OBSTETRICS & GYNECOLOGY

**NOTICE:** This document contains comments from the reviewers and editors generated during peer review of the initial manuscript submission and sent to the author via email.

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

**Date:** Apr 26, 2021
**To:** "Ben W. Mol" [redacted]
**From:** "The Green Journal" em@greenjournal.org
**Subject:** Your Submission ONG-21-369

RE: Manuscript Number ONG-21-369

Why and how to assess data integrity in randomized controlled trials?

Dear Dr. Mol:

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 May 10, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

I read with interest the article entitled "why and how to assess data integrity in randomized controlled trials?" by Li et al. This manuscript was submitted as a Clinical Expert Series. The authors' provide a commentary on the increased number of retracted articles, especially in 2020, in OB/GYN literature. They comment on the ethical and research implications of falsification of data and call for newer or better methods to screen trials for bad data or falsification.

1. The authors talk mostly about the "why" data fabrication and study retraction is a problem and less about "how" to recognize false data, as a reader. They present a couple options for ways to move forward but this aspect could be greatly expanded upon. The authors don't mention anything about processes in place today in current journals. One only has to look so far as the instructions for authors from this very journal to see the methods in place to recognize false data, promote trial registration, and data sharing. One of the listed automatic rejection criteria is lack of trial registration prior to randomization.

2. It would be advantageous for the authors to comment more on their informal data search regarding the number of manuscripts retracted. What was the time period looked at? How many studies were published in journals during this time period (number may not be exactly known but an estimate could be generated to compare the 36 retracted articles to. I'd bet that 36 easily represents far less than <1% of all articles published. And probably less than 1% of all RCTs published during this time period. So the question becomes not how bad is the practice of falsification of data (we all know it is bad) but really how prevalent is it. It really seems that a few bad apples cast a bad light on everyone.

3. Appendix 1 is a nice table of all the retracted or expressed concern studies. This should be commented more on in the article for the readers. Of the 36 studies, none are from the U.S. A comment and breakdown by country would be helpful. Maybe the authors can comment on the research standards and publication requirements in these other countries. The authors should break down the studies not only by retraction date but by publication date and even by journal. Most studies were published prior to many journals implementing more guidelines and checklists to combat this issue.

4. Similarly to #3, the authors should break down and comment by researcher more than just mentioning Yoshitaka Fujii. While he represents the largest offender, 29/35 (80.5%) of all studies listed were done by only 6 researchers (all authors with multiple retractions or calls of concern)! A nice correlation could be done by author, study year, and journal. This could be more informative than figure 1. Figure 1 likely demonstrates an increase in retraction due to increased awareness and methods to detect falsified data. There will always be a lag in this realm.

5. Table 1. The "X" and check marks look very similar to one another at quick glance. Suggest making this more distinct.

6. Table 2. Fist check box under 1) governance. As above, the green journal already automatically rejects RCTs not registered.

Reviewer #2:

Review of Manuscript ONG-21-369 "Why and how to assess data integrity in randomized controlled trials"

Li and colleagues have submitted a Clinical Expert series manuscript that aims to comment on the assessment of data integrity for RCTs. As noted, this is a significant scientific issue that may lead to patient harm among other ills. As presented, the authors do reference should either retracted obstetrical publications or ones undergoing evaluation for potential integrity concerns at present. I have the following questions and comments.

Title - Would it be worthwhile to note you are concentrating on fabrication and falsification of data in this review?

Précis - No comments

Abstract - Line 67 - Is the issue the visualization of this as an issue or not only an unwillingness to admit but to also confront?
Line 73-5 - Do you mean that publications from these disgraced authors can inform evaluation of submitted works from other authors not implicated?

Introduction - Line 108 - How about flawed rather than dirty?
Line 138 - Can the appendix be included as a table to make it easier for authors to read about these concerns?
Line 142 - Do you mean that it was " admitted to…"or that he just "committed" fabrication?
Line 147 - For a potentially important manuscript raising this issue is there a way to rephrase this or perhaps just put "tip of the iceberg" in quotes?

Methods -

Section 2 - Data integrity - Maybe a small table with the different programs that can be used and pros and cons can be added.

Tables - Table 1 - Can you make the symbols more pronounced in their differences - perhaps checks or X's only when different? At first glance everything seemed to be the same.
Table 2 - Okay

Figure 1 - Okay but really could be supplementary.

Reviewer #3:

The authors summarize available approaches to interrogate trial data and evaluate integrity, as well as proposals based on their own experience. I commend the authors because this is well-written, clearly articulated, and convincing. I do not have the expertise to know whether the authors' review is comprehensive, but I do have knowledge and experience on several relevant considerations.

Abstract

Comment 1: Please state the objective of the manuscript. From the abstract, it is not clear if this is a hypothesis-driven study, an editorial, call to action, review article, etc. Suggest the objective stated in lines 193-194. I look forward to seeing this published.

Main text:
Comment 2: The article is prescient and well-written. However, the purpose of the article is not clear until line 193. It would help to move the statement of objective earlier in the manuscript, such as at the end of the introduction (~line 120).

Comment 3: line 139 ("various reputational journals…") Do the authors mean "various reputable journals"?

Comment 4: lines 171-172. The authors state that "given the usual absence of regulatory oversight, the ability of institutions to investigate the research of their employees is largely questionable". This statement is not consistent with my experience as an investigator and is not self-evident enough to state without citation or qualification. Institutions have the ability to limit research operations, access to local resources, not to mention terminate employment contracts. Institutional motivation is certainly questionable, but "ability" should not be. I acknowledge this may be related to regional or institutional differences, but this statement needs more qualification or explanation if it is to be retained.

Comment 5: The final discussion of relevant issues and considerations would benefit from a few sentences acknowledging resource constraints of journals and editors, as well as an over-reliance on volunteer peer review. A solution to this may be to consider peer review as an activity worthy of academic credit on the part of institutions and professional societies rather than just an expected contribution that authors are expected to make in addition to other professional demands.

Comment 6: The manuscript could benefit from a table summarizing the authors' proposals to improve the process at the level of investigators, journals, and reporting and investigation processes (from section "More needs to be done…").

Comment 7: the authors mention examples of journals with data sharing policies but do not propose that journals require individual participant data be made publicly available. To me, this is appealing as it might encourage an open-source approach to checking data integrity. Please address why or why not this may be a viable option.

Comment 8: Please briefly explain/define the methods summarized in table 1 in the caption, or move the first reference to Table 1 to later in the manuscript when the contents of Table 1 are referenced. For example, Table 1 is first referenced in line 222 but the GRIMMER test, which is included in table 1, is first mentioned in the manuscript in line 303 and so is unfamiliar to the reader when they first refer to Table 1.

Comment 9: The checklist the authors provide in Table 2 strikes me as insightful and innovative. Since the table is described as a "dedicated tool" for readers, it would help if the authors could be more specific about how the tool is to be used in practice or for validation. Should a publication be considered suspect if any of the red flags are identified, or more than one, or is there another threshold? Even a comment on the authors' own experience of identifying cases of fraud would be helpful, (i.e. "in our experience, cases of fraud are likely to meet several of these criteria").

Comment 10: similar to comment 9 above, it would be helpful if the authors could suggest a path forward for testing and validating their proposed tool (Table 2) before implementation.

Comment 11: One noteworthy omission is that the authors did not comment on published reporting guidelines, such as CONSORT or Jadad, and whether or how these might be used to augment assessments of trial data integrity.

Reviewer #4:

This manuscript discusses the potential of compromised data integrity in clinical trials and provides a list of specific cases (N = 33) involving obstetrics, gynecology, and women's health from a publicly available database called 'Retraction Watch'. This is an important problem that deserves open discussion.

1. The authors are to be personally commended for the efforts that they have put into addressing this issue, not only in this manuscript but in other venues over the past several years. In addition, the authors do provide some constructive suggestions on how authors, reviewers, editors, and readers could all take this important problem into consideration (specifically, Table 2).

2. In the Screening for Integrity Issues section the authors present a series of important considerations that readers, reviewers and editors should consider when reading or reviewing manuscripts (lines 243-278). This reviewer found the following particularly noteworthy:
   a. Absent or retrospective trial registration
   b. Absent or vague description of research ethics

c. Low author-to-study size ratio
d. Intervention implausibility
e. Implausible time intervals or loss to follow up statistics
f. Implausible clinical correlations

3. Likewise, the Data Integrity Assessment section (lines 285-355) provides useful information and a list of possible data assessment tools. This reviewer found the discussion of Benford's Law particularly enlightening (lines 321-336).

4. The discussion of Individual Patient Data Assessment (lines 357-xxx) is detailed and interesting. However, it should include a comment about the implications of such sharing in the informed consent process. There are substantial societal sub-segments for whom public sharing of their research data, particularly if it is in any way individually identifiable, would preclude participation. This could further exacerbate the equally long-standing problem of under-representation of these groups.

Unfortunately, the document in its current form abounds with inflammatory rhetoric that would serve no constructive purpose if published in its current form.

ABSTRACT:
5. The authors state that 'in general there is a poor will to envisage this issue (compromised data integrity) in academia' (lines 67-68). They also state that 'a mechanism' (line 76, not otherwise specified) should 'assess all publications of one leading author or an author group who had a history of fabricating data or were suspected to do so' (lines 74-75). Who would be designated to serve as this intellectual honest organization? These inflammatory statements require documentation or else should be deleted.

INTRODUCTION:

6. Line 102: The authors state that a critical question ('do the researchers swear to tell the whole truth?') is 'unmentionable'. On what basis do they make this claim? This implies some sort of deep state conspiracy amongst clinical trialists. If such is the case, some reasonable documentation should be provided.

7. Lines 104-107: Likewise, the authors content that 'a seemingly natural and traditional belief that all researchers are inherently virtuous and honest' is 'groundless'. The authors claim that, although it is 'taboo in the research culture', examining the validity of data 'has become commonplace for business and most industries'. An example would be helpful. Note: This reviewer does believe that this latter assertion is sound.

8. Lines 113-114: The authors state that 'there has been a dramatic increase in the number of papers being retracted, most due to research misconduct.' How does this statement align with their claim that 'there is a poor will to envisage this issue (compromised data integrity) in academia'? (lines 67-68). This paragraph (lines 112-120) goes on to provide documentation that data falsification is well recognized as a reason for manuscript retraction. That said, this reviewer does agree with the authors' contention that 'euphemistic language and concealed real reasons' do sometimes obfuscate the true reasons for manuscript retraction.

A RISING TIDE OF LIES:

9. The authors provide three references to their own work on this subject, including one posted on a publicly available website entitled 'Retraction Watch', all of which focus (appropriately) on clear malfeasance from a group at an Egyptian institution (lines 123-136) [Note: Reference 8 is incomplete, but is presumably: Eur J Obstet Gynecol Reprod Biol 2020;249:72-83. PMID: 32381348]. The appendix provides a complete list of their documented manuscripts (N = 33 from the aforementioned website representing 10 institutions from 7 countries, the great majority being from Egypt (4 groups) and Japan (2 groups). While this is important documentation it is not clear that it represents 'only the tip of the iceberg in our field' (lines 146-147) or that 'reluctance to envisage the problem is more widespread in our field (line 151).

10. This reviewer believes that the authors are misrepresenting the report of Bolland et al (text lines 155-158; manuscript reference 13). The manuscript uses this reference to document that 'the attitude of publishers and journals toward warnings about research misconduct varied significantly. Some respond seriously and act timely but many are slow or tend to ignore them'. The manuscript of Bolland et al asked whether responses about possible scientific misconduct from journals to journalists would differ in speed, usefulness, and tone from responses to academics and concluded that 'journal responses to a journalist were less useful than those to academics in understanding the status or outcomes of journal investigations'.

11. Line 163: 'When there is a will to investigate' serves no constructive purpose and should be deleted.

12. Line 187: 'reflect a regretful fact'. Could this not simply state 'reflect the fact'?

METHODS TO ASSESS DATA INTEGRITY IN RCTS:

13. Lines 206-208: 'When assessing the integrity, it is important to assess all publications of one leading author or an author group who had a history of fabricating data or were suspected to do so.' The authors again describe their

investigations of the Egyptian group (previously discussed in lines 123-136). The amount of effort that they expended in this process is clearly impressive. It would be interesting to know how many person-hours this effort involved, for no other reason than to point out the challenges of taking such efforts to scale.

MORE NEED(S) TO BE DONE TO SAFEGUARD THE INTEGRITY OF TRIALS:

14. Lines 422-426: To be sure, the authors have presented in the Appendix a list of 33 manuscripts in obstetrics, gynecology, and women's health that have been retracted or classified as 'expression of concern' by Retraction Watch. This reviewer doesn't disagree with their contention that there are doubtless other such cases that have as yet not been identified. On the other hand, how many acceptable (if not high) quality clinical trials have been published in these disciplines over the past several decades? This reviewer suspects that the decimal point would need to be moved by multiple digits. This supposition leads to concerns that 'a long-suffering attitude towards manipulation of data denies the position of whistleblowers and tempts others to follow suit' and 'appeasement or overlooking does not address this rising challenge for good but rather exacerbates distrust in medical research that reared its ugly head in recent years' are both unnecessarily inflammatory in their rhetoric.

Several other minor issues were also noted during the review:

15. Lines 229-230: The meaning of the sentence 'It is important that further investigations begin performed to verify or refute any positive findings following the screening' is not clear to this reviewer.

16. Several references (specifically 1, 8, 16, 18, 20) are inadequately documented.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
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2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page. Each of your coauthors received an email from the system, titled "Please verify your authorship for a submission to Obstetrics & Gynecology." Each author should complete the eCTA if they have no yet done so.

3. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric 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.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Clinical Expert Series should be no more than 6,250 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

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

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

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

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 limit for Clinical Expert Series is 250 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. ACOG is moving toward discontinuing the use of "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

12. For standard presentation of data: 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%").

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

14. 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 reference you are citing is still current and available. If the reference you are citing has been updated (ie, 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 (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

15. 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.

16. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

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* 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 May 10, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
Torri D. Metz, MD
Associate Editor, Obstetrics

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

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