better results. Hysterectomy can have adverse effects; it is associated with menopause 4 years earlier than in women who did not have surgery 28 and is associated with a 2-fold risk of ovarian failure.29 When presented with a scenario in which the participant receives preoperative counseling that the success of surgery is similar with and without hysterectomy, 66% indicated they would decline a hysterectomy (Frick AC, et al, SGS 2011). A recent review on uterine-sparing apical prolapse repair concluded that vaginal hysterectomy was not necessary 30"
A Randomized Trial of Vaginal SurgeryApical Suspension for Uterovaginaline Prolapse: traditional vaginal hysterectomy with native tissue vault suspension vs (jamanetwork.com) Based on this, we did not feel that further comment was necessary here.
Regarding the fact that 25% of patient in the TVM group underwent hysteropexy, we believe that prior to the publication of the 5-year data on the SUPeR trial (2021), which demonstrated hysteropexy with mesh was superior to NTR, this might be considered a "disadvantage" to surgical success in the mesh group. Effect of sacrospinous hysteropexy with graft vs vaginal hysterectomy with uterosacral ligament suspension on treatment failure in women with uterovaginal prolapse: 5-year results of a randomized clinical trial - ScienceDirect
The risk or difficulty of possible future hysterectomy seemed, in our view, beyond the scope of the current study. Perhaps this may be of interest for comment in an editorial.

Reviewer #2: Comments to the authors

The authors present an FDA 522 postmarket surveillance study comparing the efficacy and safety of transvaginal mesh to native tissue repair for pelvic organ prolapse at 36 months. The study design is a prospective multi center cohort study with the primary composite end point of success and retreatment. Secondary composite outcomes include quality of life, mesh exposure and complications. Some of this data has been reported back the FDA with the following response.
"The two Boston Scientific 522 studies were completed, and the final reports (36-month follow-up data) were reviewed by the FDA. The study results showed that Boston Scientific transvaginal POP mesh had similar effectiveness and safety outcomes to native tissue repair at 36 months. The FDA continues to believe that devices of this type for transvaginal POP mesh repair presents potential additional risks compared to native tissue repair, including mesh exposure and erosion. Therefore, the FDA maintains that these devices do not have a favorable benefit-risk profile". FDA.org

Abstract:
Without reading the FDA 522 the abstract is confusing as to the prospective nature of the study. I would suggest clearly stating the FDA 522 order of the primary out come was a superiority trial vs non inferiority for secondary outcomes.
R2 Abstract Response: We have updated the abstract objective accordingly to acknowledge the co-primary endpoints of superiority and non-inferiority, per the 522 order.

Introduction:
Line 10-11 Expand on recurrence by compartments. Ie anterior, posterior and apical. The references listed are all the anterior compartment.
R2 Intro Response 1: We have updated the statement as suggested by reviewer #1 with more recent data from the Pelvic Floor Disorders Network.
Line 14-16 Discuss the evolution of materials and porous size related to infection and mesh exposure.
R2 Intro Response 2: This is an important topic, but given limitations on length of submissions, we felt this was beyond the scope of the current manuscript.

Line 25-35 The disclosure is very important and I assume with blinding the editors will be able to see this and vet any concerns.
R2 Intro Response 3: We have revised this disclosure according to Reviewer 1's request.

Methods:
Line 38-42 Reading the FDA 522 it is not clear if these patients were enrolled prior to post marketing or before. Giving a time line and dates would be helpful.
R2 Methods Response 1: "Post-market" was added to the study description, page 9, line 48. By definition, "522 studies" are all post-market studies. This may be an excellent topic for readers to learn more in an accompanying editorial.
Line 43 How did the sponsor, I assume Boston Scientific, choose sites? If they only chose high volume sites and or academic centers it may not reflect the real world experience and outcomes and underestimate risk.
R2 Methods Response 2:
Surgeons who participated in the Uphold arm of the trial had to have completed a minimum of 10 Uphold mesh procedures in order to be an investigator. Surgeons in private practice as well as those at academic centers were included. The NTR group included many patients in the PFDN network as well as other expert NTR surgeons. While it is true that there might be poorer outcomes and increased risk in other settings, we believe the surgeon groups here are comparable.
Line 48-66 Explain more about the collaborative efforts with FDA, industry and professional organizations in determining the outcomes and inclusion/exclusion criteria. What materials and or sutures were used in the NTR? I could not find details in table 1.
R2 Methods Response 3: Studies performed in response to a "522 order" are negotiated between the FDA and manufacturers. Professional organizations are not included in the process. The FDA ultimately dictates inclusion/exclusion criteria as well as outcome measures. Manufacturers choose to either carry out the study as dictated or withdraw the product from the market.

As many patients in the NTR group were from the PFD Registry, various combinations of absorbable and permanent sutures were used.
Line 77-78 Was the post procedure assessment for POP blinded or was it determined by the primary surgeon?
R2 Methods Response 4: Post-procedure POP-Q assessments were completed by the primary surgeon and were not blinded. We have added this statement as a footnote in Table 1.

Sample size
Line 104 Reviewing the references for historic success 16-20 The follow up for outcomes varied quite a bit. . Am J Obstet Gynecol. 1998;179(1):13-20 was a 4-9 year follow up for NTR vs 6 and 12 mths for mesh Obstetrics and gynecology. 2011;117(2 Pt 1):242-250. Since the primary outcome here is 36 mths the assumptions and references should be short term success and as similar as possible.
R2 Sample Size Response 1: The authors agree with the limitations of the references and ideally the assumptions should have been limited to those with similar follow up. However, at the time of study design and during the protocol discussions with the FDA in 2012, these were the only references that were deemed relevant to formulate the sample size assumptions.

Results:
Line 145-148 The loss to follow up was slightly different 76% in the mesh 83% in the NTR. This may have biased some of the outcomes. If there was dissatisfaction and or unreported complications in the mesh arm they may have been less likely to follow up.

R2 Results Response 1: A very similar question was asked by reviewer #4. Please see our response to it below (R4R34). We hope this address the concerns here.

Line 159 Was there an explanation for higher hysterectomy concurrent procedures in the NTR due to concerns for apical erosion?

R2 Results Response 2: This is a good question, but the answer is an indirect one. During the period of enrollment for this trial, the practice of surgeons participating in the NTR arm likely reflected national trends on this. The recently reported SUPeR trial (2021) addressed this topic directly: "Despite the potential for lower morbidity, according to a 2002 to 2012 United States inpatient hospital database, hysteropexy procedures only accounted for 5% of uterovaginal prolapse surgeries, whereas hysterectomies were 8 times more commonly performed." *Madsen AM, Raker C, Sung VW. Trends in hysteropexy and apical support for uterovaginal prolapse in the United States from 2002 to 2012. Female Pelvic Med Reconstr Surg 2017;23: 365–71.* Regarding reduced risk of mesh exposure by leaving the cervix in situ, this may be lower than when total hysterectomy is completed (similar to that reported for sacral-colpopexy), but that question was not studied in this trial.

Line 177-178 This is helpful knowing the driver of the composite outcome was for anterior repair.

R2 Results Response 3: Thank you.

Line 181 Although 36 mths was the predetermined follow up, POP and repairs along with erosion continues to occur. Is there plan for longer term follow up?

R2 Results Response 4: As the 5-year results of the SUPeR trial were reported last year and demonstrated superiority of TVM of NTR, many investigators in this trial now wished there was a plan in place for longer-term follow-up. Unfortunately, there is no plan for longer-term follow up, as this study is completed.

Table 2 There is overlap with the primary and secondary POP definitions. From reading the manuscript the primary outcome was at or above the hymen chosen by the FDA. Why was the secondary outcome chosen of above the hymen? It does not seem as though this is clinically relevant unless it is a proxy for long term success. Please explain in more detail the clinical relevance.

R2 Results Response 5: As described in the Methods section beginning on page 11, line 97, and also in the Discussion starting on line 242, the primary composite outcome measures included objective measures identical to study inclusion criteria (I.e., prolapse at the hymen). This meant that patients could be considered successfully treated, even if there was no overall anatomic improvement in their prolapse. Investigators believed that some objective improvement in prolapse should be required in the composite definition of success. This was the reason for adding the secondary composite outcome measure.

Discussion:

Line 224 This explains the 2nd end point proposed by investigators.

R2 Discussion Response 1: We are glad to know this description is sufficiently explanatory for the reader.

Line 230 Where were the mesh exposures? When did they show up?

R2 Discussion Response 2: These exposures are detailed in Supplemental Table 3 (referenced in Results, page 16, line 227), including time to event and compartment.

Line 262-267 This addresses some of the comments in the beginning. I would recommend stating this position in the Introduction to help the reader understand the rationale for superiority vs non inferiority.

R2 Discussion Response 3: The study design, including superiority and non-inferiority endpoints, was established and the study was begun years before the February 2019 advisory committee events referenced in this section of the discussion, so we feel it would be misleading or confusing to contextualize this as a rationale for the design. However, we have added the phrase "of superiority and

non-inferiority" to page 11, line 97 in the Methods to clarify that those endpoints were determined by the FDA.

Reviewer #3:

This is a prospective study of the Uphold LITE mesh (Boston Scientific) vs. native tissue repair with 36 months outcomes. Patients included were recruited in the Uphold LITE 522 study, or from the American Urogynecologic Society Pelvic Floor Disorders Registry (shared control pool for other 522 studies). Results show similar composite outcomes in both groups when using the hymen as a cut off for prolapse recurrence. When using recurrence past the hymen as an endpoint, transvaginal mesh appeared superior to native tissue repair. Adverse events were similar in both groups. Mesh complications were uncommon (4.9% mesh exposure, with only 1 individual requiring outpatient excision, others resolved conservatively). This study was conducted and reported rigorously to satisfy the FDA's 522 study requirements. Some clarifications are recommended.

Abstract:
- methods: recommend to specify that the primary composite outcome includes both subjective and objective measures
R3 Abstract Response 1: We have updated the abstract to more clearly describe the composite outcome, per this comment as well as Reviewer 1's first comment.
- results: first sentence: specify this is primary composite treatment success?
R3 Abstract Response 2: We have replaced "treatment" with the words "primary endpoint composite" here.
Methods:
- line 43: Why did this study use separate centers for the study arms? This could introduce further bias as surgeon factors/center factors could impact results. Please clarify.
R3 Methods Response 1: Per study protocol, investigational sites could potentially enroll subject in both arms. However, Boston Scientific prefers each site to only enroll subjects in one arm or the other to reduce bias. There were no investigational sites that enrolled subject into both arms of the Uphold LITE study. For patient selection, investigators evaluated potential study subjects against the protocol to ensure each patient met all of the inclusion criteria and none of the exclusion criteria. If it was the medical opinion of the investigator that the study procedure would address the patients' medical need, the patient was then presented with the option to participate in the study.
Results:
- There is no mention of what the native tissue repairs were. Were they all vaginal repairs, or all approaches? Please add information on type of native tissue repairs (uterosacral vs. sacrospinous ligament suspensions). Did the type of native tissue repair influence recurrence rate in that group, and could this affect the comparison?
R3 Results Response 1: Detailed information on repairs in all compartments in the NTR group have been reported to the FDA. This includes type of procedure, sides repaired and suture type. If desired the table with all this information could be submitted (as an appendix?) for this manuscript. To summarize, all NTR repairs were completed vaginally. For apical suspension, ~70% of patients underwent USLS and ~30% underwent SSLF. 35-47% of patients in this group had a combination of permanent and absorbable sutures placed. Regarding the question of the possibility that the type of NTR apical prolapse repair influenced the recurrence rate, the 5-year results reported in the OPTIMAL trial examined this question specifically and found no difference in success between the groups. Thus, we doubt the type of apical repair influenced recurrence rates in this trial. Effect of Uterosacral Ligament

Suspension vs Sacrospinous Ligament Fixation With or Without Perioperative Behavioral Therapy for Pelvic Organ Vaginal Prolapse on Surgical Outcomes and Prolapse Symptoms at 5 Years in the OPTIMAL Randomized Clinical Trial - PubMed (nih.gov)

- In the native tissue repair group, there were more hysterectomies and less hysteropexies. Was there an association between hysteropexy and recurrence rate in either group?
R3 Results Response 2: The association between concurrent hysteropexy and recurrence rate in the TVM and NTR groups is explored in the tables below. It appears that there is a higher recurrence rate associated with hysteropexy in the NTR group (please note that p-values were not adjusted for multiplicity and for descriptive purposes). Due to space limitations, we have not included this in the manuscript. If the editors would like this included, we are happy to add it.

Recurrence with Hysteropexy in Uphold Arm

	Hysteropexy		
	No (N=170)	**Yes (N=55)**	**pvalue**
Primary Efficacy at 36M			0.650
No (%)	13 (10.6%)	6 (13.0%)	
Yes (%)	110 (89.4%)	40 (87.0%)	
Revision for Prolapse Free Efficacy at 36M			0.636
No (%)	4 (2.4%)	2 (3.6%)	
Yes (%)	166 (97.6%)	53 (96.4%)	

Recurrence with Hysteropexy in NTR Arm

	Hysteropexy		
	No (N=465)	**Yes (N=20)**	**pvalue**
Primary Efficacy at 36M			0.008
No (%)	69 (18.2%)	8 (47.1%)	
Yes (%)	310 (81.8%)	9 (52.9%)	
Revision for Prolapse Free Efficacy at 36M			0.010
No (%)	18 (3.9%)	4 (20.0%)	

	Hysteropexy		
	No (N=465)	**Yes (N=20)**	**pvalue**
Yes (%)	447 (96.1%)	16 (80.0%)	

- lines 146-148: include a lost to follow-up %
R3 Results Response 3: We have added these numbers to what is now lines 160-161.
- line 208: add % of mesh exposure rate here as well (already included in the discussion)
R3 Results Response 4: We have added this rate to the results.
- Tables 6 and 9: include posterior compartment as well
R3 Results Response 5: Posterior compartment data has been added into table 6 and 9. Please note that the posterior compartment result is included for reference purpose which is not a component of the primary efficacy endpoint.
- would recommend adding other important postoperative outcomes in the tables including: de novo SUI (as well as persistent SUI, and reoperation for SUI), de novo OAB (and persistent OAB), voiding dysfunction, sexual function scores (mean +/- SD), de novo dyspareunia, non-sexual pelvic pain.
R3 Results Response 6: No significant differences between the groups were noted on any of these outcomes and a table (Table 11) with the detailed data on these and other outcomes has been added.
Discussion:.
- line 258: what is meant by "lower volume type" mesh. The Uphold has both a lower overall surface area of mesh and a lighter weight density than the Prolift used in many previous studies. Both these factors should be specified.
R3 Discussion Response 1: Thank you. We have added this to the manuscript on page 19, line 280.
- line 266: would be more conservative in this sentence and rephrase to " suggests that TVM MAY BE superior..."
R3 Discussion Response 2: Thank you. We have revised what is now lines 289-290 to reflect on the study timeline rather than emphasizing possible superiority.
- Would emphasize that there was no difference in patient symptomatology or quality of life demonstrated in either study.
R3 Discussion Response 3: Subjective outcomes (symptoms) were included as part of the primary and secondary composite outcome measures. These were high and similar in both groups (NTR: 92.8% v TVM: 92.4%). Quality of life measures on many scales improved in both groups and we plan to report these data in separate reports.

Reviewer #4:
Abstract Results section, line 3: The (6.5%, CI -0.2%,13.2%) needs clarification, since it represents the propensity adjusted treatment vs that available to the reader from the crude rates. Should cite all the primary outcomes first, then any relevant secondary ones.
R4 Response 1: We have added “propensity-adjusted treatment difference” before the rate and CI.

lines 102-112 and Table 2: There were actually 4 primary endpoints, so the inference threshold would need to be stricter than 0.05, to account for multiple hypothesis testing. That makes the study underpowered for the various primary outcomes cited. It would have been preferable to stipulate one primary (e.g., non-inferiority of treatment success rates at 36 months) and made the remainder as secondary outcomes.

R4 Response 2: Thanks for the comments. Per FDA's 522 Order, the primary efficacy endpoint (the composite treatment success at 36 months) and the primary safety endpoint (device and/or procedure related SAEs) are co-primary endpoints. Non-inferiority hypothesis tests for both primary endpoints were performed first, and only after both of the non-inferiority objectives were met could the hypothesis testing be performed for other outcomes. Therefore, the overall type I error for the primary endpoints was controlled at 0.05 level. In addition, both non-inferiority hypothesis testing yielded a p-value less than 0.001 and so is true for the superiority hypothesis test for the secondary efficacy endpoint (p = 0.009), these evidence together support the conclusion on the treatment efficacy.

Table 4: Should format LOS as median(range or IQR), unless the LOS were normally distributed. Need to include IQR or range wiht the median times and volumes.

R4 Response 3: Median (range) was updated for the variables in table 4.

Tables 5, 6: It appears from the multiple imputation vs available case analysis that there were ~56 with some missing dat in TVM and ~ 85 with missing data among the NTR group. Need to enumerate which of the characteristics were missing for each group (could in supplemental information, with relevant summary in main text. Also, did those with complete data differ in any baseline characteristics from those who had incomplete data?

R4 Response 4: The lower follow up visit compliance in the Uphold Lite arm was mainly due to a change in the study investigator at one study site. This site enrolled a total of 27 subjects into the Uphold LITE arm; however, 16 subjects exited the study when the study PI changed. For the composite efficacy endpoint, treatment success is achieved only when all the components meeting the respective criterion and in the absence of any missing measurement at 36 months. If one or more of the components data were missing but the rest were success, the subject's endpoint will be treated as missing. If any available component was not a treatment success, then a treatment failure definition is met regardless the missingness of other component(s). There were total 3 Uphold and 5 NTR subjects who had 36 month visit but some of the components were missing. The rest of the missing primary endpoint were due to lost to follow up. The comparison of the baseline characteristics between subjects who had 36 month primary endpoint with those without in each treatment group is also tabled below (please note that p-values were not adjusted for multiplicity and for descriptive purpose).

Baseline Characteristics Comparison between Subjects with and without 36M Endpoint Uphold

	36M Primary Endpoint		
	Missing (N=56)	**Not Missing (N=169)**	**pvalue**
Age at Procedure (Derived)			
Mean ± SD	64.8 ± 13.7	67.2 ± 9.7	0.150
Median (min - max)	67.7 (32.5 - 88.0)	67.5 (35.5 - 88.2)	0.437
Race white			1.000
Yes (%)	52 (92.9%)	158 (93.5%)	
No (%)	4 (7.1%)	11 (6.5%)	
Body Mass Index (BMI) at Baseline			

	36M Primary Endpoint		
	Missing (N=56)	**Not Missing (N=169)**	**pvalue**
Mean ± SD	28.3 ± 6.8	28.5 ± 5.8	0.806
Median (min - max)	27.4 (15.8 - 57.8)	27.9 (15.1 - 51.4)	0.614
Smoking, current			0.020
Yes (%)	9 (16.1%)	9 (5.4%)	
No (%)	47 (83.9%)	159 (94.6%)	
Baseline Diabetes			0.987
Yes (%)	8 (14.3%)	24 (14.2%)	
No (%)	48 (85.7%)	145 (85.8%)	
Post-menopausal			0.031
Yes (%)	48 (85.7%)	161 (95.3%)	
No (%)	8 (14.3%)	8 (4.7%)	
Previous Pelvic Surgery to Treat Prolapse			0.350
Yes (%)	12 (21.4%)	27 (16.0%)	
No (%)	44 (78.6%)	142 (84.0%)	
Previous Hysterectomy			0.006
Yes (%)	45 (80.4%)	102 (60.4%)	
No (%)	11 (19.6%)	67 (39.6%)	
Estrogen Treatment at Baseline			0.977
Yes (%)	20 (35.7%)	60 (35.5%)	
No (%)	36 (64.3%)	109 (64.5%)	
C Measurement at Baseline			
Mean ± SD	-2.3 ± 3.2	-1.2 ± 3.8	0.067
Median (min - max)	-3.0 (-9.0 - 5.5)	-3.0 (-8.0 - 10.0)	0.108
Ba Measurement at Baseline			
Mean ± SD	2.0 ± 1.5	2.6 ± 1.4	0.007
Median (min - max)	2.0 (-1.5 - 5.5)	2.0 (0.0 - 7.5)	0.005
Concurrent Anti-Incontinence Procedures?			0.850

	36M Primary Endpoint		
	Missing (N=56)	**Not Missing (N=169)**	**pvalue**
Yes (%)	31 (55.4%)	96 (56.8%)	
No (%)	25 (44.6%)	73 (43.2%)	
Surgeon cases > median			0.844
Yes (%)	25 (44.6%)	78 (46.2%)	
No (%)	31 (55.4%)	91 (53.8%)	

NTR

	36M Primary Endpoint		
	Missing (N=89)	**Not Missing (N=396)**	**pvalue**
Age at Procedure (Derived)			
Mean ± SD	59.0 ± 11.2	63.2 ± 10.3	<.001
Median (min - max)	58.6 (27.1 - 81.9)	64.7 (33.9 - 91.0)	<.001
Race white			0.379
Yes (%)	72 (81.8%)	337 (85.5%)	
No (%)	16 (18.2%)	57 (14.5%)	
Body Mass Index (BMI) at Baseline			
Mean ± SD	29.2 ± 6.3	27.9 ± 5.1	0.036
Median (min - max)	28.6 (17.2 - 47.5)	26.8 (17.7 - 56.5)	0.077
Smoking, current			<.001
Yes (%)	16 (18.0%)	22 (5.6%)	
No (%)	73 (82.0%)	374 (94.4%)	
Baseline Diabetes			0.058
Yes (%)	17 (19.1%)	46 (11.6%)	
No (%)	72 (80.9%)	350 (88.4%)	
Post-menopausal			0.193
Yes (%)	70 (78.7%)	334 (84.3%)	

	36M Primary Endpoint		
	Missing (N=89)	**Not Missing (N=396)**	**pvalue**
No (%)	19 (21.3%)	62 (15.7%)	
Previous Pelvic Surgery to Treat Prolapse			0.276
Yes (%)	12 (13.5%)	38 (9.6%)	
No (%)	77 (86.5%)	358 (90.4%)	
Previous Hysterectomy			0.572
Yes (%)	29 (32.6%)	117 (29.5%)	
No (%)	60 (67.4%)	279 (70.5%)	
Estrogen Treatment at Baseline			0.650
Yes (%)	27 (30.3%)	130 (32.8%)	
No (%)	62 (69.7%)	266 (67.2%)	
C Measurement at Baseline			
Mean ± SD	-1.0 ± 4.1	-0.8 ± 3.7	0.592
Median (min - max)	-2.0 (-8.0 - 12.0)	-1.0 (-9.0 - 10.0)	0.467
Ba Measurement at Baseline			
Mean ± SD	1.8 ± 2.3	1.9 ± 2.0	0.611
Median (min - max)	1.0 (-3.0 - 12.0)	2.0 (-3.0 - 10.0)	0.337
Concurrent Anti-Incontinence Procedures?			0.446
Yes (%)	46 (51.7%)	187 (47.2%)	
No (%)	43 (48.3%)	209 (52.8%)	
Surgeon cases > median			0.770
Yes (%)	45 (50.6%)	207 (52.3%)	
No (%)	44 (49.4%)	189 (47.7%)	
Propensity Score			
Mean ± SD	0.2 ± 0.2	0.3 ± 0.2	0.529
Median (min - max)	0.2 (0.0 - 0.7)	0.2 (0.0 - 0.8)	0.640

Table 7: The differences were NS, but the rates of adverse outcomes was low and the power to discern any difference was also low, so one cannot generalize the NS treatment differences from these data.

R4 Response 5: While the authors agree that the rates of adverse outcomes were low and the power to discern a small difference is low in the context of the superiority trial design, the small difference in rate is not a concern for the non-inferiority design. The study is adequately powered for the pre-specified non-inferiority margin at 10% for the safety endpoint. The propensity score adjustment difference between the Uphold Lite and NTR arms is -0.4% with a 90% CI of [-2.7%, 1.9%]. The upper bound of the 90% CI is 1.9%, far below the pre-defined 10% non-inferiority margin. The almost symmetric confidence interval around zero does indicate non-significant treatment difference between the two groups.

Table 8,9: Same issues as with Tables 5,6 re: missing data and any differences between the groups with complete data vs those who required imputation.
R4 Response 6: All the datapoints are the same for secondary endpoint as the primary endpoint. Please see comment for response 4.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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.
We choose to opt in, and have indicated this in the cover letter above.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.
This information has been added as indicated.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

Per my Jan. 24 email exchange with Randi Zung in the editorial office, it seems the co-author contacts were not entered at the time of initial submission; thus they have not yet received and completed these forms. I will enter these at the time of resubmission as Randi advised.

4. 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.
We have added this statement to the cover letter.