OBSTETRICS & GYNECOLOGY

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

Date: Jul 20, 2018
To: "Wen Jie Zhang" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1163

RE: Manuscript Number ONG-18-1163

A sensitive single-visit cervical screening incorporating visual inspection, Pap smear and the same-day biopsy in low-income communities

Dear Dr. Zhang:

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

REVIEWER COMMENTS:

Reviewer #1: The authors are to congratulated on carrying out a large trial to try to improve cervical cancer screening in remote areas that are hard to access.

1) A general question for the authors: you talk a great deal about the advantage of a "single visit" approach where the "single visit" means both a screening test and a diagnostic test (biopsy). However, typically "single visit" approach means screening and treatment at the same visit, without necessarily including the diagnostic step. So your paper shows you can do same day biopsy, but it is confusing to call it "single visit" approach because "single visit" typically implies screening and treatment on the same day.

2) Your study designed evaluated the likelihood of getting a biopsy done, and then they were referred for treatment. 54/59 CIN2/3+ received treatment with 5/59 lost to follow up. You state in the paper on line 246/247 the reasons are stated in Fig 1, but it was not clear to this reader the reasons for this loss to follow up. can you elaborate?

3) can you speak more about how you validated "mpap"?

4) can you explain line 175/176: Colposcopy used to "reduce variables"? I am not sure what that means

5) can you explain why you screened "only married" women aged 30-59 years?

6) the onsite biopsy within 1-2 hours of screening revealed 46/219 were lost (21%). This seems high, and makes this editor wonder why screen/treat was not chosen vs. screen/diagnostic test (eg biospsy)? please explain

7) the introduction could be shortened to one paragraph, or two paragraphs maximum.

8) consider combining Figure 1A and 1B.

9) consider eliminating Figure 2.

10) between the patients lost between screening and biopsy and the patients lost between biopsy and treatment, this study does demonstrate challenges to a successful population based approach. Can the authors comment on how they plan to use their mpap/VIA biopsy same day a "scale up" and how they will address the loss to follow up this study demonstrates if/when they scale up? This really could be one of the major contributions of the paper - but is not well discussed or reflected upon.

Reviewer #2: The authors present a study about pap tests and visual inspection with acetic acid of the cervix. The study was conducted in rural China. The authors consider that a rapid modified pap test can increase treatment for CIN in rural China.

The authors do not make a statement about ethical approval.

There are other major weaknesses:

1. No clear Primary outcome is stated.

2. The introduction needs to provide more specifics about how this proposed approach would benefit women

Reviewer #3: A sensitive single-visit cervical screening incorporating visual inspection, Pap smear and the same-day biopsy in low-income communities

This manuscripts details a single-visit cervical cancer screening algorithm that utilizes visual inspection with acetic acid, a modified pap test, and same day biopsy for women in low income communities. The authors are congratulated on presenting an alternative method for screening for cervical cancer in a low income communities that addresses several of the barriers to appropriate screening, including cost and loss to follow up.
The author presents and propose an alternative method to classic pap and HPV testing (and alternative to see and treat methods) to improve sensitivity and NPV. The authors present two low income communities in which to pilot and validate the screening strategy. They detail the modified pap and VIA (visual inspection with acetic acid) procedures, and reported that combined this screening strategy had a sensitivity of 96%, which was superior to either method alone, with an increased SN and minimized loss to follow up rate. They conclude that compared to VIA or pap alone, the same day combined modified pap and VIA single visit screen and biopsy approach has increased sensitivity to detect high grade CIN, resulting in more referrals for biopsy and reduced loss to follow up.

The authors present a well researched and well written manuscript detailing the screen and biopsy approach to cervical cancer screening in low income communities. The background lays the ground work for the justification for finding alternative methods for screening in lower income countries, as cost and loss to follow up have a large impact. The methods and materials are well presented.

The authors may consider spending more time explaining this method's superiority over the "see and treat" methods that would negate the loss to follow up that the author's method may have - as patients are required to follow up for treatment of dysplasia with the presented method.

Minor edits:

Line 89- misplaced period. Should be a comma

STATISTICAL EDITOR'S COMMENTS:

1. lines 65-67 and Suppl Table 4: Need to include CIs to put these prevalence rates in context, since they were based on ~ 4000 women.

2. Table 1:Should include CIs for the proportions cited.

3. Table 2: Should cite referred for biopsy as n(%). The NPV is not a useful metric, since it depends on the prevalence of CIN2+, which could vary in other cohorts. A more useful metric would be either AUC (with CIs) or likelihood ratios (+) and (-), which are independent of prevalence.

4. Table 3: Need to include CIs for the sensitivity and specificity. As stated re: Table 2, NPV and also PPV are not useful metrics, should employ other metrics.

5. Fig 1A: should include in flow diagram the number of "double positives", which appears to be 269-219=50.

6. Fig 1B: should include in flow diagram the number of "double positives", which appears to be 243-197=46

EDITORIAL OFFICE COMMENTS:

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3. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

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

*The first paragraph of the introduction is nearly verbatim from another paper by the author. While items are cited, this is still self-plagiarism, and significant variance must be added.

5. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic

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6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com /AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words. Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

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

8. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

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* 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).

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

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

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Figure 1B: Please check the n values or explain n=197 (106+91+46=243).
Please break Figures 1A and 1B into Figures 1 and 2. Due to size constraints, these will not fit in print as A and B. Please update the manuscript as Editorial Manager as needed.
Figure 2: Please upload a second version of this figure without lower case letters on the images. These will be added back per journal style. Additionally, please break this figure up into Figure 3 A–3, Figure 4 A–E, Figure 5 A–E, and Figure 6 A–3. This is required per journal style. Also, please update the manuscript as Editorial Manager as needed."

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

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